Influenza Vaccine for Healthy Working Adults

To the Editor: Dr Bridges and colleagues[1] found that provision of influenza vaccination to healthy working adults did not provide significant economic benefits. However, their findings should be applied to other settings with caution.

The trial was adequately sized and carefully executed. During year 1, however, there was a poor vaccine–circulating virus strain match. Vaccine efficacy was 50% ($P=.33$) against laboratory-confirmed influenza illness, but vaccine recipients otherwise tended to fare worse than placebo recipients. It is difficult to interpret these findings, given the impressive safety record of this vaccine and numerous studies demonstrating its clinical effectiveness. In year 2 there was a good vaccine–circulating virus match. Vaccine efficacy was 86%, and vaccination reduced clinical outcomes. However, net vaccination costs were $11.17 per person.

Two key parameters for the economic analysis in year 2 were rates of illness and time lost from work. The illness rate among unvaccinated persons in year 2 was 10%, a rate consistent with rates seen in other studies. However, the amount of time lost from work was low. Unvaccinated persons missed 72 workdays during 128 influenzalike illnesses (0.56 work-loss days per illness); vaccination reduced total work loss by only 4 days per 100 persons. Other US studies have estimated 2 to 3.5 work days lost per influenza illness.[2,3] Thus, vaccination should reduce work loss by 16 to 28 days per 100 persons (assuming an attack rate of 10% and vaccine efficacy of 80%). In a systematic review, vaccination was found to reduce work loss by 0.34 days per person (about 34 days per 100 persons).[4] If the work-loss rate observed among unvaccinated participants had been closer to the expected rate, Bridges et al likely would have found vaccination to be cost-effective and even cost-saving.

The low work-loss rates might be explained partly by the demographics of the study participants, who were predominantly highly paid males older than 40 years. Male sex and older age are associated with lower work-loss rates due to influenza. In 1996, women aged 18 to 44 years reported 76.9 work days lost per 100 from influenza while men aged 45 years and older reported 25.7 work days lost per 100.[5] Other studies suggest that increasing income and professional occupations may also be associated with lower work-loss rates.

What benefits should be expected with influenza vaccination of healthy working adults? The body of evidence strongly suggests that vaccination provides significant health benefits. The nature and magnitude of economic benefits for typical workers averaged over multiple seasons are less clear. A formal cost-benefit analysis that does not rely on the results of any single study would help to clarify this point. In the meantime, it is instructive to revisit a cost-effectiveness analysis from the 1980s.[6] Even though indirect costs were excluded, that study found that influenza vaccination might be highly cost-effective for adults younger than 65 years, with costs to society of $64 per year of healthy life gained for persons aged 25 to 44 years and $23 for persons aged 45 to 64 years (about $260 and $95 in 1999 dollars, respectively).[6] Vaccination may not need to be cost-saving to be cost-effective and therefore economically justifiable, even for healthy working adults.

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To the Editor: There have now been 3 randomized controlled trials investigating the effectiveness of influenza vaccine in preventing sick leave by healthy working adults.[1-3] Two trials[1,2] explicitly calculated the cost-effectiveness of vaccine provision but appear to give conflicting results. The relative newness of randomized cost-effectiveness trials is reflected in several unresolved methodological issues, which we believe to be the source of the disagreement.

A useful notion in determining the cost of sick leave is the lost-time threshold, T. If the cost of administering vaccine is $\$V$ per employee and the cost of 1 employee being absent is $\$D$ per day, then $T=V/D$ days. This is the average number of sick days per employee that the vaccination program must prevent to recoup the cost of immunization. For example, in the study by Dr Bridges and colleagues,[1] the cost of administering vaccine was

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$24.70 per person and the cost of a day's labor estimated at $235. Hence, approximately $T = 0.1$ day per employee per influenza season must be saved if the vaccine is to be cost-effective.

In each year of the study by Bridges et al, members of the placebo group took on average only 0.2 days sick leave per person-winter. Hence the vaccine would need to be more than 50% effective in preventing sick leave to be cost-effective. This is implausibly high for a nonspecific outcome, so the failure to achieve a cost benefit might have been expected. By comparison, the population studied by Nichol et al[2] had a placebo sick leave rate of 2.03 days per person in winter. The study by Wilde et al[3] of health professionals found an absentee rate similar to that among the Ford Motor Company workers studied by Bridges et al. However, the use of e-mail recruitment, together with the reported 75% of participants with household incomes greater than $70 000, suggest that the participants in the study by Bridges et al were not representative of the US working population.

Due to the variability in salary (and hence in T) and average rates of sick leave, vaccine cost-effectiveness should ideally be evaluated on an industry-specific basis. The study design should consider the baseline rate of sick leave and its seasonal variation, with sick leave related to influenzalike illness expected to occur principally in winter.

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1. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA*. 2000;284:1655-1663.
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To the Editor: Dr Bridges and colleagues[1] attempted to evaluate the economic costs and benefits of influenza vaccination among healthy workers in the United States using a sample of workers at a Ford Motors plant in Dearborn, Mich. It is not possible to conduct a cost-benefit analysis using the results of their study alone because the results of this study were not generalizable to the US population as a whole and because the sample size was too small to capture all relevant health events, such as hospitalizations or deaths. The authors' failure to include all relevant costs from representative data resulted in an inaccurate and incomplete tabulation of societal costs.

When a cost-benefit analysis (CBA) assumes the societal perspective, it estimates the economic cost or benefit of a medical intervention to society as a whole. A CBA tabulates the cost of the intervention minus the future savings produced by the intervention. If the benefits outweigh the costs (ie, if the value is less than $0), the intervention should be implemented; if the costs outweigh the benefits, it should not.

The societal perspective requires that all costs be expressed at their true social value and that all relevant costs be included. While it is acceptable to underestimate model inputs related to savings (or to exclude such inputs altogether) when the CBA outcome is less than $0, it is by no means acceptable to do so when the outcome value is greater than $0.

The analysis by Bridges et al should have included hospitalizations, deaths averted by vaccination, the time the patient spent receiving treatment, and the time provided by caregivers. In a violation of economic and epidemiologic principles, the hospitalization costs that they did include were based on a single hospitalization.

If they had included caregiver costs alone, which average $53.56 based on the average wage of Americans and 0.4 days of caregiving per person with influenzalike illness,[2] the analysis would have proven to be cost-beneficial over the 2 seasons studied, even though the vaccine was poorly matched to circulating viruses in 1 of those seasons. On the other hand, using estimates generated by Bridges et al, the average probability of hospitalization for healthy adults is approximately 20 per 100 000 persons and the cost of hospitalization is $7790.[3] Thus, the cost of hospitalization would be just $1.56 per person during the average influenza season. Until an externally valid analysis is conducted, the question of whether influenza vaccination is cost-beneficial among healthy adults will remain open.

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To the Editor: Dr Bridges and colleagues[1] found that providing influenza vaccination to healthy working adults did not result in overall economic savings. These results are timely in light of the recent recommendation by the Advisory Committee on Immunization Practices (ACIP) calling for vaccination of all adults aged 50 years and older.[2]

To date, however, no information is available on the economic impact or the improvement in vaccine coverage that could result when the vaccine is offered in the workplace to the entire population of adult workers, including those with chronic conditions such as heart disease, asthma, diabetes, or immunosuppression. Persons with these conditions are at higher risk of complications from influenza, and influenza vaccination programs that specifically include such high-risk individuals may provide substantial economic benefits. Thus, the findings in the study by Bridges et al should not be automatically generalized to entire workplace populations, which typically include persons with high-risk conditions.

In most years, influenza vaccine provides significant health benefits to those who receive it, supporting the ACIP's recommendation to add all persons aged 50 to 64 years to the target groups for annual influenza vaccination. The major reason the ACIP expanded the recommendation for annual influenza vaccination was to increase coverage among persons in this age group with high-risk medical conditions and their close contacts.[2] Of the 41 million persons aged 50 to 64 years in the United States, an estimated 10 to 13 million have high-risk conditions and another 7 to 9 million live with a person at high risk (Centers for Disease Control and Prevention, unpublished data, 2000). In 1997, only about 40% of adults aged 50 to 64 years with a high-risk condition were vaccinated.[2] The ACIP's new, broader, age-based strategy aims in part to increase this coverage. Workplace vaccination programs provide 1 opportunity to implement this strategy; other approaches should be explored, and additional information on all of these approaches would be useful.

As the study by Bridges et al shows, vaccination remains one of the safest, most effective ways to reduce influenza-related disease. While Bridges et al did not show cost savings from vaccinating healthy working adults, economic benefit is not the only criterion by which to judge the value of a preventive measure. As with many preventive measures, the reduction in morbidity and mortality is often judged to be worth the cost.

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In Reply: Dr Nichol and Drs Byrnes and Kelly correctly point out that persons in our study had considerably fewer total lost workdays due to influenzalike illness during the winter months than persons included in the inactivated influenza vaccine study by Nichol et al.[1] However, our results were similar to those found among health care worker placebo recipients in a study by Wilde et al[2] and in a multicenter randomized study of live attenuated influenza by Nichol et al.[3] Thus, results found in our study, which were consistent over 2 years, are unlikely to be an aberration. Furthermore, the number of lost workdays per illness in our study were very similar to that of Nichol et al[1] (0.56-0.84 days per illness vs 0.87 days per illness, respectively). The overriding difference between our study and that by Nichol et al was that the influenza-attributable illness rate was more than 3 times higher in the study by Nichol et al.

Dr Muennig correctly stated that when a CBA ". . . assumes the societal perspective, it estimates the economic cost or benefit . . . to society as a whole." However, a CBA does not have to model the entire society. The societal perspective can be used to examine a segment of society. Our sample size was more than adequate to measure the most relevant outcomes for healthy adults, work absenteeism, and outpatient visits. For young healthy adults, no excess rate of influenza-related deaths and very low excess rates of hospitalization, estimated at 13 to 25 per 100 000, have been reported.[4]

We agree that our results may not be generalizable to the entire US population. The number and value of lost workdays per illness can vary substantially by job category, industry, and locale.[1-3,5] Our sample had a household income notably higher than the national average. Lower salaries would reduce the cost of vaccination, but would also reduce the value of a workday and reduce the benefit of lower absenteeism.

Muennig criticizes nonreporting of caregiver costs. Although participants were asked about these costs in bimonthly surveys, very few such costs were reported in study year 1; thus, caregiver costs were not analyzed in study year 2 and were not reported. Retrospectively, we have analyzed the 1998 through 1999 study year caregiver costs and found 0.086 caregiver days per illness in the placebo group and 0.012 days in the vaccine group. However, inclusion of this cost does not alter the fact that vaccination resulted in a net societal cost. Neither Nichol et al[1] nor Wilde et al[2] reported caregiver costs, so a comparison is not available in a healthy working US population.

We disagree with Muennig's statement that only interventions with net savings should be implemented. Cost benefit is only 1 of many factors to consider when developing health programs. In our study, as in many others, influenza vaccination had substantial health benefits.[1-3,5] Healthy adults may choose to be vaccinated to avoid the inconvenience and discomfort associated with influenza illness and to prevent transmission of influenza to high-risk persons whom they care for or live with, and employers may choose to offer work-sponsored vaccination programs as a relatively inexpensive health benefit and as a means to improve vaccination of high-risk workers. However, influenza vaccination programs targeting healthy adults should not be implemented solely with the expectation of yearly cost savings.

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RESEARCH LETTERS

Bogus Participation in Clinical Trials

To the Editor: Increased commercialization and competition in clinical research has led to difficulties in enrolling human subjects in a timely manner to satisfy sponsors.[1] As a result, clinical trials increasingly recruit participants outside the traditional clinic- or hospital-based settings. Investigators often advertise via radio or newspapers and promise payment for participation. These new approaches have the potential to recruit large numbers of participants to central locations and to allow faster subject accrual.

Methods. Family Health International has begun to use recent technological advances, such as interactive voice response systems (IRVSs) and the Internet, to explore the impact on data quality of more commercialized methods of recruiting subjects for clinical research. We initiated a randomized controlled trial of 2 approved barrier methods to further characterize their contraceptive effectiveness. Subjects were offered $150 for participating in the trial. To increase speed of recruitment, we advertised in 5 metropolitan newspapers and enrolled participants by telephone. The initial telephone call lasted about 30 minutes. Once patients were enrolled and randomized, we sent the study materials to the home addresses of the participants. During this 1-month study, participants were asked to call a toll-free IVRS daily and answer a few questions using the keypad of their telephone. We monitored these daily calls to evaluate participant compliance with the protocol and potential bogus participation.

Results. Of the first 25 participants randomized into the trial, our monitoring system identified 4 participants who consistently placed their IVRS calls from the same telephone number, usually only minutes apart. When our staff attempted to contact these 4 participants, they failed to respond and stopped participating in the trial. A fifth participant placed a single telephone call from the number used by the above-mentioned participants. Through an Internet search of an address database, we discovered that 2 additional participants had provided suspicious home addresses. These 2 participants ceased participating in the trial when our staff tried to contact them. A eighth participant provided an invalid address, and the study material was returned. Thus, 8 of 25 participants (32%; 95% confidence interval, 15%-54%) provided information that led to their exclusion from the trial.

Comment. Our small study detected big problems. We were forced to terminate the trial because of the unacceptably high exclusion rate. We caution researchers who embark on studies with remuneration of participants and no face-to-face contact that bogus participation may threaten data validity. We suspect that many trials, even those in which face-to-face contact does occur, enroll participants who knowingly provide invalid data. For example, we recently excluded a participant in a trial requiring exclusive use of male condoms because the site investigator discovered that the participant had been receiving prescriptions for oral contraceptives during the trial. While increasing attention is being placed on improving the quality of trials by reducing investigator fraud[2,3] and improving methodology,[4,5] bogus participation also needs to be scrutinized for its potential threat to the validity of clinical trials.

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Exercise-Induced Oxygen Desaturation as a Late Complication of Meningococcal Septic Shock Syndrome

To the Editor: Children who survive meningococcal septic shock syndrome (MSSS) may have long-term lung damage secondary to mechanical ventilation or to the disease itself. We studied the long-term pulmonary sequelae of MSSS and their relationship with several clinical variables during the acute phase of the disease.

Methods. We measured lung function parameters (forced expiratory volume in 1 second, forced vital capacity, total lung capacity, residual volume, and diffusing capacity of carbon monoxide) and transcutaneous arterial oxygen saturation (SaO_2) during maximal exercise in 18 children an average of 3.4 years (range, 2.2-4.9 years) after receiving mechanical ventilation for MSSS. Median age at the acute phase of disease was 4.7 years (range, 1.6-15.4 years).

Results. At follow-up, all children had normal lung function parameters and SaO_2 values at rest. During maximal exercise, the median decrease in SaO_2 was 2.5% (range, 0%-20%). In 6 children (desaturation group), SaO_2 dropped below 95% (median decrease from resting value, 12.5%; range 5%-20%).

None of the ventilatory parameters during the first 24 hours of the acute illness were associated with exercise-induced desaturation using repeated measures analysis of variance. However, children in the desaturation group had consistently lower peripheral temperatures during the first 24 hours of the acute illness, with a mean 3.3°C (95% confidence interval [CI], 1.4°C-5.2°C) lower peripheral temperature, which remained constant over time (ie, there was no group by time interaction). There were no statistical differences in central temperature.

We also compared groups on results of prior blood gas analyses (pH, partial pressure of carbon dioxide, partial pressure of oxygen, base excess, and bicarbonate level), hematological parameters (hemoglobin, leukocyte count, and platelet count) and the overall Pediatric Risk of Mortality (PRISM) score[1] on day 1 and day 2 of the original hospitalization. All hematological variables were obtained prior to any transfusion. We also compared the groups on a number of metabolic variables (fluid balance and blood urea nitrogen, creatinine, sodium, potassium, glucose, calcium, albumin, C-reactive protein, and lactic acid levels) on day 2 only, after the patients had been stabilized. We used the most abnormal value for each variable on each day and compared the groups by using 2-sided Mann-Whitney U tests.

The desaturation group had higher PRISM scores (16.5 vs 10; $P = .03$) and lower platelet counts (49.5×10^9 vs 143.5×10^9; $P = .008$) on day 1, although differences in these variables were not significant on day 2. The desaturation group had higher C-reactive protein levels (265 mg/L vs 148 mg/L; $P = .04$) and fluid balance (97.0 mL/kg vs 8.1 mL/kg; $P = .01$) on day 2.

Comment. We found a high incidence (33%) of long-term exercise-induced deoxygenation in children who survived MSSS. None of the initial ventilatory parameters were related to this outcome, although other studies have shown that mechanical ventilation can be associated with long-term lung dysfunction.[2] Perhaps this can be explained by the current use of lung-protective ventilator strategies.[3]

Children in the desaturation group had significantly higher PRISM scores during the initial phase of their illness, suggesting that exercise-induced desaturation is related to the initial severity of meningococcal disease.[4] Although other clinical parameters in the acute phase were significantly related to outcome, these results should be interpreted with caution in light of the large number of statistical comparisons and small sample size.

Circulatory failure and disseminated intravascular coagulation are the predominant clinical features of MSSS and lead to formation of microthrombi in all organs, which eventually may lead to necrosis of the skin extremities.[5] Furthermore, several reports have described skeletal lesions consistent with osteonecrosis,[6] which may manifest as growth abnormality months or years after the acute disease. It is possible that similar vasculitis and microthrombi in peripheral lung arterioles and venules during the acute phase and subsequent pulmonary vascular remodeling may result in long-term desaturation during maximal exercise.

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It does not require many words to speak the truth.
—Chief Joseph (1840-1904)