Strengthening the Nation's Influenza Vaccination System

A National Vaccine Advisory Committee Assessment

Charles M. Helms, MD, PhD, Fernando A. Guerra, MD, MPH, Jerome O. Klein, MD, William Schaffner, MD, Ann M. Arvin, MD, Georges Peter, MD

Introduction

Each year more Americans are vaccinated for influenza than for any other disease. Although vaccine shortages and delays have garnered much attention during the past several years, it is important to highlight the success of the program: Millions of people are vaccinated in a short time period each year; good collaboration exists between the public and private sectors, which have documented an ability to respond appropriately to vaccine supply problems and other events; and healthcare providers and the public have acted responsibly in targeting vaccines to those who need it most at times of shortage. Nevertheless, one cannot underestimate the importance and impacts of vaccine supply shortage, particularly that occurring for the 2004–2005 season. A sufficient and predictable vaccine supply is critical for a successful prevention effort.

Several interventions have been implemented to reduce the risk of disruptions to the future supply of vaccine, to strengthen influenza vaccine security, and to foster preparedness for an influenza pandemic. In 2004, the Acting Assistant Secretary for Health, Department of Health and Human Services (DHHS) requested that the National Vaccine Advisory Committee (NVAC) evaluate strategies and capabilities to improve influenza prevention efforts in the United States. An NVAC Influenza Vaccine Working Group evaluated both published and unpublished data and held discussions with stakeholders—including industry, public health officials, providers, purchasers, and consumers—to develop a set of recommendations. Based on the findings, the Working Group developed several recommendations that can be used to improve influenza prevention efforts in the United States. This report summarizes those recommendations.

Background

The Centers for Disease Control and Prevention (CDC) and its Advisory Committee on Immunization Practices (ACIP) recommend annual influenza vaccinations for people at increased risk of severe influenza infection, their close contacts, and all healthcare workers.[1] Influenza vaccination uptake increased dramatically through the 1990s. However, since the late 1990s, of the 185 million people for whom the vaccination is recommended, only about 80 million are vaccinated in a typical influenza season.[1] Vaccination coverage falls far short of the goals established by the DHHS in the *Healthy People 2010* (*HP 2010*) objectives,[2] which include influenza vaccine coverage of 90% among adults aged ≥65 years, children between 6 and 23 months, and those in long-term institutional care or nursing homes; and 60% coverage in noninstitutionalized adults who are aged <65 years and have medical conditions that place them at increased risk of mortality and serious morbidity.[1] Although influenza vaccine supply disruptions have affected the amount or timeliness of vaccine availability in recent years, even when vaccine supply is adequate there is no evidence of a trend toward higher vaccine coverage.[3] This suggests that in the absence of substantial systematic changes, *HP 2010* coverage goals will not be met.

One question that must be asked: Will meeting influenza vaccine coverage goals lead to the substantial reduction in influenza disease and death, as has been seen with the pediatric vaccination program? For every routinely recommended childhood vaccine, when coverage rates have exceeded 90%, reductions in disease have been for similar or greater magnitude.[4] By contrast, the impact of increased influenza vaccination coverage under current recommendations is likely to be of a lesser magnitude. The effectiveness of inactivated influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. Influenza vaccines

From the National Vaccine Advisory Committee, Department of Health and Human Services, Washington DC

Address reprint requests to: Bruce G. Gellin, MD, MPH, Director, National Vaccine Program Office, Department of Health and Human Services, 200 Independence Avenue, SW, Room 725H, Washington DC 20201-0004

Address correspondence to: Charles M. Helms, MD, PhD, Professor of Medicine, Chief of Staff, University of Iowa Hospital and Clinics, 200 Hawkins Drive, C512 GH, Iowa City IA 52242. E-mail: charles-helms@uiowa.edu.

0749-3797/05/$–see front matter
doi:10.1016/j.amepre.2005.05.011

must be changed annually to match the strains that are predicted to circulate in the population during the influenza season. In most years the match is good, but occasionally the vaccine does not match the circulating strain, and vaccine effectiveness is diminished, as occurred during the 2003–2004 season.[5,6]

When the match is good, influenza vaccine prevents influenza illness among approximately 70% to 90% of healthy adults aged <65.[7–12] Vaccination of healthy adults has resulted in decreased work absenteeism, and decreased use of healthcare resources, including the use of fewer antibiotics.[10,11] Older people and those with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza.[13–15] Among adults aged ≥65 not living in nursing homes or chronic-care facilities, influenza vaccine is 30% to 70% effective in preventing hospitalization for pneumonia and influenza diagnoses.[16,17] Among older nursing home residents aged ≥65, influenza vaccine can be 50% to 60% effective in preventing hospitalization or pneumonia, and 80% effective in preventing death, although the effectiveness in preventing uncomplicated influenza illness often ranges from only 30% to 40%.[18,19]

In spite of numerous studies demonstrating effectiveness in small settings, national trend data raise questions regarding the overall impact in reducing mortality of the influenza vaccination program under current recommendations. During the past several decades, as annual influenza vaccine use increased from about 20 million doses in the 1980s to the current total of about 80 million doses per year, there has not been a commensurate decrease in influenza mortality.[20] Even when controlling for the aging of the U.S. population, expected program impacts have not been observed. In addition, the risk of mismatch between vaccine and circulating strains and the suboptimal vaccine effectiveness, particularly in high-risk populations, suggest that research is needed to develop better influenza vaccines that can provide improved prevention.

The fragility of the U.S. influenza vaccine supply threatens the ability to implement an effective vaccination program, increase coverage, and prevent disease. Rates and severity of influenza disease vary annually, affecting demand for vaccine by both the public and providers. Against this backdrop, production issues in recent years have led to delays, spot shortages, and the substantial shortfall experienced for the 2004–2005 influenza season. Yet, in other years, there has been substantial excess vaccine, and millions of vaccine doses have not been administered.[21] Even in 2003–2004, when the combination of early widespread influenza outbreaks coupled with the reports of influenza-related deaths in children led to increased demand for inactivated influenza vaccine, several million doses of a newly licensed and more expensive live, attenuated influenza vaccine (FluMist®) went unused. Because vaccine supply and investments in the development of new technologies are related to the size and predictability of the market and vaccine price, there is an intrinsic relationship between vaccine recommendations and program implementation and vaccine supply and research. Thus, although the NVAC Working Group recommendations do not focus directly on vaccine supply, their implementation would have a major and positive impact on vaccine supply, uptake, and investments in new vaccines and technologies.

Process

At the request of Cristina Beato, MD, the Acting Assistant Secretary for Health, NVAC established a working group to evaluate strategies to reduce the impact of influenza disease in the United States and to make recommendations on how to substantially improve the prevention of influenza and reduce disease burden. The working group was encouraged to ask challenging questions and consider new strategies, paradigms, infrastructures, and technologies as well as incremental changes that could be made to the current system. In February 2004, the NVAC Influenza Working Group was appointed, chaired by Charles Helms, MD, current NVAC chair. The Working Group was divided into the following three subgroups to focus on separate key issues:

The Influenza Vaccine Delivery, Financing, and Demand Subgroup was chaired by Fernando Guerra, MD. This subgroup examined private and public delivery systems, communications issues, and vaccine demand.

The Influenza Vaccine Recommendations and Strategies Subgroup was chaired by Jerome Klein, MD. This subgroup studied issues related to the measurement of the burden of disease, the impact of the vaccination program, and vaccine efficacy; and consideration of alternative vaccine recommendations.

The Influenza Vaccine Research, Development, and Production Subgroup was chaired by Ann Arvin, MD. This subgroup assessed the influenza vaccine research and development enterprise in the public and private sectors.

During the spring of 2004, the subgroups reviewed published and unpublished data, consulted with DHHS agencies and their advisory committees, influenza vaccine manufacturers, clinicians, professional and advocacy associations, researchers, vaccine distributors, and healthcare providers to thoroughly review the program. Based on these investigations, the subgroups developed key findings and recommendations that were presented and discussed at the NVAC meetings in June and October 2004. This report was developed following those discussions and

was approved by the Committee for presentation to the Acting Assistant Secretary for Health in December 2004.

Recommendations and Rationales

Vaccine Financing and Demand

1. Improve vaccination coverage among recommended groups by facilitating the delivery of influenza vaccines in a range of settings, especially in "medical homes," other medical sites, workplaces, and community sites where people have not previously had access to vaccination.

Rationale: Several barriers exist to achieving high rates of influenza vaccine coverage among recommended groups through vaccination at primary care provider offices.[22,23] While children commonly make routine age-based well-child visits, most adults seek health care only in the context of an acute or chronic illness. In this setting, time to focus on the delivery of preventive services such as vaccination is unlikely. Many women receive their primary care from gynecologists, and some adults with chronic illness receive primary care from subspecialists, both of whom may be less likely to deliver vaccinations.[24,25] Financial barriers may also decrease the likelihood that vaccination will be provided by primary care physicians.[22]

To increase influenza vaccine coverage rates, effective strategies must be implemented to increase vaccination at sites where adults receive health care or where preventive services could be delivered.[26,27] Every contact with the healthcare system should be used as an opportunity to vaccinate.[28] Emergency departments, which are increasingly being used as sources of care by the poor and underinsured, may be cost-effective sites for delivering preventive services such as vaccination and preventing future hospitalization among the most medically and socially vulnerable.[29,30] A strategy of routinely offering influenza vaccination to emergency room patients between September and December (and later if the vaccine supply allows) could markedly decrease missed opportunities for vaccination (CDC, unpublished data).

Provision of vaccination at places not used for health care, such as work sites, grocery stores, pharmacies, shopping malls, detention centers, and other places where people can conveniently be reached during the months before influenza season has been shown to increase vaccination coverage among groups who do not usually receive influenza vaccination.[31] Increasing vaccination at these sites requires overcoming barriers that may include limits on who can administer vaccinations and the need for a physician's order before vaccination. The use of "standing orders" avoids the need for individual physician's orders and has been effective in increasing vaccination at sites outside of provider offices.[32,33] The development of toolkits that include model standing orders and other materials to facilitate vaccination at alternate sites, active distribution of these materials and promotion of program goals, and active follow-up are all needed for effective implementation. Resources to coordinate these programs should be made available to state and local immunization programs.

2. Make influenza vaccine purchase less of a burden and financial risk for providers.

Rationale: Studies have shown that providers have concerns regarding the costs of purchasing and administering influenza vaccine and their level of reimbursement. Health plan payment rates may not adequately compensate for these costs, and, for many providers, influenza vaccination is a financial loss. When all costs for influenza vaccine, its administration, office staff time, and practice overhead are compared with average 2003 Medicare immunization reimbursement payments of $17.76, one study indicated that providers' per-shot losses ranged from $3.36 to $32.76.[34] A recent Centers for Medicare and Medicaid Services (CMS) decision to increase reimbursement for influenza vaccine administration from an average of $8 to $18 will significantly improve the financial balance for office-based vaccination; however, in some settings, the balance will still remain negative. In addition, providers must order and purchase vaccine months before it is administered resulting in a substantial capital outlay. Finally, manufacturers have adopted a "no return" policy for influenza vaccine; thus, providers are wary about potentially ordering excess vaccine and receiving no reimbursement for unused product. Given these factors, there has been little incentive for healthcare providers to increase coverage rates for influenza vaccination within a practice. Because private insurers generally have followed the lead of Medicare in reimbursement policy, the recent policy change by CMS to increase influenza vaccination coverage may increase the use of influenza vaccination by providers nationwide. Further consideration with CMS of financial issues for providers may be an efficient and effective approach to the identification of additional solutions.

3. Explore options for supporting a comprehensive vaccination program for adults.

Rationale: Financial barriers limit health care providers' willingness and ability to increase influenza vaccination among adults. Costs also may limit the willingness of people in recommended groups to be vaccinated in the absence of health insurance or when reimbursement does not cover all costs. Studies have shown a 10% to 30% increment in coverage when vaccine is provided without charge to patients.[35–38] In Ontario, Canada, the combination of free vaccine and a universal recommendation has resulted in 77% coverage among the elderly (about 10% higher than in the

United States), and 42% coverage in the entire population of the province.

Cost may be a substantial barrier, particularly among those who are poor, uninsured, or disabled. In 2000, only two state Medicaid programs met the standards for a comprehensive adult immunization policy, which includes covering ACIP recommended vaccines, permitting only a nominal co-pay, providing vaccine replacement, and allowing separate billing for vaccine administration. One option to improve this would be to establish a comprehensive program nationwide, focusing on the poor and uninsured, analogous to the Vaccines for Children program; other approaches may also be envisioned. A systematic evaluation of options that include discussion with stakeholder groups could provide information to DHHS that can lead to policy decisions.

4. Increase the rate of annual influenza vaccination among healthcare workers.

Rationale: Despite longstanding recommendations for vaccination of healthcare workers (HCWs), many still do not get vaccinated. Vaccination of HCWs has been shown to prevent mortality in their patients,[39] as well as to reduce influenza infection and absenteeism in the HCWs[7] themselves; it may result in financial savings to the sponsoring healthcare institutions.[7] Despite this, only 38% of HCWs received influenza vaccine the previous year, according to the 2002 National Health Interview Survey.[1] Federal advisory committees including the ACIP and NVAC have highlighted the need to improve vaccine uptake in this recommended group. As is the case for the general public, making receipt of influenza vaccine convenient and eliminating costs to HCWs are effective interventions, particularly when combined with comprehensive programs to increase influenza vaccination coverage. Reducing barriers to vaccination may be particularly important in settings such as nursing homes where many HCWs' salaries are low, and where residents are at highest risk for severe and fatal influenza. As professional organizations and advisory committees emphasize the importance of recommendations for HCW vaccination, and healthcare organizations implement programs to improve influenza vaccination coverage, identifying successful strategies, promoting large-scale organizational change, and monitoring coverage are all important.

Influenza Burden and Program Impacts

5. Develop a working group to consider critical issues and barriers to expanded influenza vaccination recommendations and to propose solutions.

Rationale: The current burden of influenza-related deaths and hospitalizations, despite increased vaccine coverage over the past decades, raises questions about program effectiveness and impact. This has led to an evaluation of influenza-prevention strategies including the possible need to expand vaccination recommendations. Expanded vaccination recommendations that include school-aged children, for example, might enhance protection of older adults and those at high risk of serious illness by decreasing transmission of disease within families and communities. In addition, vaccine recommendations based on age groups may be more effectively implemented than current recommendations to vaccinate only people aged 2 to 49 years with high-risk medical conditions.

United States vaccination recommendations are made by the CDC, based on advice from the ACIP. In February 2004, the ACIP Influenza Working Group began evaluation of a possible expansion of influenza vaccination recommendations. Expanding vaccination recommendations raises important issues, including the capability of our immunization system to implement a broader program and achieve high vaccination coverage, the capability of our vaccine supply system to reliably produce the doses necessary, and the nation's ability to finance vaccination and achieve equitable implementation among the economically disadvantaged. The NVAC will continue to work closely with the ACIP as expanded influenza vaccination recommendations are considered.

Vaccine supply can be a critical barrier to expanding influenza vaccination recommendations. Current production capacity is insufficient to support a substantial increase in vaccine use. Continued efforts are needed to promote an expanded production capacity and the diversification of supply across more manufacturers and technologies to support increased annual vaccination under current or expanded recommendations.

The ability to effectively deliver vaccine under expanded vaccination recommendations also is important. One likely target for vaccination will be school-aged children, yet this population is not targeted by current vaccine recommendations, and the ability to achieve high coverage in this group has not been documented, especially in a sustained annual program. Strategies for the vaccination of school-aged children and adolescents need to be defined and evaluated, both because of their importance for the implementation of expanded influenza vaccination recommendations and because many of the vaccines currently being developed will also focus on this population. Given that traditional vaccination delivery using needle and syringe may be unwieldy and unpopular in school-aged populations, new delivery systems such as nasal spray or a transcutaneous patch should be assessed. The experience gained during the introduction of the live, attenuated influenza vaccine (FluMist®) in the U.S. market in the 2003–2004 season and the lessons from the launch of this product should be examined.

6. Implement systems to better understand the burden of influenza illness in the United States and to

better assess program impacts and vaccine effectiveness.

Rationale: Annual influenza vaccine use in the United States has increased from about 10 million doses in 1976, at the time of the swine influenza scare, to about 80 million doses in recent years. Despite this increase, influenza is estimated to cause an average of 36,000 deaths and >200,000 hospitalizations each year.[40,41] Ecologic or trend studies have suggested that increased vaccination coverage has not been accompanied by similar increases in preventing death, even when controlling for the aging of the U.S. population. By contrast, epidemiologic studies using other methods to evaluate the impact of vaccine have shown significant effectiveness for disease and death outcomes.[42] Reconciling the differences in study results is important in considering possible new influenza vaccine recommendations and whether alternative vaccination strategies are needed.

The conflicting results of epidemiologic studies and the need to estimate influenza-related hospitalization and death by modeling also highlight the current inability to directly assess influenza disease burden and measure the impacts of the vaccination program. Efforts to characterize the impacts of the vaccination program on influenza are hampered by several factors: annual variations in influenza outbreaks, which make it difficult to track disease trends, the absence of a unique clinical influenza syndrome and lack of an etiologic diagnosis in most persons with febrile or respiratory illness, and the contribution of influenza in exacerbating nonrespiratory illnesses such as acute myocardial infarction or congestive heart failure. While influenza surveillance systems in the United States have been developed to monitor annual spread, causative strains, and the location and timing of an outbreak, directly assessing disease burden, program impacts, and annual vaccine effectiveness have not been primary objectives.

New sentinel surveillance systems should be implemented to help fill this gap. One approach is to measure hospitalizations from influenza disease directly in facilities where etiologic diagnosis is enhanced, and to link these data with vaccination rates among patients and in the surrounding community. A pilot program using this approach in children has been implemented in three metropolitan areas. Surveillance of pediatric populations is particularly important as new recommendations for universal vaccination of children aged 6 to 23 months were adopted in 2004, and further expansions of the vaccination program are being considered. Strategies to directly assess influenza disease and program impacts also should be implemented among adults. The CDC recently has begun a project to assess vaccine effectiveness during the influenza season based on rapid analysis of an administrative managed-care database.

Research

7. Conduct a comprehensive review of the influenza research program to identify gaps and areas for additional support.

Rationale: Scientific research leads to the development of tools that make effective disease prevention possible. New diagnostic tests using molecular approaches can improve surveillance and assessment of program impacts. Genomic analysis of influenza strains identified globally and studies of how disease spreads from animals to humans and between human populations can provide critical information that will improve the ability to predict which strains will emerge and should therefore be included in the vaccine. This expanding database of genomic information should be made available to the research community.

An improved understanding of the immune mechanisms of protection against influenza, immune response in young infants, and changes in immunity that occur with aging can lead to the development of better prevention strategies in vulnerable populations. Improved methods to develop vaccine reference strains and process development improvements can increase the speed and volume of vaccine production. The development of new vaccine delivery systems can increase the safe mass delivery of influenza vaccine. Research on new influenza vaccines may lead to vaccines that accelerate the immune response to the first dose, which is important during a rapidly moving epidemic. Research to improve vaccine immunogenicity may yield ways to provide better protection in elderly and high-risk populations or provide more long-lasting protection so that annual vaccine would no longer be needed.

Concluding Remarks

A wide range of influenza disease- and prevention-related research is being supported and conducted by multiple agencies in the public and private sectors. An influenza research program review that describes ongoing activities, defines key objectives, and also identifies gaps in the research portfolio is an important first step in strengthening the program and providing the techniques and tools that will improve the ability to prevent the most common and most deadly of all vaccine-preventable diseases in the United States.

We are grateful to Bruce Gellin, MD, MPH, Sarah Landry, Ben Schwartz, MD, Ray Strikas, MD, Dan Fishbein, MD, Jeff Davis, and Jon Abramson, MD, for their help in writing this paper.

We would also like to acknowledge the current members of NVAC: Gary Freed, MD, MPH, Alan Hinman, MD, David Johnson, MD, MPH, Ruth Katz, JD, MPH, Mary Beth Koslap-Petraco, MS, CPNP, Richard Raymond, MD, Patricia Whitley-

Williams, MD, and Adele Young, PhD. The agency liaison representatives to NVAC are Steven Black, MD, Gary Overturf, MD, and Myron Levin, MD.

No financial conflict of interest was reported by the authors of this paper.

References

1. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2004;53:1–40.
2. U.S. Department of Health and Human Services. Healthy People 2010. 2nd ed. Washington DC: U.S. Government Printing Office 2000.
3. Pleis JR, Gentleman JF. Using the National Health Interview Survey: time trends in influenza vaccinations among targeted adults. Eff Clin Pract 2002;5:E3.
4. Centers for Disease Control and Prevention. Achievements in public health, 1900–1999 impact of vaccines universally recommended for children—United States, 1990–1998. MMWR Morb Mortal Wkly Rep 1999;48:243–8.
5. Centers for Disease Control and Prevention. Assessment of the effectiveness of the 2003–04 influenza vaccine among children and adults—Colorado, 2003. MMWR Morb Mortal Wkly Rep 2004;53:707–10.
6. Centers for Disease Control and Prevention. Preliminary assessment of the effectiveness of the 2003–04 inactivated influenza vaccine—Colorado, December 2003. MMWR Morb Mortal Wkly Rep 2004;53:8–11.
7. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA 1999;281:908–13.
8. Fleming DM, Watson JM, Nicholas S, Smith GE, Swan AV. Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989–90 using a general practice database. Epidemiol Infect 1995;115:581–9.
9. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy, working-age population. J Occup Environ Med 1997;39:408–14.
10. 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;284:1655–63.
11. Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2004;CD001269.
12. Smith JW, Pollard R. Vaccination against influenza: a five-year study in the Post Office. J Hyg (Lond) 1979;83:157–70.
13. Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. Clin Infect Dis 1996;22:295–302.
14. Dorrell L, Hassan I, Marshall S, Chakraverty P, Ong E. Clinical and serological responses to an inactivated influenza vaccine in adults with HIV infection, diabetes, obstructive airways disease, elderly adults and healthy volunteers. Int J STD AIDS 1997;8:776–9.
15. McElhaney JE, Beattie BL, Devine R, Grynoch R, Toth EL, Bleackley RC. Age-related decline in interleukin 2 production in response to influenza vaccine. J Am Geriatr Soc 1990;38:652–8.
16. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998;158:1769–76.
17. Gaglani M, Riggs M, Kamenicky C, Glezen WP. A computerized reminder strategy is effective for annual influenza immunization of children with asthma or reactive airway disease. Pediatr Infect Dis J 2001;20:1155–60.
18. Patriarca PA, Weber JA, Parker RA, et al. Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. JAMA 1985;253:1136–9.
19. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol 2001;154:155–60.
20. Simonsen L, Reichert TA, Blackwelder WC, Miller MA. Benefits of influenza vaccination on influenza-related mortality among elderly in the US: an unexpected finding. In: Options for the control of influenza V. New York: Elsevier Science, 2004:163–7.
21. Fukuda K, O'Mara D, Singleton JA. How the delayed distribution of influenza vaccine created shortages in 2000 and 2001. Proc Annu Symp Comput Appl Med Care 2002;27:235–42.
22. Weingarten S, Riedinger M, Bolton LB, Miles P, Ault M. Barriers to influenza vaccine acceptance. A survey of physicians and nurses. Am J Infect Control 1989;17:202–7.
23. Zimmerman RK, Silverman M, Janosky JE, et al. A comprehensive investigation of barriers to adult immunization: a methods paper. J Fam Pract 2001;50:703.
24. Silverman NS, Greif A. Influenza vaccination during pregnancy. Patients' and physicians' attitudes. J Reprod Med 2001;46:989–94.
25. Nichol KL, Zimmerman R. Generalist and subspecialist physicians' knowledge, attitudes, and practices regarding influenza and pneumococcal vaccinations for elderly and other high-risk patients: a nationwide survey. Arch Intern Med 2001;161:2702–8.
26. Grabenstein JD, Hartzema AG, Guess HA, Johnston WP, Rittenhouse BE. Community pharmacists as immunization advocates. Cost-effectiveness of a cue to influenza vaccination. Med Care 1992;30:503–13.
27. Slobodkin D, Kitlas J, Zielske P. Opportunities not missed—systematic influenza and pneumococcal immunization in a public inner-city emergency department. Vaccine 1998;16:1795–1802.
28. Centers for Disease Control and Prevention. Missed opportunities for pneumococcal and influenza vaccination of Medicare pneumonia inpatients—12 western states, 1995. MMWR Morb Mortal Wkly Rep 1997;46:919–23.
29. Babcock IC, Wyer PC, Gerson LW. Preventive care in the emergency department. Part II: Clinical preventive services—an emergency medicine evidence-based review. Society for Academic Emergency Medicine Public Health and Education Task Force Preventive Services Work Group. Acad Emerg Med 2000;7:1042–54.
30. Husain S, Slobodkin D, Weinstein RA. Pneumococcal vaccination: analysis of opportunities in an inner-city hospital. Arch Intern Med 2002;162:1961–5.
31. Grabenstein JD, Guess HA, Hartzema AG, Koch GG, Konrad TR. Effect of vaccination by community pharmacists among adult prescription recipients. Med Care 2001;39:340–8.
32. Lawson F, Baker V, Au D, McElhaney JE. Standing orders for influenza vaccination increased vaccination rates in inpatient settings compared with community rates. J Gerontol 2000;55A:M522–6.
33. Centers for Disease Control and Prevention. Facilitating influenza and pneumococcal vaccination through standing orders programs. MMWR Morb Mortal Wkly Rep 2003;52:68–9.
34. Coleman M, Fontanesi J, Meltzer MI, et al. Estimating medical practice expenses from administering adult influenza vaccinations. Vaccine 2005;23:915–23.
35. Nexoe J, Kragstrup J, Ronne T. Impact of postal invitations and user fee on influenza vaccination rates among the elderly. A randomized controlled trial in general practice. Scand J Prim Health Care 1997;15:109–12.
36. Etkind P, Simon M, Shannon S, et al. The impact of the Medicare Influenza Demonstration Project on influenza vaccination in a county in Massachusetts, 1988–1992. J Community Health 1996;21:199–209.
37. Moran WP, Nelson K, Wofford JL, Velez R. Computer-generated mailed reminders for influenza immunization: a clinical trial. J Gen Intern Med 1992;7:535–7.
38. Satterthwaite P. A randomised intervention study to examine the effect on immunisation coverage of making influenza vaccine available at no cost. Impact of postal invitations and user fee on influenza vaccination rates among the elderly. A randomized controlled trial in general practice. N Z Med J 1997;110:58–60.
39. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of healthcare workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 2000;355:93–7.
40. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86.
41. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333–40.
42. Mangtani P, Cutts F, Hall AJ. Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence. Lancet Infect Dis 2003;3:71–8.