Current Recommendations for the Prevention and Treatment of Influenza in the Older Population

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Summary   Influenza is a major cause of morbidity and mortality in the elderly. Influenza vaccine is recommended for people aged 65 years and older and those in long term care. Currently only 30% of high risk persons are vaccinated. Vaccination generally stimulates an adequate immune response, is well tolerated and is to be encouraged. Prophylactic amantadine 100 mg/day should be given for 2 weeks with influenza vaccine in the aged population when they have not been previously immunised. Broad application of these preventive measures would have a significant impact on reducing influenza prevalence in the elderly and other high risk groups.

1. Impact of Influenza Virus

If we were more aware of the full impact of influenza on our lives, we would be more concerned about preventing it. In the United States alone more than 10 000 deaths are attributed to influenza virus in an average epidemic year (Recommendations of the Immunization Practices Advisory Committee 1990). In some epidemics, the death toll has risen to more than 40 000. The majority of deaths – 80 to 90% – occur in persons 65 years of age and older (Liu & Kendal 1987).

The estimated economic loss from influenza in the United States is estimated to be more than

$US1 billion each year (Schoenbaum 1987). In reality, the cost is probably 3 to 5 times greater. While much has been written on the cost-benefit ratio for influenza vaccine, in persons 65 years of age and above the benefit clearly outweighs the cost. Despite the favourable impression gained from economic models, however, individual patients and their physicians do not as a rule perceive the benefit. As a result, only a small percentage of the elderly population are vaccinated each year.

What is influenza? Is it easy to diagnose? How effective is influenza vaccine? Are the side effects a frequent concern? What efforts have been and can be made to improve vaccine acceptance? These are some of the important questions we attempt to answer in this article.[1]

2. Diagnosis of Clinical Disease

Influenza virus was first isolated from humans in the 1930s (Ruben 1987). The clinical syndrome of a typical case of influenza begins with fever, cough and myalgias that last for a few days to a week (Cate, 1987). The clinical course may be complicated by laryngotracheobronchitis and pneumonia. Secondary bacterial pneumonia may occur simultaneously or a few days later. Hospitalisation is more likely to occur in individuals who are elderly or have pre-existing cardiac or pulmonary disease. Children aged under 12 years taking aspirin during the early phases of infection are more likely to get Reye's syndrome. Late complications of infection such as fatigue, chronic cough, and small-airway disease may last for weeks.

Making a diagnosis of influenza virus infection is difficult because the acute respiratory syndromes may be confused with other viral respiratory agents such as parainfluenza viruses, adenoviruses, respiratory syncytial viruses as well as the more common rhinoviruses and coronaviruses. Laboratory

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1 Educational materials on influenza are available from the Centers for Disease Control [Technical Information Services, Center for Prevention Services, Mailstop E06, CDC, Atlanta, GA 30333, USA; phone (404) 639-1819] as well as from state and local health departments in the USA.

tests can distinguish among these agents, and rapid, sensitive tests are now available to diagnose influenza virus (Reichelderfer et al. 1987). A specific diagnosis of influenza can be made in a few hours to a few days, rather than in a week or more as was the case several years ago.

3. Morbidity and Mortality

While influenza virus infection may be difficult to distinguish from other respiratory viruses on clinical grounds, influenza virus is unique among the respiratory viruses for the high mortality associated with it. Since the sixteenth century, people have recognised the increased mortality resulting from an influenza epidemic (Monto 1987). Excess mortality from influenza has been documented since 1889. On occasion, influenza outbreaks reach pandemic proportions, as occurred in 1918. Influenza epidemics occur almost every winter.

Quantifying the mortality from influenza begins with describing the known seasonal variation in mortality from all causes, as shown in figure 1. To reduce the chance of error a dashed line equal to 1.645 standard deviations (the 'epidemic threshold') is drawn above the known season incidence line. When the mortality rate exceeds the standard deviation, it is considered significant. This so-called excess mortality is invariably associated with an outbreak of influenza. Excess deaths, therefore, are considered to be due to epidemics of influenza virus.

Quantifying morbidity from influenza is more difficult. While excess mortality occurs in the elderly and those with certain chronic diseases, morbidity is generally more common among healthy children and young adults. The severe morbidity associated with influenza, such as hospitalisation, is most common among the elderly and chronically ill. A number of studies have documented the toll influenza exacts among the infirm and the elderly. The most recent large scale study on influenza-related mortality is by Barker and Mullooly (1980). In 2 influenza A (H_3N_2) epidemics, they report that 11 to 13 excess deaths occurred per 100 000 persons. When they examined those aged
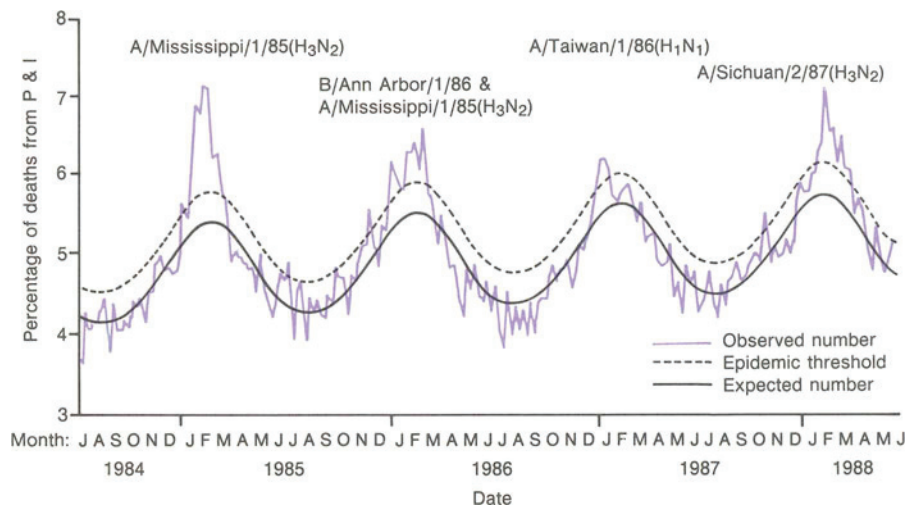
Fig. 1. Pneumonia and influenza deaths as a percentage of total deaths reported to the Centers for Disease Control from 121 US cities, July 1984 to June 1988. Pneumonia and influenza deaths include all deaths for which pneumonia is listed as a primary or underlying cause or for which influenza is listed on the death certificate. The predominant virus strain is shown above the peak of mortality for each epidemic season. The epidemic threshold for the 1987-88 influenza season was estimated at 1.645 standard deviations above the values projected on the basis of a periodic regression model applied to observed pneumonia and influenza deaths for the previous 5-year period but excluding the observations during influenza outbreaks (reproduced with permission from Morbidity and Mortality Weekly Report 37: 502, 1988).

65 years and older, the incidence of excess deaths increased to between 68 and 104 per 100 000. These estimates should in reality be even higher because pneumonia or influenza is often omitted from the diagnoses listed on death certificates (Barker & Mullooly 1981).

Glezen et al. (1987) showed that the risk of hospitalisation for acute respiratory disease (ARD) during influenza epidemics was 19.7 per 10 000 persons with high risk conditions for which influenza vaccine is indicated, compared to 9.3 per 10 000 for persons without these conditions. Chronic pulmonary disorders followed by chronic cardiac conditions were the most common high-risk conditions. Renal failure, diabetes and long term care residence are other risk factors. For persons over 65 years of age with a concomitant chronic pulmonary condition the hospitalisation rate for ARD soared to 87.5 per 10 000. The peak of hospitalisations for ARD typically followed by

one week the peak of influenza virus isolations (Perrotta et al. 1985).

4. Genetic Basis for Strain Variation

The disease severity varies according to the influenza strain and the age of the patient. The H_3N_2 subtype of influenza A causes the most severe illness, while the H_1N_1 subtype of influenza A is associated with the mildest illness (Monto et al. 1985). Type B influenza causes an illness intermediate in severity between the 2 A subtypes. A third type of influenza, type C, is rarely responsible for epidemic disease.

But why is influenza a problem year after year? Becoming infected with each of the 3 strains of influenza does not confer long-lasting immunity; in contrast, becoming infected naturally with, for example, measles does confer long-lasting immunity. Why the difference? There is only 1 strain of measles and its nonsegmented genome preserves its

singularity. Influenza virus, on the other hand, has a segmented genome. The multiple RNA segments – there are 8 in all – predispose to the genetic instability of the influenza virus (table I, fig. 2). The nucleotide sequences in the RNA segments are inherently unstable, and when 2 different strains of the same subtype infect the same host the RNA segments can reassort, giving rise to progeny that are different from the 2 parents.

The naming of influenza viruses is straightforward. For example, influenza A/Shanghai/16/89 (H_3N_2) is so named because this strain is a type A influenza virus first isolated in Shanghai in 1989. It was the sixteenth isolate of the subtype H_3N_2 detected in that year. Haemagglutinin (H) and neuraminidase (N) proteins exist in types A, B, and C influenza virus. But only haemagglutinin and neuraminidase proteins of influenza A are sufficiently diverse to warrant subtype designations. For the type A influenza viruses, 3 haemagglutinins (H_1, H_2 and H_3) and 2 neuraminidases (N_1 and N_2) have been described. Currently, only 2 subtypes of influenza A are circulating and causing disease in humans, and they are the H_3N_2 and the H_1N_1 subtypes.

The genetic changes that occur have been referred to by the terms antigenic drift and antigenic shift. Antigenic *drift* is a minor change that occurs
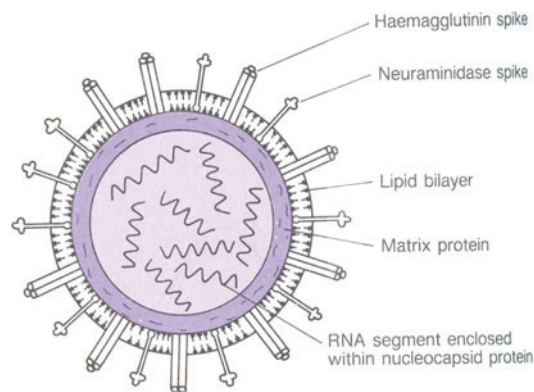

Fig. 2. Schematic representation of influenza virion.

when amino acid sequence changes appear, usually in the haemagglutinin protein. The change from influenza A/Shanghai/11/87 (H_32N_2) to influenza A/Shanghai/16/89 (H_3N_2) is an example of this (Kendal 1987). Minor changes also occur when antigens are glycosylated and camouflage the previously exposed antigenic site. Antigenic *shift* is a major change that occurs by gene reassortment resulting in a new subtype. The change from the influenza A (H_2N_2) to the influenza A (H_3N_2) subtype that occurred in 1968 is such an example. Gene reassortment probably occurs when 2 different subtypes coinfect the same host.

5. Influenza Vaccine

Serum antibody to the surface haemagglutinin and neuraminidase proteins is important in protection against infection and the development of disease. Humoral antibody to the haemagglutinin component is the most critical, but the importance of cell-mediated immunity is less clear (Lamb et al. 1987). The humoral immune response is highly specific for certain epitopes on the surface of the virus. The cellular response, in contrast, is less specific and more cross-reactive. The B cells which produce humoral antibody recognise antigenic determinants, or epitopes, adjacent in space but not in sequence, while T cells recognise epitopes adjacent in sequence but not necessarily in space. The

Table I. Influenza genome

RNA segment	Protein	Present in virus
1	Polymerase (PB2)	+
2	Polymerase (PB1)	+
3	Polymerase (PA)	+
4	Haemagglutinin (HA)	+
5	Neuraminidase (NA)	+
6	Nucleoprotein (NP)	+
7	Matrix (M1)	+
	Matrix (M2 and NB)	–
8	Nonstructural (MS1)	–
	Nonstructural (MS2)	–

implication here is that B cell epitopes are intact external molecules such as haemagglutinins, while T cell epitopes appear to be linear sequences exposed by enzymatic breakdown of the original molecule.

A killed (inactivated) vaccine against influenza virus was first developed in the 1940s. Since then the manufacturing process has resulted in a more pure vaccine. The virus is grown in embryonated eggs. Most of the egg protein is now eliminated and the side effects have been reduced markedly. Killed vaccines are referred to as either whole virus or split virus: whole virus vaccines are inactivated by formalin; split or subunit vaccines use whole virus which is treated with a detergent to free up the haemagglutinin and neuraminidase subunits from the viral surface, then formalin is added. In children who have not previously been vaccinated, split virus vaccines cause fewer side effects such as fever and myalgias than whole virus vaccines.

Live attenuated vaccines have been in the development stages for over 10 years and are currently being tested; they are not commercially available. A genetically stable method of production was the initial problem but this has since been solved. However, it has been difficult to show a clear advantage of live over killed vaccines.

5.1 Composition and Administration

The currently licensed influenza vaccine contains 3 strains: influenza A/Shanghai/16/89 (H_3N_2); influenza A/Taiwan/1/86 (H_1N_1); and influenza B/Yamagata/16/88. There are 15μg of haemagglutinin for each strain in the vaccine. It should be given intramuscularly in the deltoid in adults and in the anterolateral thigh in infants and young children. Administration in the buttock is not recommended because it may result in a poorer immune response due to inadequate absorption from the subcutaneous fat. The strains to be included in the vaccine change from year to year according to World Health Organization (WHO) recommendations.

5.2 Target Population

The primary target groups are as follows (Recommendations of the Immunization Practices Advisory Committee 1990).

Groups at increased risk for influenza-related complications:
1. Persons aged 65 years or older.
2. Residents of nursing homes and other chronic-care facilities housing persons of any age with chronic medical conditions.
3. Adults and children with chronic disorders of the pulmonary or cardiovascular systems, including children with asthma.
4. Adults and children who have required regular medical follow-up or hospitalisation during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, haemoglobinopathies, or immunosuppression (including immunosuppression caused by medications).

Groups that can transmit influenza to high-risk persons:
1. Physicians, nurses and other personnel in both hospital and outpatient-care settings who have contact with high-risk persons in all age groups, including infants.
2. Employees of nursing homes and chronic-care facilities who have contact with patients or residents.
3. Providers of home care to high risk persons (e.g. visiting nurses, volunteer workers).
4. Household members (including children) of high-risk persons.

Other groups merit consideration (Recommendations of the Immunization Practices Advisory Committee 1990): (a) in the general population, anyone who wishes to reduce the chance of acquiring influenza infection; (b) anyone who provides essential community services and persons living or working in an institutional setting; (c) persons infected with HIV should be vaccinated, although they may not respond as well if their disease is far advanced; and (d) foreign travellers should be immunised when travelling to the trop-

ics at any time of the year or from the Southern to the Northern Hemisphere between August and March and the Northern to the Southern Hemisphere between April and September.

The vaccine is contraindicated in persons with anaphylaxis to eggs and in those with an acute febrile illness. A protocol is available for giving vaccine to allergic patients at high risk of influenza complications (Recommendations of the Immunization Practices Advisory Committee 1990).

Other vaccines can be given along with influenza vaccine, such as pneumococcal, measles-mumps-rubella, *Haemophilus influenzae* type b, and oral polio vaccines. Pertussis vaccine, however, should not be given within 3 days of influenza virus vaccine.

For optimal effect, the vaccine should be given in November in the Northern Hemisphere or May in the Southern Hemisphere, before the winter influenza season begins. Effective antibody levels develop within 2 weeks in most previously immunised persons. The levels decline a few months later, when they may be suboptimal.

5.3 Efficacy

Studies investigating vaccine efficacy are difficult to conduct and to evaluate. They are hard to conduct because randomisation to control and vaccinated groups raises ethical questions in high risk patients. Evaluation is difficult because other respiratory infectious agents also cause colds, pneumonia, occasionally death, and often result in hospitalisation – the criteria used to determine efficacy.

Vaccine immunogenicity and protective efficacy in the elderly have had mixed reviews. Immunogenicity, the vaccine's ability to stimulate protective levels of antibody, appears to be adequate in many studies. Protective levels of serum antibody are considered to be equal to or greater than the reciprocal of serum dilutions at 1 : 32 or 1 : 40, depending on the dilution method. Protective levels are usually achieved in 70 to 90% of vaccine recipients.

Beyer et al. (1989) reviewed 17 papers on this subject published between 1968 and 1988. A total of 30 comparisons were available in the 17 papers. In 10, the immune response was superior in young subjects; in 4, the elderly responded better, and in 16, no significant difference was noted between the young and old subjects; in this instance, the lack of differences may have been due to a type 2 error because the numbers studied were low. Beyer et al. (1989) pointed out 3 methodological limitations. The studies included, firstly, subjects with illnesses or taking drugs, which affect the immune system; secondly, patients immunised previously with influenza vaccine; and finally, those with protective antibody levels before immunisation. Inclusion of patients with any of these 3 factors would tend to underestimate the ability of elderly subjects to respond to immunisation. The association between increasing age and a poor immune response to influenza vaccine has thus not yet been convincingly made.

Perhaps a small subgroup of the elderly population respond poorly while most respond normally. This was originally suggested in a study by Phair et al. (1978) examining the T cell response of infirm elderly to influenza antigens. More recently, in a study by Gross et al. (1989), bedridden, infirm elderly patients appeared to respond less well to influenza vaccine than did healthy, ambulatory elderly patients. Alternative approaches to the standard immunisation have been tried. Two doses 1 month apart did not improve the immune response (Gross et al. 1987), neither did 2 and 3 times the standard dose (Gross et al. 1988b).

From currently available information we can conclude that the recommended single standard dose of killed influenza vaccine will stimulate an adequate immune response in most elderly persons. Finally, and most importantly, in a number of recent studies influenza vaccine has been shown to reduce mortality from influenza virus infection (Arden et al. 1986; Barker & Mullooly 1986; Gross et al. 1988a).

5.4 Tolerability

Recent studies on the adverse effects of influenza vaccine show that the vaccine is typically well

tolerated. For example, Margolis et al. (1990a,b) reported that in elderly chronically ill patients fever and significant disability could not be attributed to the vaccine compared to a control group. A flu-like illness, however, was attributable to vaccine in 5.5%. They concluded that the overall frequency of adverse effects was low.

Another area of concern is the effect of vaccine on drug metabolism. The mechanism postulated is vaccine suppression of oxidative hepatic metabolism. Interferon production induced by vaccination is supposed to block the oxidative cytochrome P450 system, resulting in accumulation of certain drugs. Metabolism of theophylline, chlordiazepoxide, lorazepam, warfarin, phenytoin and phenobarbital (phenobarbitone) has been studied, with variable results. For theophylline, in particular, most studies seem to indicate that the effect of vaccine is minor (Gomolin et al. 1985; Grabowski et al. 1985; Jann & Fidone 1986; Meredith et al. 1985).

6. Strategies for Improving Vaccine Usage

Less than 30% of high risk persons are vaccinated annually. Consequently many studies have been undertaken to determine the best strategies for immunising appropriate groups. The current strategies for implementing the influenza vaccine recommendations include immunising persons in the following settings (Recommendations of the Immunization Practices Advisory Committee 1990).

1. In outpatient clinics and physicians' offices label medical records of high risk persons; use mail or telephone reminders; begin vaccinating in September (Northern Hemisphere) [Buchner et al. 1987] and March (Southern Hemisphere).

2. In facilities providing episodic or acute care (e.g. emergency rooms, walk-in clinics) healthcare providers be aware of high risk groups; provide written information in appropriate languages.

3. In nursing homes and other residential long term care facilities vaccinate all residents with the prior aggreement of attending physicians; do not require individual physician orders; obtain permission for vaccination on admission to facility.

4. In acute-care hospitals encourage vaccination before discharge between September and April (Northern Hemisphere), and March to August (Southern Hemisphere) of all persons aged 65 years or over, or with high risk conditions at any age (Fedson 1987).

5. In outpatient facilities providing continuing care to high risk patients (e.g. haemodialysis centres, hospital speciality care clinics, outpatient rehabilitation programmes); facilities providing services to people 65 years and older (e.g. retirement communities, recreation centres); clinics and other centres providing healthcare for travellers; healthcare workers, visiting nurses and others providing home care to high risk persons provide educational materials; encourage vaccination; emphasise to staff in intensive care units, medical/surgical units, employees in nursing homes and long term care facilities; make vaccine available for all work shifts, including night and weekend.

7. Antiviral Agents

Two antiviral agents are effective in the prevention and treatment of influenza type A infections – amantadine and rimantadine. Only amantadine is currently available commercially in the United States. It has no effect against influenza type B (Douglas 1990).

The primary use of amantadine is in preventing influenza A infection. Preventive efficacy varies between 50 and over 90%. When influenza A is in the community, an unvaccinated elderly person should receive vaccine plus 2 weeks of amantadine at a dose of 100 mg/day (Nicholson & Wiselka 1991). Amantadine does not interfere with the immune response to vaccine, and after 2 weeks the vaccine-induced immune response should be sufficient to prevent influenza. Amantadine treatment should not be stopped if the high risk person cannot be vaccinated or is immunodeficient. It should be continued for as long as influenza is epidemic – usually about 5 to 6 weeks.

Amantadine has also been used for the treatment of influenza A. When the drug is started within 48 hours of the onset of illness it produces

Table II. Recommended dosage of amantadine depending on age and renal function (manufacturer's recommendations)

	Amantadine dosage
Age (years)	
< 65	100mg bid or 200 mg/day
≥ 65	100 mg/day
Creatinine clearance (ml/min/1.73m²)	
30-50	200mg day 1, then 100 mg/day
15-29	200mg day 1, then 100mg alternate days
< 15	200 mg/week
Haemodialysis	200 mg/week

Abbreviation: bid = twice daily.

a therapeutic effect. The duration of illness decreases by 50%, virus shedding decreases more rapidly, and peripheral airway resistance is reduced faster. Serum antibody still develops despite the use of amantadine. Amantadine treatment for the acute illness should be continued for 5 days. Studies on the therapeutic efficacy of amantadine have been done in healthy adults; there are no data on its efficacy in high risk persons (Recommendations of the Immunization Practices Advisory Committee 1990). Resistance of influenza A virus to amantadine has been reported (Belshe et al. 1989).

The adverse effects of amantadine at a dose of 200 mg/day involve the central nervous system (nervousness, anxiety, insomnia, difficulty concentrating and lightheadedness) and the gastrointestinal tract (anorexia and nausea). They usually decrease or stop after the first week of use or when amantadine is discontinued. Using a smaller dose, 100 mg/day, reduces the adverse effects, apparently without diminishing efficacy. The manufacturer's recommendations should be read carefully to adjust the dose for age, renal function, weight, and interactions with other drugs and diseases (see table II).

Rimantadine is a structural analogue of amantadine. It has 2 advantages over amantadine: it has fewer central nervous system side effects at doses of 200 mg/day, and, because most of the drug is

metabolised, elimination from the body is not dependent on renal excretion.

8. Conclusion

The use of influenza vaccine in the elderly is no longer an option to be exercised only occasionally. Administration of influenza vaccine and the use of amantadine when indicated should become a standard part of the care given our elderly population (Nicholson 1990).

References

Arden NH, Patriarca PA, Kendal AP. Experiences in the use and efficacy of inactivated influenza vaccine in nursing homes. In Kendal AP & Patriarca PA (Eds) Options for the control of influenza, pp. 155-158, Alan R. Liss, New York, 1986

Barker WM, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. American Journal of Epidemiology 112: 798-811, 1980

Barker WM, Mullooly JP. Underestimation of the role of pneumonia and influenza in causing excess mortality. American Journal of Public Health 71: 643-645, 1981

Barker WM, Mullooly JP. Effectiveness of inactivated influenza vaccine among non-institutionalized elderly persons. In Kendal AP & Patriarca PA (Eds) Options for the control of influenza, pp. 169-182, Alan R. Liss, New York, 1986

Belshe RB, Burk B, Newman F, Cerrute RL, Sim S. Resistance of influenza A virus to amantadine and rimantadine: results of one decade of surveillance. Journal of Infectious Diseases 159: 430-4535, 1989

Beyer WEP, Palache AM, Baljet M, Masurel N. Antibody induced by influenza vaccines in the elderly: a review of the literature. Vaccine 7: 385-394, 1989

Buchner DM, Larson EB, White RF. Influenza vaccination in community elderly: a controlled trial of postcard reminders. Journal of the American Geriatric Society 35: 755-760, 1987

Cate TR. Clinical manifestations and consequences of influenza. American Journal of Medicine 82 (6A): 15-19, 1987

Douglas Jr RG. Antimicrobial agents: antiviral agents. In Goodman and Gilman (Eds) The pharmacological basis of therapeutics, 8th ed., pp. 1182-1201, Pergamon Press, New York, 1990

Fedson DS. Immunizations for health care workers and patients in hospitals. In Wenzel RP (Ed.) Prevention and control of nosocomial infections, pp. 116-174, Williams & Wilkins, Baltimore, 1987

Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. American Review of Respiratory Diseases 136: 550-555, 1987

Gomolin IH, Chapron DJ, Luhan PA. Lack of effect of influenza vaccine on theophylline levels and warfarin anticoagulation in the elderly. Journal of the American Geriatric Society 33: 269-272, 1985

Grabowski N, May JJ, Pratt DS, Richtsmeier WJ, Bertino JS. The effect of split virus influenza vaccination on theophylline pharmacokinetics. American Review of Respiratory Diseases 131: 934-983, 1985

Gross PA, Quinnan GV, Rodstein M, et al. Association of influenza immunization with reduction in mortality in an elderly

population: a prospective study. Archives of Internal Medicine 148: 562-565, 1988a

Gross PA, Quinnan Jr GV, Weksler ME, Gaerlan PF, Denning CR. Immunization of elderly people with high doses of influenza vaccine. Journal of the American Geriatric Society 36: 209-212, 1988b

Gross PA, Quinnan Jr GV, Weksler ME, Setia U, Douglas Jr RG. Relation of chronic disease and immune response to influenza vaccine in the elderly. Vaccine 7: 303-308, 1989

Gross PA, Weksler ME, Quinnan Jr GV, Douglas Jr RG, Gaerlan PF, et al. Immunization of elderly people with two doses of influenza vaccine. Journal of Clinical Microbiology 25: 1763-1765, 1987

Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. Clinical Pharmacy 5: 817-820, 1986

Kendal AP. Epidemiologic implications of changes in the influenza virus genome. American Journal of Medicine 82 (6A): 4-14, 1987

Lamb JR, McMichael AJ, Rothbard JB. T-cell recognition of influenza viral antigens. Human Immunobiology 19: 79-89, 1987

Liu KJ, Kendal AP. Impact of influenza epidemic on mortality in the United States from October 1972 to May 1985. American Journal of Public Health 77: 712-716, 1987

Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. Journal of the American Medical Association 264: 1139-1141, 1990a

Margolis KL, Poland GA, Nichol RH, MacPherson DS, Meyer JD, et al. Frequency of adverse reactions after influenza vaccine. American Journal of Medicine 88: 27-30, 1990b

Meredith CG, Christian CD, Johnson RF, Troxell R, Davis GL, et al. Effects of influenza virus vaccine on hepatic drug metabolism. Clinical Pharmacology and Therapeutics 37: 396-401, 1985

Monto AS. Infleunza: quantifying morbidity and mortality. American Journal of Medicine 83 (64); 20-25, 1987

Monto AS, Koopman JS, Longini Jr JM. Tecumsah study of illness. XIII: influenza infection and disease, 1976-1981. American Journal of Epidemiology 121: 811-822, 1985

Nicholson KG. Influenza vaccination and the elderly. British Medical Journal 301; 617-618, 1990

Nicholson KG, Wiselka MJ. Amantadine for influenza A. British Medical Journal 302: 425-426, 1991

Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalizations as a measure of impact of epidemic influenza. American Journal of Epidemiology 122: 468-476, 1985

Phair J, Kaufman CA, Bjoruson A, Adams L, linneman Jr C. Failure to respond to influenza vaccine in the aged: correlation with B-cell number and function. Journal of Laboratory and Clinical Medicine 92: 882-888, 1978

Recommendations of the Immunization Practices Advisory Committee (ACIP). Prevention and control of influenza. And addendum clarification. Morbidity and Mortality Weekly Report 39 (RR-7): 1-15, 1990 Morbdity and Mortality Weekly Report 39: 469, 1990

Reichelderfer PS, Kappus KD, Kendal AP. Economical laboratory support system for influenza virus surveillance. Journal of Clinical Microbiology 25: 947-948, 1987

Ruben FL. Prevention and control of influenza: role of vaccine. American Journal of Medicine 82 (6A): 31-34, 1987

Schoenbaum SC. Economic impact of influenza: the individual's perspective. American Journal of Medicine 83 (6A): 26-30, 1987

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