REVIEW ARTICLE

Targeted Vaccine Selection in Influenza Vaccination

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SUMMARY

Background: The main target groups for influenza vaccination are the elderly, the chronically ill, infants, and toddlers. Influenza vaccines are needed that suit the immunological particularities of each of these age and risk groups. Recent years have seen the approval of influenza vaccines that are more immunogenic than before, but whose use in Germany is limited by the restriction of reimbursement to a small number of vaccines.

Methods: The Medline database was selectively searched for pertinent literature.

Results: The suboptimal immunogenicity of conventional influenza vaccines that contain inactivated viral cleavage products and subunits can be markedly improved by the use of squalene-based adjuvant systems, by the integration of viral antigens in virosomal particles, or by intradermal administration. The vaccination of elderly persons with a vaccine containing the adjuvant MF59 was found to lower the risk of hospitalization for influenza or pneumonia by 25% compared to vaccination with a trivalent inactivated vaccine (TIV). On the other hand, the adjuvant AS03 was found to be associated with an up to 17-fold increase in the frequency of narcolepsy among 4- to 18-year-olds. In a prospective study, a virosomal vaccine lowered the frequency of laboratory-confirmed influenza in vaccinated children by 88% compared to unvaccinated children (2 versus 18 cases per 1000 individuals). A live, attenuated influenza vaccine lowered the rate of disease in children up to age 7 by 48% compared to a TIV (4.2% versus 8.1%).

Conclusion: The newer vaccines possess improved efficacy when used for primary and booster immunization in certain age and risk groups, and they are superior in this respect to conventional vaccines based on viral cleavage products and subunits. The risk/benefit profiles of all currently available vaccines vary depending on the age group or risk group in which they are used.

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Seasonal influenza vaccination is recommended in Germany as a standard procedure for all persons aged 60 and above. Moreover, vaccination is also recommended for all persons at elevated risk of serious disease, for pregnant women, and for persons exposed to a higher than usual risk of infection (e1). In April 2012, the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) recommended the extension of national vaccination recommendations to children aged 6 to 59 months. Thus, the spectrum of target groups ranges from infants to very old persons, and from healthy persons with intact immune systems to the chronically ill. There is a corresponding variety in the tasks that influenza vaccines are required to fulfill. For example, a naive immune system that has never yet been in contact with influenza virus antigens cannot be effectively stimulated by the highly purified antigens contained in conventional influenza vaccines. The generation of robust immunity after primary vaccination requires a suitable vaccine, for example, one with added adjuvant or one containing live, attenuated virus (1).

The elderly have a less effective immune system that has become accustomed to influenza virus antigens through decades of exposure to naturally occurring viruses and repeated immunizations. They therefore need a strong, age-specific immunologic stimulus to achieve lasting protection against disease due to infection with currently circulating influenza viruses. The same is true of influenza vaccines for the chronically ill.

A number of influenza vaccines with improved immunogenicity have been approved in the last few years, and others are currently being clinically tested. In this article, we present the clinically relevant differences between conventional and newer influenza vaccines for each of the target groups in which they are used, and we discuss their optimal application.

Methods

This review is based on a search in the Medline database for publications that appeared from January 2000 to February 2013 and that included the search terms “influenza vaccine,” “immunogenicity,” “efficacy,” and “effectiveness.” Particular emphasis was laid on randomized, controlled trials and meta-analyses.

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Classes of vaccines

The influenza viruses that are needed for antigen production in the manufacturing process of the currently approved seasonal, pandemic, and pre-pandemic vaccines are replicated either in incubated hen's eggs (egg-based influenza vaccines) or in permanent cell lines (cell-based influenza vaccines, made with the use of Madin-Darby canine kidney cells [MDCK] or Vero simian kidney cells). These viruses for vaccination, once they have been inactivated with formaldehyde or β -propiolactone and then purified in a multistep process, can either be incorporated whole into a vaccine (whole-virus vaccines) or else used for the extraction of the viral hemagglutinin surface glycoprotein (HA). Depending on the intensity of the purification steps that follow, the final product is designated as either a split-virus vaccine or a subunit vaccine (*Table 1*).

Split-virus vaccines contain larger amounts of other viral components than subunit vaccines, which have been subjected to more intense purification. These additional components, however, are neither characterized nor quantified. The more intensely a viral preparation has been purified, the better tolerated it will be when administered, but at the cost of lower immunogenicity (e2).

Both split-virus and subunit antigens can be incorporated in virosomal particles (virosomal influenza vaccines) or given in combination with adjuvant systems (adjuvanted influenza vaccines) (*Table 1*). Whole-virus vaccines are generally formulated without adjuvant.

Seasonal trivalent inactivated vaccines (TIV) contain antigens of subtypes A/H1N1, A/H3N2, and B-strain. In Germany, in March 2013, the first quadrivalent inactivated vaccine (QIV) against influenza was approved, containing the HA antigens of the two different genetic lines of influenza B viruses (Victoria and Yamagata) (2, e3). Inactivated influenza vaccines for protection against zoonotic ("pre-pandemic") or pandemic influenza viruses contain only the antigen of a single, relevant viral strain and are therefore called monovalent inactivated influenza vaccines. The alternative to inactivated vaccines is represented by live attenuated influenza vaccines (LAIV), which, like the inactivated vaccines, are produced in incubated eggs—in this case, in eggs that have been very thoroughly tested for contaminating foreign material (specific-pathogen-free or SPF eggs). LAIV have been approved in trivalent (EU, USA) and quadrivalent (USA) varieties. The efficacy of influenza vaccines depends to a large degree on the correspondence between the viral strains incorporated in the seasonal vaccine and the influenza viruses that are actually circulating during the current season (e4).

Vaccines with improved efficacy

TIV with increased antigen content

For healthy adults and older children, the efficacy of conventional TIV in the prevention of laboratory-confirmed influenza infection is well documented (e5,

e6). Nonetheless, for persons at increased risk, elderly persons, and children under 8 years of age, the efficacy of these vaccines is moderate at best (e5–e8). For children under 2 years of age, a TIV was not found to be any more effective than placebo (e5).

Multiple studies have shown that raising the antigen dose from 15 to 60 μ g HA increases the immunogenicity of TIV, in the sense of elevating the concentration of antibodies measured in the hemagglutination inhibition test (3–5). On the other hand, the higher antigen dose is also associated with a higher frequency of moderate to severe local and systemic reactions, of which the most common types are pain (5% versus 0%) and myalgia (7% versus 1%) (4). A TIV of this type was approved in the USA in 2009 for use in persons aged 65 and above (6). A comprehensive phase IIIb trial of this high-dose vaccine was carried out during the 2009/2010 influenza season but did not yield any conclusion about its clinical efficacy, as the strain of virus for which the vaccine was designed was strongly divergent from the H1N1 pandemic virus that prevailed at that time (e9).

It remains an open question whether the currently approved non-adjuvanted TIV with higher antigen doses are suitable for the primary immunization of immunologically naive persons. Evidence that this may be the case comes from a prospective cohort study carried out in Finland, where small children are given two adult doses of 15 μ g HA at a 4-week interval for primary immunization (this is not the practice in other countries) (7).

Adjuvanted trivalent influenza vaccines

Extensive studies of candidate pandemic vaccines have clearly shown the superiority of adjuvanted vaccines over conventional ones for inducing immunity to the vaccine antigens (8, e10). This holds both for primary immunization of the naive immune system and for boosters to reinforce immunity that is already present. Squalene-based adjuvant systems like AS03 and MF59 make it possible to reduce antigen content by half (to 7.5 μ g) or three quarters (to 3.75 μ g) without lowering the immunogenicity of the HA antigens, as measured by the titer of induced protective antibodies (9, 11). The large-scale use of pandemic H1N1 vaccines in Scandinavia and England was associated with an up to 17-fold increase in cases of narcolepsy in persons aged 4 to 18 who had received an AS03-adjuvanted vaccine (e12–e14). No such increase has yet been observed in connection with the MF59-adjuvanted pandemic vaccine (e15, e16), but the total number of children and adolescents vaccinated with this vaccine is too small for an association with narcolepsy to be definitively excluded.

As for seasonal vaccines, clinical experience with the MF59 adjuvant system goes back many years. This is an oil-in-water emulsion based on squalene, which is a natural intermediate product of human endogenous cholesterol metabolism and a cellular

TABLE 1

The properties and uses of approved influenza vaccines and those whose approval is pending^{*1}

	Properties ^{*2}							Uses	
	Whole-virus vaccine	Split-virus vaccine	Subunit vaccine	Egg-based ^{*4}	Cell-based ^{*4}	Adjuvanted	Viro-somal	Seasonal	Pandemic Pre-pandemic
Monovalent ^{*2} , inactivated	•	•	•	•	•	•			•
Trivalent ^{*2} , inactivated		•	•	•	•	•	•	•	
Quadrivalent, inactivated		•		•				•	
Monovalent, live attenuated ^{*3}	•			•					•
Trivalent, live attenuated	•			•				•	
Quadrivalent, live attenuated ^{*3}	•			•				•	
Trivalent, intradermal administration		•		•				•	

^{*1}Modified from Pfeiderer M: Impfkolloquium Potsdam-Hermannswerder, 29–30 April 2011

^{*2}The product properties reflect combinations of different attributes, including the substrate for viral replication and other attributes; for example, split-virus vaccine/egg-based/adjuvanted, subunit vaccine/egg-based/virosomal, subunit vaccinated/cell-based/adjuvanted, etc.

For some of these combinations, e.g., split-virus vaccine/cell-based/virosomal, there is no approved product.

^{*3}Approved in the USA, but not in the EU

^{*4}Egg-based = replicated in incubated eggs; cell-based = replicated in cell culture

component. In Germany, an MF59-adjuvanted influenza vaccine (MF59-TIV) has been available since the 2000/2001 influenza season but is only approved for persons aged 65 and above. The vaccine is well tolerated aside from a somewhat higher frequency of local reactions, which are usually mild and of brief duration.

Vaccination with MF59-TIV induces an immune response in elderly and/or chronically ill persons that is 1.2 to 1.8 times stronger than that induced by a non-adjuvanted TIV (10–12). The effect is particularly strong in persons who are both elderly and chronically ill, and in persons with a low antibody titer before vaccination (10, 11). Moreover, the vaccine induces immune response to influenza A strain variants (13, 14).

Observational studies on the clinical efficacy of MF59-TIV have shown that vaccinated persons have a 68% to 87% relative risk reduction (compared to non-vaccinated persons) with respect to hospitalization for pneumonia, cerebrovascular accidents, or acute coronary syndrome (15, 16). In a further observational study on a cohort of persons aged 65 and above, MF59-TIV was found to lower the rate of hospitalization for influenza or pneumonia by 25% in comparison to TIV (17).

Immunogenicity studies in children aged 6 months to <72 months have shown that age-appropriate vaccination with MF59-TIV on two separate occasions elicited a stronger immune response than TIV did, even in very young children (18). An extensive field study on children in this age group showed that MF59-TIV lowered the rate of laboratory-confirmed influenza in comparison to conventional TIV (19). The difference in efficacy between the adjuvanted and the conventional vaccine was most marked in

children under 2 years of age: in this group, the absolute efficacy of M59-TIV was 77%, while that of TIV was only 11%.

Virosomal influenza vaccines

Virosomal vaccines consist of liposomes with a virus-like structure that present HA antigens of the relevant seasonal influenza viruses on their surface. As in a natural infection, the virosomal particles bind and fuse with the host cell, leading to an increased immune response (20, 21). Virosomal influenza vaccines are considered immunogenic, well tolerated, and safe, also for children aged 6 months and above (22, 23, e17).

Two studies of the relative immunogenicity of a virosomal influenza vaccine and MF59-TIV in elderly patients have yielded conflicting results. In one study (24) the two vaccines did not differ in efficacy, while in the other study (25) MF59-TIV was found to induce a stronger immune response.

The only study to date of the clinical efficacy (i.e., protective effect) of a virosomal influenza vaccine is a prospective cohort study performed in children aged 3 to 14 years, with non-vaccinated children as a control group. The vaccine prevented 75% of influenza-like illnesses (27 versus 102 cases per 1000) and 88% of laboratory-confirmed cases of influenza (2 versus 18 cases per 1000) (26).

Influenza vaccines for intradermal administration

Because of the large number of macrophages and dendrites in the skin, intradermal vaccination is thought to be more efficacious than intramuscular or subcutaneous antigen application (e18). Novel microinjection systems are now available for practical intradermal vaccination (e19). In 2009, an influenza vaccine for intradermal administration was approved in Europe for

TABLE 2

Opportunities for the targeted use of influenza vaccines

Target group	Immunological features	Suitable vaccine classes	Approved vaccine available?	Vaccines in advanced clinical testing
1. Immunologically naive children	Primary immunization ("priming") needed	Live-attenuated	Yes (from age 2 yr)	
		TIV-adjuvanted	No	For children aged 6–71 months
		TIV-virosomal?	Yes (from age 6 mo)	
2. Children with basic immunity, persons aged 9 or older	Booster immunization sufficient	TIV	Yes	
		TIV-virosomal	Yes	
		TIV-intradermal	Yes (from age 18 yr)	
3. Persons aged 65 or older	Stronger immunological stimulus needed	TIV-adjuvanted	Yes (from age 65 yr)	
		TIV-high-dose antigen	No	Approved in the USA for persons aged 65 and above
4. Chronically ill persons*	As in the corresponding age group	Vaccine depending on presumed immune status	Cf. groups 1–3	

* No clinical data are available regarding the efficacy of influenza vaccines in immunocompromised persons.
TIV, trivalent inactivated influenza vaccine

use in persons aged 18 and over, on the basis of immunogenicity studies (e20, e21). In patients under age 60, an antigen dose of 9 µg per virus component is used; older persons are given 15 µg of antigen. A randomized, multicenter phase III study showed no difference in immunogenicity and safety between the intradermal vaccine and MF59-TIV when given to persons over age 65 (27). More recent studies have shown that intradermal vaccination also leads to the formation of antibodies against drift variants (28). No studies of clinical efficacy are available.

Live attenuated influenza vaccines

Live vaccines are based on influenza strains that are repeatedly passaged at decreasing temperatures, with the result that they replicate best at 25°C but can hardly do so any more at 37°C. Gene segments of these adapted "master" strains are then combined with gene segments that encode the hemagglutinins and neuraminidases of the currently prevalent epidemic strains. These viruses developed for the purpose of creating vaccines are highly genetically stable and do not undergo reverse mutation (e22–e24).

Given intranasally as a spray, the live viruses in the vaccine replicate in the upper respiratory tract, potentially inducing mild respiratory symptoms. Being temperature-sensitive, they do not replicate in the warmer lower portion of the respiratory tract.

A live attenuated influenza vaccine (LAIV) was approved in the European Union in 2011 for use in children and adolescents aged 2 to 17 years. The advantage of LAIV over conventional, inactivated vaccines is that they not only induce humoral and cellular immunity, but also lead to the formation of secretory IgA,

which exerts a direct protective effect at the portal of entry of influenza virus (29, 30, e25).

Multiple clinical studies have shown that LAIV is effective in children (31–34) and most effective in those up to age 7 (35). A study comparing LAIV to TIV showed that the former lowered the frequency of disease by 48% compared to the latter (4.2% versus 8.1%) (36). This effect was strongest against A/H1N1 infection (97%) and weakest against influenza B infection (32%). LAIV also protects well against influenza A virus variants (33, 37). The rate of influenza-associated otitis media in small children is lower after vaccination with LAIV than after vaccination with TIV (85% versus 54%) (38).

Children aged 2 years and above tolerate LAIV well. The vaccine sometimes induces a local reaction: about 10% of children vaccinated with LAIV have nasal congestion or coryza in the first ten days after vaccination, while fewer children develop these symptoms after vaccination with TIV or placebo (37). LAIV is not approved for use in children aged 6–23 months, because there is a higher frequency of acute wheezing in this age group from the 7th to the 28th day after the initial vaccination (39).

The optimal use of influenza vaccines

Influenza vaccines are still commonly used without any special attention to product-specific data on their efficacy and tolerability in different age and risk groups. This generic attitude is rooted in the past, a holdover from a previous era in which only high-dose, whole-virus vaccines were used and the clinical profiles of all available products were essentially the same—that is, they all had very high immunogenicity, combined with

relatively high reactogenicity (40). The occurrence of poorly tolerated side effects of whole-virus vaccines in seasonal use led at first to a reduction of their antigen content and then to the development of the better-tolerated split-virus vaccines and subunit vaccines. Markedly better tolerability was associated with markedly lower immunogenicity to the vaccine antigens.

Despite these major differences in product properties, it is commonly assumed that the products available today have exactly the same efficacy as the earlier ones. That this is not the case has been demonstrated by recent clinical studies on the development of so-called mock-up vaccines against viral strains that could cause a pandemic. It is questionable, for example, whether and under what circumstances (in terms of the dosage and number of required partial doses) the currently approved, non-adjuvanted, inactivated split-virus vaccines and subunit vaccines are suitable for the primary immunization of immunologically naive persons. In contrast, the suitability of adjuvanted and live attenuated influenza vaccines for this purpose is well documented. These findings clearly suggest that product specificity should be a major consideration in determining which vaccine is best for patients in the main risk groups (the elderly and the chronically ill) and what the optimal dosage and mode of administration should be.

It follows from the above that influenza vaccines should be selected individually for each target group. The most important conclusion of this review is that none of the currently available influenza vaccines has an identical risk/benefit profile in all age groups and risk groups. The optimal use of influenza vaccines in each age group and risk group is only possible on the basis of an individual risk/benefit analysis in the light of up-to-date scientific knowledge. A reasonable scheme for using the currently approved vaccines (and those now in advanced clinical testing) in various age groups and risk groups is given in *Table 2*. For some time now, reimbursement of the costs of influenza vaccination in Germany has been restricted to one or a few vaccines; this restriction is clearly an impediment to optimal evidence-based medical practice.

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Conflict of interest statement

Prof. Wutzler has received payment for serving on advisory boards for AstraZeneca and Sanofi Pasteur as well as lecture honoraria from AstraZeneca, GSK, and Novartis.

Prof. Hardt has received lecture honoraria from Sanofi Pasteur MSD and has received payment for serving on its advisory board. He has also received research support (third-party funding) from the same company.

Prof. Knuf received lecture honoraria and payment for serving on advisory boards from the AstraZeneca, GSK, and Novartis companies until 1 April 2012. He has received research support (third-party funding) from Novartis and reimbursement of travel expenses from AstraZeneca and Novartis.

Prof. Wahle has received lecture honoraria from Sanofi Pasteur MSD and GSK.

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KEY MESSAGES

- The currently approved influenza vaccines differ in their immunogenicity, protective efficacy, and side effects. They all have risk/benefit profiles that vary depending on the age and risk groups in which they are used.
- The immunogenicity of conventional trivalent inactivated influenza vaccines can be increased by adjuvant systems, by the incorporation of viral antigens in virosomal particles, or by intradermal administration.
- Children vaccinated with live attenuated influenza vaccines contract influenza less often than those vaccinated with conventional inactivated vaccines (4.2% vs. 8.2%).
- The new vaccines with improved immunogenicity are superior to conventional inactivated vaccines for the primary immunization of children and for booster immunization of elderly and/or chronically ill persons. This has been demonstrated in clinical studies with age-specific endpoints, e.g., laboratory-confirmed influenza for children and pneumonia or hospitalization for the elderly.
- The most suitable vaccine should be made available to each target group.

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