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Recommendations of the Immunization Practices Advisory Committee Prevention and Control of Influenza

These recommendations update information on the vaccine and antiviral agent available for the control of influenza for the 1987-88 influenza season. They supersede the recommendations published in May 1986 (MMWR 1986;35:317-26,331). Changes include: 1) Updating the influenza strains in the trivalent vaccine for 1987-88, 2) extending the recommendation for vaccination of persons in households with a high-risk person, and 3) revising precautions for use of amantadine hydrochloride.

INTRODUCTION

Influenza A viruses are classified into subtypes on the basis of two antigens: hemagglutinin (H) and neuraminidase (N). Three subtypes of hemagglutinin (H1, H2, H3) and two subtypes of neuraminidase (N1, N2) have caused widespread human disease. Immunity to these antigens, especially hemagglutinin, reduces the likelihood of infection and the severity of disease if infection does occur. However, there may be sufficient antigenic variation (antigenic drift) within the same subtype over time so that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Although influenza B viruses have shown more antigenic stability than influenza A viruses, antigenic variation does occur. Therefore, major epidemics of respiratory disease caused by new variants of influenza continue to occur, and the antigenic characteristics of current strains provide the basis for selecting the virus strains included in each year's vaccine.

Typical influenza illness is characterized by abrupt onset of fever, sore throat, and nonproductive cough. Unlike many other common respiratory infections, it can cause extreme malaise lasting several days. More severe disease can result if influenza virus invades the lungs (primary viral pneumonia) or if secondary bacterial pneumonia occurs. High attack rates of acute illness and lower respiratory tract complications usually result in dramatic increases in the number of persons visiting physicians' offices, walk-in clinics, and emergency rooms.

Persons who are poorly able to cope with the disease because of their age or underlying health problems are at high risk for complications from influenza. These persons are more likely than the general population to require hospitalization. One recent study showed that, during major epidemics, hospitalization rates for adults with high-risk medical conditions increased among different age groups by about twofold to fivefold. During influenza epidemics, healthy children and adults may also require hospitalization for influenza-related complications, but the relative increase in hospitalization rates is much less than the increase for high-risk groups.

The significant increase in mortality that often occurs during influenza epidemics is a further indication of their impact. Such excess mortality is a direct result not only of pneumonia, but also of cardiopulmonary or other chronic diseases that may be exacerbated by influenza infection. Ten thousand or more excess deaths were documented in each of 19 different epidemics from 1957-1986. More than 40,000 excess deaths occurred in each of several recent epidemics. Approximately 80%-90% of the excess deaths attributed to pneumonia and influenza during epidemics have occurred among persons greater than or equal to 65 years of age. However, influenza-associated deaths among children or previously healthy adults less than 65 years of age are also reported during major epidemics.

Because the proportion of elderly persons in the United States is increasing and because age and its associated chronic diseases are risk factors for severe influenza illness, the future toll from influenza may increase unless control measures are used more vigorously than in the past. Younger populations at high risk for influenza-related complications are also increasing for various reasons, including the success of neonatal intensive-care units, better management of diseases such as cystic fibrosis, and better survival rates for organ-transplant recipients.

OPTIONS FOR THE CONTROL OF INFLUENZA

There are two measures for reducing the impact of influenza: immunoprophylaxis with inactivated (killed virus) vaccine and chemoprophylaxis or therapy with an antiviral drug. Vaccination of high-risk persons each year before the influenza season is the single most important measure for reducing the impact of influenza. This measure can be highly cost-effective 1) when it is aimed at individuals who may experience the most severe consequences and who have a higher-than-average potential for infection and 2) when it is administered to high-risk individuals during routine health-care visits before the influenza season. Recent reports indicate that, when there is a good match between vaccine and epidemic strains of virus, achieving high vaccination rates in closed populations can reduce the risk of outbreaks by inducing herd immunity. When outbreaks of influenza A do occur in closed populations, they may be stopped by chemoprophylaxis of all residents. Other indications for prophylaxis (whether with vaccine or antiviral drug) include the strong desire of any person to avoid an influenza infection, reduce the severity of disease, or reduce their chances of transmitting influenza to high-risk persons with whom they have frequent contact. Unlike immunization, which protects against influenza types A and B, chemoprophylaxis is effective only against influenza A.

Specific chemotherapy for influenza A is most likely to benefit individuals who seek medical attention promptly because of the abrupt onset of an acute respiratory infection during an influenza A epidemic. Early chemotherapy may reduce the severity and duration of illness for high-risk individuals who have not been vaccinated or for whom influenza vaccine has not prevented infection.

Influenza is known to be transmitted in medical-care settings, and measures such as isolating ill patients individually or in groups, limiting visitors, and avoiding elective admissions and surgery during an influenza outbreak are all possible ways of limiting further transmission within hospitals and other institutions. However, unlike specific antiviral prophylaxis, these measures have not been demonstrated to be effective in controlling outbreaks. Likewise, the effectiveness of closing schools or classrooms during explosive outbreaks has not been established.

INACTIVATED VACCINE FOR INFLUENZA TYPES A AND B

Influenza vaccine is made from highly purified, egg-grown viruses that have been rendered noninfectious (inactivated). Most vaccines distributed in the United States have been chemically treated (split-virus preparations) to reduce the incidence of febrile reactions in children. Influenza vaccine currently contains three virus strains (two type A and one type B) representing influenza viruses recently circulating in the world and believed likely to occur in the United States the following winter. The potency of present vaccines is such that they cause minimal systemic or febrile reactions and nearly all vaccinated young adults develop hemagglutination-inhibition antibody titers that are likely to protect them against infection by strains like those in the vaccine and, often, by related variants that may emerge. The elderly and patients with certain chronic diseases

may develop lower postvaccination antibody titers than healthy young adults and, thus, be more susceptible to infection of the upper respiratory tract. Nevertheless, influenza vaccine can still be effective in preventing lower respiratory tract involvement or other complications of influenza among these high-risk persons. Influenza vaccine will not prevent primary illnesses caused by other respiratory pathogens.

RECOMMENDATIONS FOR USE OF INACTIVATED INFLUENZA VACCINE

Influenza vaccine is recommended for high-risk persons greater than or equal to 6 months of age and for their medical-care providers or household contacts, for children and teenagers receiving long-term aspirin therapy, and for other persons wishing to reduce their chances of acquiring influenza. Vaccine composition and dosages for the 1987-88 influenza season are given in Table 1. Guidelines for the use of vaccine among different segments of the population are given below. Remaining 1986-87 vaccine should not be used. Although the current influenza vaccine often contains one or more antigens used in previous years, immunity declines in the year following vaccination. Therefore, a history of vaccination in any previous year with a vaccine containing one or more antigens included in the current vaccine does not preclude the need to be revaccinated for the 1987-88 influenza season.

During the past decade, data on influenza vaccine immunogenicity and side effects have generally been obtained when vaccine is administered intramuscularly. Because there is no adequate evaluation of recent influenza vaccines administered by other routes, the intramuscular route is preferred. The recommended site of vaccination is the deltoid muscle for adults and older children and the anterolateral aspect of the thigh for infants and young children.

TARGET GROUPS FOR SPECIAL VACCINATION PROGRAMS

Groups at greatest medical risk of influenza-related complications. Based on observations of morbidity and mortality, high-risk groups have been classified by priority. Thus, available resources can be directed toward organizing special programs to provide vaccine to those who may derive the greatest benefit. Active, targeted vaccination efforts are most necessary for the following two groups, and the objective is to vaccinate at least 80% of each group:

1. Adults and children with chronic disorders of the

cardiovascular or pulmonary systems requiring regular medical follow-up or hospitalization during the preceding year.

2) Residents of nursing homes and other chronic-care facilities housing patients of any age with chronic medical conditions.

Groups at moderate medical risk of influenza-related complications. After the above two target groups have been vaccinated, programs should make vaccine readily available to persons at moderately increased risk of serious illness compared with the general population. These include:

1. Otherwise healthy individuals >= 65 years of age.

2. Adults and children who have required regular medical

follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, anemia, or immunosuppression.

3) Children and teenagers (6 months through 18 years of age) who are receiving long-term aspirin therapy and, therefore, may be at risk of developing Reye's syndrome following influenza infection.

Groups potentially capable of nosocomial transmission of influenza to high-risk persons. During many winters, nosocomial outbreaks of influenza are reported. Although not proven, it is reasonable to believe that individuals

caring for high-risk persons can transmit influenza infection to them while they are themselves incubating infection, undergoing subclinical infection, or working despite the existence of symptoms. The potential for transmitting influenza to high-risk persons should be reduced by vaccinating:

1. Physicians, nurses, and other personnel having extensive

contact with high-risk patients (e.g., primary-care and certain specialty clinicians and staff of chronic-care facilities and intensive-care units, particularly neonatal intensive-care units.

2) Providers of care to high-risk persons in the home setting (e.g., visiting nurses, volunteer workers) as well as all household members, whether or not they provide care.

VACCINATION OF OTHER GROUPS

General Population: Physicians should administer vaccine to any persons wishing to reduce their chances of acquiring influenza infection. Persons providing essential community services (e.g., employees of fire and police departments) are not considered at increased occupational risk of serious influenza illness, but they may be considered for vaccination programs designed to minimize disruption of essential services during severe epidemics.

Pregnant Women: Pregnancy itself has not been demonstrated as a risk factor for severe influenza infection, except during the largest pandemics of 1918-19 and 1957-58. However, pregnant women with medical conditions that increase their risk of complications from influenza should be vaccinated since influenza vaccine is considered safe for pregnant women without a specific severe egg allergy. To minimize any concern over the theoretical possibility of teratogenicity, vaccine should be given after the first trimester. However, it may be undesirable to delay vaccinating a pregnant woman who has a high-risk condition and will still be in the first trimester of pregnancy when influenza activity usually begins.

PERSONS WHO SHOULD NOT BE VACCINATED

Inactivated influenza vaccine should not be given to persons who have severe allergies to eggs (see SIDE EFFECTS AND ADVERSE REACTIONS, page 378). Normally, persons with acute febrile illnesses should not be vaccinated until their temporary symptoms have abated.

TIMING OF INFLUENZA VACCINATION ACTIVITIES

The first sporadic laboratory-confirmed cases of influenza in the United States or U.S. territories are often documented in September or October. However, except in years of pandemic influenza (e.g., 1957 and 1968), high levels of influenza activity have not occurred in the contiguous United States before December. Therefore, November is the optimal time for organized vaccination campaigns in chronic-care facilities, worksites, and other places where high-risk persons are routinely accessible.. Vaccination is desirable in September or October 1) in regions that have experienced earlier-than-normal epidemic activity (e.g., Alaska) and 2) for persons who should be vaccinated and who received medical check-ups or treatment during September or October and, thus, may not be seen in November. In addition, hospitalized high-risk adults and children who are discharged between September and the time influenza activity begins to decline in their community should be vaccinated as part of the discharge procedure.

Children who have not been previously vaccinated require two doses of vaccine with at least 1 month between doses. Vaccination programs for children should be scheduled so that the second dose can be given before December. Vaccine can be given to both children and adults up to and even after influenza virus activity is documented in a region, although temporary chemophrophylaxis may be indicated during influenza outbreaks (see ANTIVIRAL AGENTS FOR INFLUENZA, page 379).

STRATEGIES FOR IMPLEMENTING INFLUENZA VACCINE RECOMMENDATIONS

More effective, well planned programs for vaccinating high-risk persons are needed in nursing homes and other chronic-care facilities and in physicans' offices, health-maintenance organizations, hospitals, and employee health clinics. Adults and children who are in high-priority target groups and do not reside in nursing homes or other chronic-care facilities should receive influenza vaccine during their last regular medical check-up before the influenza season (i.e., before December). Clinicians should contact high-risk persons not scheduled for regular medical appointments in the fall and tell them to come in specifically to be vaccinated. From September - February, hospital discharge procedures should include vaccinating high-risk patients against influenza. Medical-care personnel and auxiliary staff must be made aware of the importance of ensuring that no high-risk patient resides in or leaves a medical-care facility during the fall without having influenza vaccine offered and being strongly urged to be vaccinated.

Educational materials about influenza and its control are available from a variety of sources. For more information on these sources, contact the Centers for Disease Control, Center for Prevention Services, Technical Information Services, 1600 Clifton Road, N.E., Atlanta, Georgia 30333.

SIDE EFFECTS AND ADVERSE REACTIONS

Because influenza vaccine contains only noninfectious viruses, it cannot cause influenza. Occasional cases of respiratory disease among vaccinated persons represent coincidental illnesses unrelated to influenza infection. The most frequent side effect of vaccination is soreness around the vaccination site for 1-2 days. This occurs in less than one-third of vaccine recipients.

In addition, the following two types of systemic reactions have occurred:

1. Fever, malaise, myalgia, and other systemic symptoms of

toxicity occur infrequently and, most often, affect persons with no exposure to the influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6-12 hours after vaccination and can persist for 1-2 days.

2) Immediate, presumably allergic, reactions such as hives, angioedema, allergic asthma, or anaphylaxis may occur, but they are extremely rare. These reactions probably result from sensitivity to some vaccine component - most likely residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, the vaccine is presumed capable of inducing immediate hypersensitivity reactions in individuals with severe allergies to eggs, and such persons should not be given influenza vaccine. This includes those who develop hives, swelling of the lips or tongue, or acute respiratory distress or collapse after eating eggs. It also includes persons who have developed evidence of occupational asthma or other allergic responses from occupational exposure to egg protein.

Unlike the 1976 swine influenza vaccine, subsequent vaccines, which have been prepared from other virus strains, have not been associated with an increased frequency of Guillain-Barre syndrome. Although influenza vaccination reportedly may inhibit the clearance of warfarin and theophylline, further studies have consistently failed to show any adverse effects of influenza vaccination among patients taking these drugs.

SIMULTANEOUS ADMINISTRATION OF CHILDHOOD OR OTHER VACCINES

There is considerable overlap in the target groups for influenza and pneumococcal vaccination. Both of these vaccines can be given at the same time at different sites without increased side effects. However, it should be emphasized that, whereas influenza vaccine is given annually, pneumococcal vaccine should be given only once. Detailed immunization records, which should be provided to each patient, will help ensure that additional doses of pneumococcal vaccine are not given.

Because children are accessible when pediatric vaccines are administered, it may be desirable to administer influenza vaccine simultaneously with routine pediatric vaccine, but in a different site. Although studies have not been done, no diminution of immunogenicity or enhancement of adverse reactions should be expected.

ANTIVIRAL AGENTS FOR INFLUENZA

There are two antiviral drugs with specific activity against influenza A viruses. They are amantadine hydrochloride and its analogue rimantadine hydrochloride. Presently, only amantadine is approved for marketing in the United States, although clinical trials have been undertaken with rimantadine to determine whether it also meets the safety and efficacy standards required for marketing.

Both amantadine and rimantadine interfere with the replication cycle of type A influenza viruses, although the specific mechanisms of their antiviral activity are not completely understood. These drugs also reduce virus shedding. Both drugs are approximately 70%-90% effective in preventing illnesses caused by naturally occurring strains of type A influenza viruses, but they are not effective against type B influenza. When administered within 24-48 hours after onset of illness, they have reduced the duration of fever and other systemic symptoms and allowed a more rapid return to routine daily activities. Since they may not prevent actual infection, persons who take these drugs may still develop immune responses that will protect them when exposed to antigenically related viruses.

In spite of the above evidence, chemoprophylaxis is not a substitute for vaccination because 1) it does not protect against influenza B and 2) patients may fail to take the drug for the full 6-12 weeks of an epidemic period. Increasing the availability of rapid viral diagnostic tests and improving the dissemination of information on where laboratory-confirmed influenza A virus infections are taking place will allow for more efficient use of antivirals. Such information is reported throughout the influenza season in the MMWR and is now available to public health officials by computer telecommunication from CDC.

Specific recommendations have been made for amantadine. Should rimantadine be approved for marketing in the United States at some future date, additional recommendations will be published.

AMANTADINE PROPHYLAXIS RECOMMENDATIONS

Although amantadine is not a substitute for vaccination, it is recommended for prophylaxis under specific circumstances, particularly for control of presumed influenza A outbreaks in institutions housing high-risk persons. To reduce the spread of infection, the drug should be given as early as possible after recognition of an outbreak. Contingency planning for influenza outbreaks in institutions is needed to establish specific steps for rapidly administering amantadine to residents of chronic-care facilities when appropriate. This should include plans to obtain physicians' orders on short notice. When the decision is made to give amantadine for outbreak control, it should be administered to all residents of the affected institution, whether or not they received influenza vaccine the previous fall. Dosage recommendations and precautions (see DOSAGE AND PRECAUTIONS FOR THE USE OF AMANTADINE, page 385) and in the drug's package insert should be followed. To reduce spread of virus and to minimize disruption of patient care, it is also recommended that amantadine prophylaxis be offered to unvaccinated staff who care for high-risk residents of chronic-care institutions or hospitals experiencing a presumed influenza A outbreak. For prophylaxis, amantadine should be taken each day for the duration of influenza activity in the community.

Amantadine prophylaxis is also recommended in the following situations.

1. As an adjunct to late immunization of high-risk

individuals. It is not too late to immunize even when influenza A is known to be in the community. However, since the development of an antibody response following vaccination takes about 2 weeks, amantadine should be used in the interim. The drug does not interfere with antibody response to the vaccine.

2) To reduce spread of virus and to maintain care for high-risk persons in the home setting. Persons who have not been appropriately immunized and who care for high-risk persons in home settings (e.g., household members, visiting nurses, volunteer workers) should also receive amantadine for prophylaxis during influenza A virus outbreaks in their community.

3) For immunodeficient persons. To supplement protection afforded by vaccination, chemoprophylaxis is also indicated for high-risk patients who may be expected to have a poor antibody response to influenza vaccine (e.g., those with severe immunodeficiency).

4) For persons for whom influenza vaccine is contraindicated. Chemoprophylaxis throughout the influenza season is appropriate for those few high-risk individuals for whom influenza vaccine is contraindicated because of anaphylactic hypersensitivity to egg protein. Amantadine can also be used prophylactically in other situations (e.g., for unimmunized members of the general population who wish to avoid influenza A illness). This decision should be made on an individual basis.

THERAPY

Although amantadine has been shown to reduce the severity and shorten the duration of influenza A illness in healthy adults, there have been no well-controlled clinical studies examining the efficacy of amantadine therapy in preventing complications of influenza A in high-risk persons. Nevertheless, because of the potential benefits, amantadine should be considered for high-risk patients who develop an illness compatible with influenza during known or suspected influenza A activity in the community. The drug should be given within 24-48 hours of onset of illness and should be continued until 48 hours after resolution of signs and symptoms.

DOSAGE AND PRECAUTIONS FOR THE USE OF AMANTADINE:

In determining whether or not to use amantadine for prophylaxis or treatment of individual patients, the following information should be considered:

1. In controlled studies, 5%-10% of healthy young adults

taking amantadine at the standard adult dose of 200 mg per day have reported side effects including nausea, dizziness, insomnia, nervousness, and impaired concentration. These side effects are usually mild and cease soon after amantadine is discontinued.

2) Amantadine is not metabolized and is excreted unchanged in the urine by glomerular filtration and tubular secretion. Because of the decline in renal function associated with normal aging, it is recommended that the daily dose for persons >= 65 years of age not exceed 100 mg. When amantadine is administered to patients with impaired renal function, the dose should be reduced (see package insert). Because recommended dosages for persons with renal impairment may provide only a rough estimate of the optimal dose for a given patient, careful clinical observation is needed for such individuals so that adverse reactions can be recognized promptly and the dose reduced or the drug discontinued if necessary. Since amantadine is not metabolized, toxic levels can occur when renal function is sufficiently impaired.

3) Persons with an active seizure disorder may be at increased risk for seizures when given amantadine at a dose of 200 mg daily. Although there are limited data regarding the use of amantadine in persons with seizure disorders, currently available data suggest that any risk of increased seizure activity in such persons might be reduced by using a lower dose of the drug.

4) The use of amantadine in children <1 year of age has not been adequately evaluated. The approved dosage for children 1-9 years of age is 4.4 to 8.8 mg/kg/day, not to exceed 150 mg/day. Although further studies to determine the optimal dosage of amantadine for children would be desirable, physicians should consider prescribing the lower range of the approved dosage to reduce the risk of toxicity.

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