Influenza, whether seasonal or pandemic, causes substantial morbidity and mortality. Today, vaccines are the foundation of influenza prevention. Globally, influenza vaccine manufacturing capacity is at an all-time high [1], as are the number and types of influenza vaccines available on the market and in development. In the United States, in addition to the live attenuated and inactivated subunit and split influenza vaccines, a high-dose inactivated vaccine for persons aged ≥65 years, and an intradermally administered inactivated vaccine for persons aged 18–64 years have been recently licensed for seasonal use. This is remarkable progress, considering that as recently as the 2004–2005 influenza season, only one inactivated vaccine was available on the US market [2]. In the United States, all of these vaccines are produced in eggs, although cell-based inactivated and recombinant vaccines are in the late stages of development. Outside the United States, additional inactivated vaccines are licensed for seasonal use, including those manufactured in cell culture, subvirion vaccines combined with the oil-in-water adjuvant MF59 for persons aged ≥65 years, and whole virus and virosomal vaccines. During the 2009 H1N1 pandemic, many countries, not including the United States, also licensed and used monovalent inactivated vaccines adjuvanted with an oil-in-water adjuvant, either AS03 or MF59.

When compared with other vaccines, the range of influenza vaccines that are licensed or in development is unprecedented. The robust market and development pipeline are being driven by several factors, including the demand for more seasonal influenza vaccine. Another factor is the desire for faster production and less-expensive alternatives that will make vaccines more widely and equitably available to populations in countries with limited resources, particularly during a pandemic [1]. Additional goals are to improve vaccine performance in high-risk populations, such as the elderly, young children, and the immunocompromised, and to elicit more broadly cross-protective antibodies so vaccines do not require yearly administration.

Given the diversity in influenza vaccine formulations, determining the relative benefits of each vaccine is important but extremely challenging. Influenza vaccine performance is influenced by a number of factors, including formulation, age and immune status of the study participants, the vaccine antigen, the match to the circulating strain, and whether the study outcome is immunogenicity or vaccine efficacy. To further complicate the evaluation, the standard measure of influenza vaccine immunogenicity for inactivated vaccines, the hemagglutination inhibition (HAI) assay, exhibits significant variability within and between laboratories. HAI assay results are also affected by the type of vaccine administered and the previous experience of the vaccinee [3]. Thus, it can be extremely difficult to compare the performance of various vaccines between studies. Comparing multiple vaccines within a single clinical trial has the distinct advantage of controlling for the population and strain differences, as well as the assay variability, and offers the best approach for comparing different vaccines.

In this issue of the Journal, Ferguson and colleagues compare the immunogenicity and reactogenicity of 1 or 2 doses of a tocopherol-based oil-in-water (AS03) adjuvanted H1N1 monovalent vaccine with 1 or 2 doses of the unadjuvanted vaccine [4]. For the reasons given above, the multiple-group comparisons possible within this single study are a strength. The results support previous observations that inactivated influenza vaccines are more immunogenic in younger adults than in older adults, in individuals previously seropositive to the vaccine antigen at baseline, and in recipients of the adjuvanted vaccines. As shown in this article, the 3.75-μg dose of adjuvanted vaccine was superior to 3.75 mg of unadjuvanted vaccine after a single dose in younger and older adults. Likewise, the lower doses of adjuvanted vaccines were noninferior to higher doses of the unadjuvanted vaccine, confirming the dose-sparing aspects of adjuvants [4, 5]. These dose-sparing effects are particularly
important during pandemics, when vaccine supplies are limited and demand is high. Also similar to other studies, the adjuvanted vaccines elicited significantly more injection-site reactions when compared with the unadjuvanted formulations, but the percentage of persons with grade 3 reactions was low [5].

Despite these strengths, the study has several limitations. First, the actual antigen content included in the study vaccines was lower than planned (5.6 and 11 µg rather than the conventional 7.5 and 15-µg doses, respectively). Second, the study was conducted during the pandemic when wild-type H1N1 virus was circulating in the study communities and might have influenced the immune responses seen in some participants. Finally, the study compared the immunogenicity of the vaccines and not efficacy for the prevention of laboratory-confirmed influenza.

Although the enhanced immunogenicity of the oil-in-water adjuvanted vaccines is likely to translate into improved protection, in the absence of comparative efficacy studies, this remains an assumption. As mentioned earlier, immunogenicity is generally measured by HAI assay, which has been used as a relative correlate of protection for influenza in adults for many years, based on a limited number of studies of inactivated vaccines [6–8]. Head-to-head comparisons of different influenza vaccines in efficacy studies with laboratory-confirmed clinical influenza as the end point are needed to determine whether the higher HAI titers seen with adjuvanted vaccines will translate into enhanced protection. Such a comparison was recently reported. In that efficacy study of a different oil-in-water (MF59) adjuvanted seasonal vaccine in young children, the superior efficacy of the adjuvanted vaccine was shown [9]. This study could be invaluable in identifying a correlate of protection for adjuvanted vaccines in children that would guide the interpretation of studies without efficacy end points. Similarly, comparative studies of live-attenuated vaccines versus inactivated vaccines have helped to elucidate the better performance of the live vaccines in children but not in adults, although a correlate of protection for live-attenuated vaccines remains elusive [10].

Any decision on the relative merits of different formulations of influenza vaccines for different populations must include safety. Recently, the AS03-adjuvanted vaccine used in the study by Ferguson et al (Pandemrix) was reported to be associated with narcolepsy in children in certain European countries. Although further epidemiological studies are underway, the World Health Organization’s Global Advisory Committee on Vaccine Safety concurs with a recent European Medicines Agency recommendation to restrict use of Pandemrix in persons ≤20 years of age but indicates that, overall, the benefit-risk of the vaccine remains positive [11]. Such findings emphasize the importance of rigorous postmarketing surveillance systems to monitor both the safety and effectiveness of new vaccines.

Continued research and development into improved influenza vaccines are welcome and necessary. Comparative studies such as the one by Ferguson et al provide a uniform way to evaluate the relative performance of different vaccines. Such studies should continue to be pursued to better elucidate safety, immunogenicity, and efficacy of influenza vaccines in different populations. The evidence generated can guide policy decisions aimed at reaching target populations worldwide and achieving the greatest possible reductions in influenza-related morbidity.

Notes

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