

## EDITORIALS



## Different Approaches to Influenza Vaccination

Keiji Fukuda, M.D., M.P.H., and Marie Paule Kieny, Ph.D.

In this issue of the *Journal*, two important and timely studies address basic questions related to the use and performance of influenza vaccines.<sup>1,2</sup> The findings are also informative because both studies were conducted in the 2004–2005 influenza season when the influenza A (H3N2) components in both the inactivated and the live attenuated influenza vaccines were not optimally matched to the circulating strains.

In one of the studies, King et al. investigated whether the vaccination of children 5 years of age or older with a live attenuated influenza vaccine reduced the spread of influenza to households and the community through “herd immunity” (the indirect protection from influenza at the community level).<sup>1</sup> Herd immunity is an attractive concept, particularly because it could extend protection to certain highly vulnerable groups — especially the very young and the elderly — who often do not have an adequately protective immune response to immunization. Apart from health care workers, for whom vaccination is recommended largely to avoid transmitting the infection to patients, influenza vaccine is currently administered mostly to prevent individual recipients from having severe complications from influenza — not, as is sometimes believed, to “control” the spread of an influenza epidemic throughout communities. This distinction is fundamental. The planned use of influenza vaccination to induce herd immunity would mark a considerable departure from, or addition to, current approaches in most countries. Although this use could theoretically provide substantial benefits, very convincing evidence that vaccination can induce substantial levels of community protection through herd immunity will be required before such an approach is embraced widely.

King et al. offered the vaccine to the children attending several intervention schools but not to

children attending control schools. Using questionnaires provided to all households, the researchers assessed clinical outcomes and outcomes related to the use of health care and medications among the children and household members. In addition, work and school absences were assessed. Overall, there were significant, but relatively modest, reductions in the numbers of symptoms of respiratory illness and visits to physicians among the intervention-school households as compared with the control-school households. Absenteeism from elementary and high school, but not middle school, was also reduced in the intervention-school households, as was the number of paid work-days missed.

The findings strongly suggest, but do not conclusively demonstrate, that the vaccination of these children reduced the spread of influenza to their households and to other student populations. As noted by the authors, parents or guardians knew whether their child had received the live attenuated vaccine, which could have biased how questionnaires were answered. Also, some schools were designated for the intervention for administrative reasons, which might have had an effect. Finally, no laboratory testing was done to confirm the study outcomes. Although the need for such confirmation can be disputed, confirmatory laboratory tests add a unique degree of certainty to the interpretation of vaccination studies, above and beyond demonstrations of statistical significance. Although not definitive, this study provides useful supporting information for discussions of whether the recommendations for influenza vaccination should integrate population-level and individual-level approaches.

In the other study, Ohmit et al. directly compared the efficacies of the inactivated influenza vaccine and the live attenuated influenza vaccine.<sup>2</sup> Since an earlier large, multiyear, head-to-head

comparison<sup>3</sup> reported very similar efficacies for the inactivated and live attenuated vaccine formulations, the absence of additional studies has been an important gap. As the use of the live attenuated vaccine becomes more widespread, there is an increased need for such comparisons among specific age groups.

The randomized, double-blind, placebo-controlled trial by Ohmit et al. involved healthy adults, 18 to 46 years of age. Laboratory tests were used to confirm illness outcomes, but the study was underpowered for some comparisons. The fact that the type of laboratory test used to confirm symptomatic influenza (culture, polymerase chain reaction, or serologic determination) affected the cumulative incidence of influenza clearly underscores the potential of diagnostic methods to affect the results and interpretation of any influenza study. Several findings were reported, the most important of which was that the inactivated and live attenuated influenza vaccines appeared to have similar efficacies against culture-confirmed type A (H3N2) influenza infections (74%). The inactivated vaccine was superior to the live attenuated vaccine against culture-confirmed type B influenza infections — 80% (95% confidence interval [CI], 8 to 97) versus 40% (95% CI, -103 to 81) — which led to an overall higher efficacy of the inactivated vaccine against influenza A and B infections combined.

The degree to which these findings can be generalized is uncertain, because of the wide CIs for some analyses and because the relative performances of the vaccines may vary according to the age of the recipient, the preexisting levels of immunity, and the specific virus. However, the findings of Ohmit et al. and those of Edwards et al.<sup>3</sup> indicate that the two types of vaccines can confer similar protection against influenza A to healthy adults. Additional studies are needed to determine whether these vaccines are similarly efficacious in other age groups and to determine the relative efficacy of the live attenuated influenza vaccine against influenza B infections.

The annual development of influenza vaccines is an exemplary model of public-private cooperation. The World Health Organization (WHO) coordinates global influenza-virus surveillance so that appropriate vaccine candidates can be identified by the WHO and national authorities and vaccines can be reformulated each year. Vaccine viruses must be selected every year, since genetic mutations arise continuously in influenza

viruses — a process termed “drift” that results in the emergence of immunologically distinct variant viruses. Several regulatory and production steps to ensure safe, effective, and adequate vaccine supplies must then be completed before the vaccine is administered in time for each influenza season. The process is repeated each year, which imposes severe time restrictions on all groups involved.

Some have questioned whether the substantial effort to produce and deliver influenza vaccine is justified.<sup>4</sup> The answer is, unambiguously, yes. Indeed, the critical public health question is not whether influenza vaccines should be used, but how they can be used to advantage. Although year-to-year variations in efficacy and effectiveness are expected because of differences among viruses, target age groups, antigenic matches, and study methods, such variations do not fundamentally undermine the value of vaccination against influenza in responding to seasonal epidemics as well as potential influenza pandemics.

In line with these conclusions, the WHO recently convened international experts to help address issues related to preparedness for pandemic influenza and to develop a “global pandemic influenza action plan to increase vaccine supply.”<sup>5</sup> This plan is timely because of rising concerns about pandemic influenza. It emphasizes the fact that the increased use of influenza vaccine, the increased and more broadly distributed capacity to produce influenza vaccine, and accelerated research to develop better influenza vaccines are needed to address all forms of influenza.

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From the Global Influenza Programme, Department of Epidemic and Pandemic Response (K.F.), and the Initiative for Vaccine Research, Department of Immunization, Vaccines, and Biologicals (M.P.K.), World Health Organization, Geneva.

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