厚生労働科学研究費補助金（新興・再興感染症研究事業）
分担研究報告書

Recommendations for Using Inactivated Influenza Vaccines

分担研究者　**Timothy M. Uyeki**

Influenza Division,
National Center for Immunization and Respiratory Diseases,
Centers for Disease Control and Prevention (CDC)

Summary

The 2006 recommendations include new and updated information. Principal changes include 1) recommending vaccination of children aged 24-59 months and their household contacts and out-of-home caregivers against influenza; 2) highlighting the importance of administering 2 doses of influenza vaccine for children aged 6 months-<9 years who were previously unvaccinated; 3) advising health-care providers, those planning organized campaigns, and state and local public health agencies to a) develop plans for expanding outreach and infrastructure to vaccinate more persons than the previous year and b) develop contingency plans for the timing and prioritization of administering influenza vaccine, if the supply of vaccine is delayed and/or reduced; 4) reminding providers that they should routinely offer influenza vaccine to patients throughout the influenza season; 5) recommending that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A in the United States until evidence of susceptibility to these antiviral medications has been re-established among circulating influenza A viruses.

Recommendations for Using Inactivated and Live, Attenuated Influenza Vaccines

The inactivated influenza vaccine and live, attenuated influenza vaccines (LAIV) can be used to reduce the risk for influenza virus infection and its complications. Trivalent inactivated influenza vaccine (TIV) is Food and Drug Administration (FDA)-approved for persons aged ≥6 months, including those with high-risk conditions, whereas LAIV is approved only for use among healthy persons aged 5-49 years (see Inactivated Influenza Vaccine Recommendations).

Target Groups for Vaccination

Annual influenza vaccination is recommended for the following groups:

Persons at Increased Risk for Complications

Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for severe complications from influenza:

- children aged 6-23 months;
- children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza virus infection;
- women who will be pregnant during the influenza season;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- 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, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by human immunodeficiency virus [HIV]);
- adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions; and
- persons aged ≥65 years.

Vaccination with inactivated influenza vaccine also is recommended for the following persons because of an increased risk for influenza-associated clinic, emergency department, or hospital visits, particularly if they have a high-risk medical condition:

- children aged 24-59 months and
- persons aged 50-64 years.

Persons Who Live With or Care for Persons at High Risk for Influenza-Related Complications

In addition, to prevent transmission to persons identified above, vaccination with TIV or LAIV is recommended for the following persons, unless contraindicated:

- healthy household contacts and caregivers of children aged 0-59 months and persons at high risk for severe complications from influenza and
- health-care workers.

Additional Information Regarding Vaccination of Specific Populations

Healthy Young Children Aged 6-59 Months

Because children aged 6-23 months are at substantially increased risk for influenza-related hospitalizations and because children aged 24-59 months are at increased risk for influenza-related clinic and emergency department visits (1), the Advisory Committee on Immunization Practices (ACIP) recommends vaccination of

children aged 6-59 months. The current LAIV and inactivated influenza vaccines are not approved by FDA for use among children aged <6 months, the pediatric group at greatest risk for influenza-related complications (2-4). Vaccination of their household contacts and out-of-home caregivers also is recommended because it might decrease the probability of influenza virus infection among these children.

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation (5-12). The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by cocirculation of respiratory syncytial virus that causes serious respiratory viral illness among children and that frequently circulates during the same time as influenza viruses (13-15). One study assessed rates of influenza-associated hospitalizations among the entire U.S. population during 1979-2001 and calculated an average rate of approximately 108 hospitalizations per 100,000 person-years in children aged <5 years (16). Two studies have attempted to separate the impact of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions (2,6). Both studies indicated that otherwise healthy children aged <2 years and possibly children aged 2-4 years are at increased risk for influenza-related hospitalization compared with older healthy children (Table 1). Among the Tennessee Medicaid population during 1973-1993, healthy children aged 6 months-2 years had rates of influenza-associated hospitalization comparable with or higher than rates among children aged 3-14 years with high-risk conditions (2,7). Another Tennessee study indicated a hospitalization rate per year of 3-4/1,000 healthy children aged <2 years for laboratory-confirmed influenza (17).

The ability of providers to implement the recommendation to vaccinate all children aged 24-59 months during the 2006-07 season, the first year the recommendation will be in place, might vary depending upon vaccine supply (See http://www.cdc.gov/nip/news/shortages/default.htm).

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918-19 and 1957-58 (18-21). Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza (22-27). One study of influenza vaccination of approximately 2,000 pregnant women demonstrated no adverse fetal effects associated with inactivated influenza vaccine (28); similar results were observed in a study of 252 pregnant women who received inactivated influenza vaccine within 6 months of delivery (29). No such data exist on the safety of LAIV when administered during pregnancy.

Breastfeeding Mothers

TIV is safe for mothers who are breastfeeding and their infants. Because excretion of LAIV in human milk is unknown and because of the possibility of shedding vaccine virus given the close proximity of a nursing mother and her infant, caution should be exercised if LAIV is administered to nursing mothers. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.

Persons Aged 50-64 Years

Vaccination is recommended for persons aged 50-64 years because this group has an increased prevalence of persons with high-risk conditions. In 2002, approximately 43.6 million persons in the United States were aged 50-64 years, of whom 13.5 million (34%) had one or more high-risk medical conditions (30). Influenza vaccine has been recommended for this entire age group to increase the low vaccination levels among persons in this age group with high-risk conditions (see Persons at Increased Risk for Complications). Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. Persons aged 50-64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics (31-34). Furthermore, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended (35,36).

Health-Care Workers and Other Persons Who Can Transmit Influenza to Those at High Risk

Persons who are clinically or asymptomatically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. In two studies, vaccination of health-care workers was associated with decreased deaths among nursing home patients (37,38), and hospital-based influenza outbreaks frequently occur where unvaccinated health-care workers are employed. Administration of LAIV has been demonstrated to reduce medically attended acute respiratory illness (MAARI) in contacts of vaccine recipients (39,40) and to reduce influenza like illness (ILI) -related economic and medical consequences (such as work days lost and number of health-care provider visits). In addition to health-care workers, additional groups that can transmit influenza to persons at high risk and that should be vaccinated include the following:

- employees of assisted living and other residences for persons in groups at high risk,
- persons who provide home care to persons in groups at high risk, and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged 0-23 months are at increased risk for influenza-related hospitalization (2,6,7), vaccination is recommended for their household contacts and out-of-home

caregivers, particularly for contacts of children aged 0-5 months, because influenza vaccines have not been approved by FDA for use among children aged <6 months (see Healthy Young Children Aged 6-59 Months).

Healthy persons aged 5-49 years in these groups who are not contacts of severely immunocompromised persons can receive either LAIV or inactivated influenza vaccine. All other persons in this group should receive inactivated influenza vaccine.

All health-care workers should be vaccinated against influenza annually (41-43). Facilities that employ health-care workers are strongly encouraged to provide vaccine to workers by using approaches that maximize vaccination levels. An improvement in vaccination coverage levels might help to protect health-care workers, their patients, and communities; improve prevention of influenza-associated disease and patient safety; and reduce disease burden. Influenza vaccination levels among health-care workers should be regularly measured and reported. Although vaccination levels for health-care workers are typically <40%, with moderate effort, organized campaigns can attain higher levels of vaccination among this population (44,45). In 2005, seven states had legislation requiring annual influenza vaccination of health-care workers or the signing of an informed declination (41), and 15 states had regulations regarding vaccination of health-care workers in long-term-care facilities (46). Physicians, nurses, and other workers in both hospital and outpatient-care settings, including medical emergency-response workers (e.g., paramedics and emergency medical technicians), should be vaccinated, as should employees of nursing home and chronic-care facilities who have contact with patients or residents.

Persons Infected with HIV

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection (47,48). However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases (49). Another study estimated that the risk for influenza-related death was 9.4-14.6/10,000 persons with acquired immunodeficiency syndrome (AIDS), compared with 0.09-0.10/10,000 among all persons aged 25-54 years and 6.4-7.0/10,000 among persons aged ≥65 years (50). Other reports indicate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons (51-53).

Vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high CD4+ T-lymphocyte cell

counts (54-57). A limited, randomized, placebo-controlled trial determined that inactivated influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza virus infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm^3; a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (58). A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (53). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, inactivated influenza vaccine might not induce protective antibody titers (56,57); a second dose of vaccine does not improve the immune response in these persons (57,58).

One case study determined that HIV RNA (ribonucleic acid) levels increased transiently in one HIV-infected person after influenza virus infection (59). Studies have demonstrated a transient (i.e., 2-4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (56,60). Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV (61-64). Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease has not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons (57,65). Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza virus infection or influenza vaccination (47,66). Because influenza can result in serious illness and because vaccination with inactivated influenza vaccine might result in the production of protective antibody titers, vaccination might benefit HIV-infected persons, including HIV-infected pregnant women. Therefore, influenza vaccination is recommended.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April-September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (e.g., on cruise ships) that include persons from areas of the world where influenza viruses are circulating (67,68). Persons at high risk for complications of influenza and who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- travel to the tropics,
- travel with organized tourist groups at any time of year, or
- travel to the Southern Hemisphere during April-September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated during the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine the following fall or winter. Persons aged ≥50 years and persons at high risk should consult with their health-care provider before embarking on travel during the summer to discuss the symptoms and risks for influenza and other travel-related diseases.

General Population

In addition to the groups for which annual influenza vaccination is recommended, vaccination providers should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected (the vaccine can be administered to children aged ≥6 months), depending on vaccine availability. A strategy of universal influenza vaccination is being assessed by ACIP.

Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics (69).

Inactivated Influenza Vaccine Recommendations

TIV Dosage

Dosage recommendations vary according to age group (Table 2). Among previously unvaccinated children aged 6 months-<9 years, 2 doses of inactivated vaccine administered ≥1 month apart are recommended for eliciting satisfactory antibody responses (70-73). If possible, the second dose should be administered before the onset of influenza season. If a child aged 6 months-<9 years receiving influenza vaccine for the first time does not receive a second dose of vaccine within the same season, only 1 dose of vaccine should be administered the following season. Two doses are not required at that time. ACIP does not recommend that a child receiving influenza vaccine for the first time be administered the first dose of vaccine in the spring as a priming dose for the following season (71,73).

Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (74-76). Even when the current influenza vaccine contains one or more antigens administered in previous years, annual vaccination with the vaccine is necessary because immunity declines during the year after vaccination (77,78). Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season (see Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine).

TIV Route

The intramuscular route is recommended for inactivated influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥1 inch should be considered for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (79).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh (80). ACIP recommends a needle length of 7/8-1 inch for children aged <12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8-1.25 inches is recommended (80).

TIV Side Effects and Adverse Reactions

When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza, and 2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

TIV Local Reactions

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts <2 days (34,81-83). These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities. One blinded, randomized, cross-over study among 1,952 adults and children with asthma demonstrated that only body aches were reported more frequently after inactivated influenza vaccine (25.1%) than placebo-injection (20.8%) (84). One study reported 20%-28% of children with asthma aged 9 months-18 years experienced local pain and swelling (85), and another study reported 23% of children aged 6 months-4 years with chronic heart or lung disease had local reactions (86). A different study reported no difference in local reactions among 53 children aged 6 months-6 years with high-risk medical conditions or among 305 healthy children aged 3-12 years in a placebo-controlled trial of inactivated influenza vaccine (87). In a study of 12 children aged 5-32 months, no substantial local or systemic reactions were noted (88). The interpretation of these findings should be made with caution given the small number of children studied.

TIV Systemic Reactions

Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination with inactivated vaccine and most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (89,90). These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (e.g.,

fever, malaise, myalgia, and headache) when compared with placebo injections (34,81-83).

In a randomized cross-over study among both children and adults with asthma, no increase in asthma exacerbations was reported for either age group (84). An analysis of 215,600 children aged <18 years and 8,476 children aged 6-23 months enrolled in one of five health maintenance organizations (HMOs) reported no increase in biologically plausible medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3-4 weeks before and after vaccination (91). In a study of 791 healthy children (92), postvaccination fever was noted among 11.5% of children aged 1-5 years, among 4.6% of children aged 6-10 years, and among 5.1% of children aged 11-15 years. Among children with high-risk medical conditions, one study of 52 children aged 6 months-4 years indicated that 27% had fever and 25% had irritability and insomnia (86); another study among 33 children aged 6-18 months indicated that one child had irritability and one had a fever and seizure after vaccination (93). No placebo comparison group was used in these studies.

A published review of the Vaccine Adverse Event Reporting System (VAERS) reports of TIV in children aged 6-23 months documented that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures. The majority of the small total number of reported seizures appeared to be febrile (94). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is usually not possible using VAERS data alone. A population-based study of TIV safety in children aged 6-23 months who were vaccinated during 1993-1999 indicated no vaccine-associated adverse events that had a plausible relationship to vaccination (95).

Health-care professionals should promptly report to VAERS all clinically significant adverse events after influenza vaccination, even if the health-care professional is not certain that the vaccine caused the event. The Institute of Medicine has specifically recommended reporting of potential neurologic complications (e.g., demyelinating disorders such as Guillain-Barré syndrome [GBS]), although no evidence exists of a causal relation between influenza vaccine and neurologic disorders in children.

Immediate, presumably allergic, reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination (96). These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue or who have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who

have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered (97-99). Persons with a history of severe hypersensitivity (e.g., anaphylaxis) to eggs should not receive influenza vaccine.

Hypersensitivity reactions to any vaccine component can occur theoretically. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (100,101). When reported, hypersensitivity to thimerosal usually has consisted of local, delayed hypersensitivity reactions (100).

Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician. Chemoprophylactic use of antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who also are at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components is located in package inserts from each manufacturer. Persons with moderate-to-severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine, particularly among children with mild upper-respiratory tract infection or allergic rhinitis.

References

1. Poehling KA, Edwards KM, Weinberg GA, et al. The Under-Recognized Burden of Influenza Illness in Young Children. N Engl J Med. In press 2006.

2. Neuzil KM, Wright PF, Mitchel EF Jr, et al. The burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr 2000;137:856-64.

3. Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004;113:1758-64.

4. Schrag SJ, Shay DK, Gershman K, et al. Multistate surveillance for laboratory-confirmed influenza-associated hospitalizations in children, 2003-2004. Pediatr Infect Dis J 2006;25:395-400.

5. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. Am Rev Respir Dis 1987;136:550-5.

6. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000;342:232-9.
7. Neuzil KM, Mellen BG, Wright PF, et al. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225-31.
8. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40.
9. Simonsen L, Fukuda K, Schonberger LB, et al. The impact of influenza epidemics on hospitalizations. J Infect Dis 2000;181:831-7.
10. Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. Am J Public Health 1982;72:1008-16.
11. Glezen WP, Decker M, Joseph SW, et al. Acute respiratory disease associated with influenza epidemics in Houston, 1981-1983. J Infect Dis 1987;155:1119-26.
12. Louie JK, Schechter R, Honarmand S, et al. Severe pediatric influenza in California, 2003--2005: Implications for immunization recommendations. Pediatrics 2006;117:610-8.
13. Cooney MK, Fox JP, Hall CE. The Seattle Virus Watch. VI. Observations of infections with and illness due to parainfluenza, mumps and respiratory syncytial viruses and Mycoplasma pneumoniae. Am J Epidemiol 1975;101:532-51.
14. Glezen WP, Taber LH, Frank AL, et al. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543-6.
15. Glezen WP. Morbidity associated with the major respiratory viruses. Pediatr Ann 1990;19:535-6, 538, 540, passim.
16. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40.
17. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis 2002;185:147-52.
18. Noble G. Epidemiological and clinical aspects of influenza. In: Beare AS, ed. Basic and applied influenza research. Boca Raton, FL: CRC Press; 1982:11-50.
19. Harris JW. Influenza occurring pregnant women: a statistical study of thirteen hundred and fifty cases. JAMA 1919;72:978-80.
20. Widelock D, Csizmas L, Klein S. Influenza, pregnancy, and fetal outcome. Public Health Rep 1963;78:1-11.
21. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol 1959;78:1172-5.
22. Shahab SZ, Glezen WP. Influenza virus. In: Gonik B, ed. Viral diseases in pregnancy. New York, NY: Springer-Verlag; 1994:215-23.
23. Schoenbaum SC, Weinstein L. Respiratory infection in pregnancy. Clin Obstet Gynecol 1979;22:293-300.
24. Kirshon B, Faro S, Zurawin RK, et al. Favorable outcome after treatment with amantadine and ribavirin in a pregnancy complicated by influenza pneumonia. A case report. J Reprod Med 1988;33:399-401.
25. Kort BA, Cefalo RC, Baker VV. Fatal influenza A pneumonia in pregnancy. Am J Perinatol 1986;3:179-82.
26. Irving WL, James DK, Stephenson T, et al. Influenza virus infection in the second

and third trimesters of pregnancy: a clinical and seroepidemiological study. BJOG 2000;107:1282-9.
27. Neuzil KM, Reed GW, Mitchel EF, et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094-102.
28. Heinonen OP, Shapiro S, Monson RR, et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol 1973;2:229-35.
29. Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol. 2005;192:1098-106.
30. O'Mara D, Fukuda K, Singleton JA. Influenza vaccine: ensuring timely and adequate supply. Infect Med 2003;20:548-54.
31. Wilde JA, McMillan JA, Serwint J, et al. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA 1999;281:908-13.
32. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995;333:889-93.
33. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy, working-age population. J Occup Environ Med 1997;39:408-14.
34. 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.
35. CDC. Assessing adult vaccination status at age 50 years. MMWR 1995;44:561-3.
36. Fedson DS. Adult immunization. Summary of the National Vaccine Advisory Committee Report. JAMA 1994;272:1133-7.
37. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis 1997;175:1-6.
38. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care personnel on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 2000;355(9198):93-7.
39. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. Vaccine 2005;23:1540-8.
40. King JC Jr, Cummings GE, Stoddard J, et al. A pilot study of the effectiveness of a school-based vaccination program. Pediatrics 2005;116:868-73.
41. Poland GA, Tosh P, Jacobson RM. Requiring influenza vaccination for health care workers: seven truths we must accept. Vaccine 2005;23:2251-5.
42. CDC. Influenza vaccination of healthcare personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-2).
43. Talbot TR, Bradley SF, Cosgrove SE, et al. SHEA Position Paper: Influenza vaccination of healthcare workers and vaccine allocation for health care workers during vaccine shortages. Infection Control and Hospital Epidemiology 2005;26:882-90.

44. National Foundation for Infectious Diseases. Call to action: influenza immunization among health-care personnel, 2003. Bethesda, MD: National Foundation for Infectious Diseases; 2003. Available at http://www.nfid.org.
45. CDC. Interventions to increase influenza vaccination of health-care workers — California and Minnesota. MMWR 2005;54:196-9.
46. Stewart A, Cox M, Rosenbaum S. The epidemiology of U.S. immunization law: immunization requirements for staff and residents of long-term care facilities under state laws/regulations. Available at http://www.gwumc.edu/sphhs/healthpolicy/immunization/EUSIL-LTC-report.pdf.
47. Couch RB. Influenza, influenza virus vaccine, and human immunodeficiency virus infection. Clin Infect Dis 1999;28:548-51.
48. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. Vaccine 1998;16:1039-42.
49. Neuzil KM, Reed GW, Mitchel EF Jr, et al. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA 1999;281:901-7.
50. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. Arch Intern Med 2001;161:441-6.
51. Safrin S, Rush JD, Mills J. Influenza in patients with human immunodeficiency virus infection. Chest 1990;98:33-7.
52. Radwan HM, Cheeseman SH, Lai KK, et al. Influenza in human immunodeficiency virus-infected patients during the 1997-1998 influenza season. Clin Infect Dis 2000;31:604-6.
53. Fine AD, Bridges CB, De Guzman AM, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. Clin Infect Dis 2001;32:1784-91.
54. Chadwick EG, Chang G, Decker MD, et al. Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children. Pediatr Infect Dis J 1994;13:206-11.
55. Huang KL, Ruben FL, Rinaldo CR Jr, et al. Antibody responses after influenza and pneumococcal immunization in HIV-infected homosexual men. JAMA 1987;257:2047-50.
56. Staprans SI, Hamilton BL, Follansbee SE, et al. Activation of virus replication after vaccination of HIV-1-infected individuals. J Exp Med 1995;182:1727-37.
57. Kroon FP, van Dissel JT, de Jong JC, et al. Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study. Vaccine 2000;18:3040-9.
58. Miotti PG, Nelson KE, Dallabetta GA, et al. The influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. JAMA 1989;262:779-83.
59. Ho DD. HIV-1 viraemia and influenza. Lancet 1992;339(8808):1549.
60. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. Human immunodeficiency virus-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. Blood 1995;86:1082-9.
61. Glesby MJ, Hoover DR, Farzadegan H, et al. The effect of influenza vaccination on

human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. J Infect Dis 1996;174:1332-6.
62. Fowke KR, D'Amico R, Chernoff DN, et al. Immunologic and virologic evaluation after influenza vaccination of HIV-1-infected patients. AIDS 1997;11:1013-21.
63. Fuller JD, Craven DE, Steger KA, et al. Influenza vaccination of human immunodeficiency virus (HIV)-infected adults: impact on plasma levels of HIV type 1 RNA and determinants of antibody response. Clin Infect Dis 1999;28:541-7.
64. Amendola A, Boschini A, Colzani D, et al. Influenza vaccination of HIV-1-positive and HIV-1-negative former intravenous drug users. J Med Virol 2001;65:644-8.
65. Sullivan PS, Hanson DL, Dworkin MS, et al. Effect of influenza vaccination on disease progression among HIV-infected persons. AIDS 2000;14:2781-5.
66. Gunthard HF, Wong JK, Spina CA, et al. Effect of influenza vaccination on viral replication and immune response in persons infected with human immunodeficiency virus receiving potent antiretroviral therapy. J Infect Dis 2000;181:522-31.
67. Miller JM, Tam TW, Maloney S, et al. Cruise ships: high-risk passengers and the global spread of new influenza viruses. Clin Infect Dis 2000;31:433-8.
68. Uyeki TM, Zane SB, Bodnar UR, et al. Large summertime influenza A outbreak among tourists in Alaska and the Yukon Territory. Clin Infect Dis 2003;36:1095-102.
69. Nichol KL, D'Heilly S, Ehlinger E. Colds and influenza-like illness in university students: impact on health, academic and work performance, and health care use. Clin Infect Dis 2005;40:1263-70.
70. Ritzwoller DP, Bridges CB, Sheetterly S, et al. Effectiveness of the 2003-04 influenza vaccine among children 6 months to 8 years for 1 versus 2 doses. Pediatrics 2005;116:153-9.
71. Neuzil KM, Dupont WD, Wright PF, et al. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J 2001;20:733-40.
72. Neuzil KM, Jackson LA, Nelson J, et al. Immunogenicity and reactogenicity of one versus two doses of trivalent inactivated influenza vaccine in vaccine-naïve 5-8-year-old children. J Infect Dis. In press 2006.
74. Gross PA, Weksler ME, Quinnan GV Jr, et al. Immunization of elderly people with two doses of influenza vaccine. J Clin Microbiol 1987;25:1763-5.
73. Englund JA, Walter EB, Fairchok MP, et al. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. Pediatrics 2005;115:1039-47.
75. Feery BJ, Cheyne IM, Hampson AW, et al. Antibody response to one and two doses of influenza virus subunit vaccine. Med J Aust 1976;1:186, 188-9.
76. Levine M, Beattie BL, McLean DM. Comparison of one- and two-dose regimens of influenza vaccine for elderly men. CMAJ 1987;137:722-6.
77. Cate TR, Couch RB, Parker D, et al. Reactogenicity, immunogenicity, and antibody persistence in adults given inactivated influenza virus vaccines--1978. Rev Infect Dis 1983;5:737-47.

78. Kunzel W, Glathe H, Engelmann H, et al. Kinetics of humoral antibody response to trivalent inactivated split influenza vaccine in subjects previously vaccinated or vaccinated for the first time. Vaccine 1996;14:1108-10.
79. Poland GA, Borrud A, Jacobson RM, et al. Determination of deltoid fat pad thickness. Implications for needle length in adult immunization. JAMA 1997;277:1709-11.
80. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(No. RR-2).
81. Govaert TM, Dinant GJ, Aretz K, et al. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ 1993;307:988-90.
82. Margolis KL, Nichol KL, Poland GA, et al. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. JAMA 1990;264:1139-41.
83. Nichol KL, Margolis KL, Lind A, et al. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo-controlled trial. Arch Intern Med 1996;156:1546-50.
84. American Lung Association Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. N Engl J Med 2001;345:1529-36.
85. Park CL, Frank AL, Sullivan M, et al. Influenza vaccination of children during acute asthma exacerbation and concurrent prednisone therapy. Pediatrics 1996;98(2 Pt 1):196-200.
86. Daubeney P, Taylor CJ, McGaw J, et al. Immunogenicity and tolerability of a trivalent influenza subunit vaccine (Influvac) in high-risk children aged 6 months to 4 years. Br J Clin Pract 1997;51:87-90.
87. Wright PF, Thompson J, Vaughn WK, et al. Trials of influenza A/New Jersey/76 virus vaccine in normal children: an overview of age-related antigenicity and reactogenicity. J Infect Dis 1977;136(Suppl):S731-41.
88. Piedra PA, Glezen WP, Mbawuike I, et al. Studies on reactogenicity and immunogenicity of attenuated bivalent cold recombinant influenza type A (CRA) and inactivated trivalent influenza virus (TI) vaccines in infants and young children. Vaccine 1993;11:718-24.
89. Scheifele DW, Bjornson G, Johnston J. Evaluation of adverse events after influenza vaccination in hospital personnel. CMAJ 1990;142:127-30.
90. Barry DW, Mayner RE, Hochstein HD, et al. Comparative trial of influenza vaccines. II. Adverse reactions in children and adults. Am J Epidemiol 1976;104:47-59.
91. France EK, Jackson L, Vaccine Safety Datalink Team. Safety of the trivalent inactivated influenza vaccine among children: a population-based study [Abstract 76]. Presented at the National Immunization Conference, Chicago, Illinois; 2003.
92. Shuler C, Iwamoto M, Neeman R, et al. Influenza vaccine effectiveness against laboratory-confirmed influenza among children age 6 to 59 Months--Georgia, 2003-2004 [Poster #1008]. Presented at the 43rd Annual Meeting of the Infectious

Diseases Society of America, San Francisco, CA; 2005.

93. Groothuis JR, Levin MJ, Rabalais GP, et al. Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. Pediatrics 1991;87:823-8.

94. McMahon AW, Iskander J, Haber P, et al. Adverse events after inactivated influenza vaccination among children less than 2 years of age: analysis of reports from the vaccine adverse event reporting system, 1990-2003. Pediatrics 2005;115:453-60.

95. France EK, Glanz JM, Xu S, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. Arch Pediatr Adolesc Med 2004;158:1031-6.

96. Bierman CW, Shapiro GG, Pierson WE, et al. Safety of influenza vaccination in allergic children. J Infect Dis 1977;136(Suppl):S652-5.

97. James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. J Pediatr 1998;133:624-8.

98. Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. J Pediatr 1985;106:931-3.

99. Zeiger RS. Current issues with influenza vaccination in egg allergy. J Allergy Clin Immunol 2002;110:834-40.

100. Aberer W. Vaccination despite thimerosal sensitivity. Contact Dermatitis 1991;24:6-10.

101. Kirkland LR. Ocular sensitivity to thimerosal: a problem with hepatitis B vaccine? South Med J 1990;83:497-9.

BOX. Persons for whom annual vaccination is recommended

- Children aged 6–59 months;
- Women who will be pregnant during the influenza season;
- Persons aged ≥50 years;
- Children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza infection;
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- 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, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by human immunodeficiency virus);
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions, or that can increase the risk for aspiration;
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- Persons who live with or care for persons at high risk for influenza-related complications, including healthy household contacts and caregivers of children aged 0–59 months; and
- Health-care workers.

TABLE 1. Estimated rates of influenza-associated hospitalization, by age group and risk group for selected studies* — United States

Study years	Population	Age group	Hospitalizations/ 100,000 persons with high-risk conditions	Hospitalizations/ 100,000 persons without high-risk conditions
1973–1993†§¶	Tennessee Medicaid	0–11 mos	1,900	496–1,038**
		1–2 yrs	800	186
		3–4 yrs	320	86
		5–14 yrs	92	41
1992–1997††§§	Two health maintenance organizations	0–23 mos		144–187
		2–4 yrs		0–25
		5–17 yrs		8–12
1968–1969	Health maintenance organization	15–44 yrs	56–110	23–25
1970–1971		45–64 yrs	392–635	13–23
1972–1973¶¶***		≥65 yrs	399–518	—
1969–1995***†††	National Hospital Discharge Data	<65 yrs	—	20–42§§§¶¶¶
1969–1995***†††		≥65 yrs	—	125–228¶¶¶
1979–2001****††††	National Hospital Discharge Data	All ages	—	88§§§§

* Rates were estimated in years and populations with low vaccination levels. Hospitalization rates can be expected to decrease as vaccination levels increase. Vaccination can be expected to reduce influenza-related hospitalizations by 30%–70% among older persons and likely by even higher percentages among younger age groups when vaccine and circulating influenza virus strains are antigenically similar.

† **Source:** Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. Effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225–31.

§ Outcomes were for acute cardiac or pulmonary conditions.

¶ **Source:** Neuzil KM, Wright PF, Mitchel EF, Griffin MR. Burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr 2000;137:856–64.

** The low estimate is for infants aged 6–11 months, and the high estimate is for infants aged 0–5 months.

†† **Source:** Izurieta HA, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000;342:232–9.

§§ Outcomes were for acute pulmonary conditions. Influenza-attributable hospitalization rates for children at high risk were not included in this study.

¶¶ **Source:** Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 1980;112:798–811.

*** Outcomes were limited to hospitalizations in which either pneumonia or influenza was listed as the first condition on discharge records (Simonsen) or included anywhere in the list of discharge diagnoses (Barker).

††† **Source:** Simonsen L, Fukuda K, Schonberger LB, Cox NJ. Impact of influenza epidemics on hospitalizations. J Infect Dis 2000;181:831–7.

§§§ Persons at high risk and not at high risk for influenza-related complications are combined.

¶¶¶ The low estimate is the average during influenza A (H1N1) or influenza B-predominant seasons, and the high estimate is the average during influenza A (H3N2)-predominant seasons.

**** Outcomes were for rate of primary respiratory and circulatory hospitalizations.

†††† **Source:** Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333–40.

§§§§ Rate for all ages of persons, both with and without high-risk conditions.

TABLE 2. Approved influenza vaccines for different age groups — United States, 2006–07 season

Vaccine*	Trade name	Manufacturer	Dose/ Presentation	Thimerosal mercury content (mcg Hg/0.5-mL dose)	Age group	No. of doses	Route
Inactivated							
TIV	Fluzone®	sanofi pasteur	0.25-mL prefilled syringe	0	6–35 mos	1 or 2†	Intramuscular§
			0.5-mL prefilled syringe	0	≥36 mos	1 or 2†	Intramuscular§
			0.5-mL vial	0	≥36 mos	1 or 2†	Intramuscular§
			5.0-mL multi-dose vial	25	≥6 mos	1 or 2†	Intramuscular§
TIV	Fluvirin™	Novartis Vaccine (formerly Chiron Corporation)	0.5-mL prefilled syringe	<1.0	≥4 yrs	1 or 2†	Intramuscular§
			5.0-mL multi-dose vial	24.5	≥4 yrs	1 or 2†	Intramuscular§
TIV	FLUARIX™	GlaxoSmithKline	0.5-mL prefilled syringe	<1.0	≥18 yrs	1	Intramuscular§
Live, attenuated							
LAIV	FluMist™	MedImmune	0.5-mL sprayer	0	5–49 yrs	1 or 2¶	Intranasal**

* A 0.5-mL dose contains 15 mcg each of A/New Caledonia/20/1999 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens. For the A/Wisconsin/67/2005 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/Hiroshima/52/2005 virus, and for the B/Malaysia/2506/2004-like antigen, manufacturers may use the antigenically equivalent B/Ohio/1/2005 virus.

† Two doses administered at least 1 month apart are recommended for children aged 6 months–<9 years who are receiving influenza vaccine for the first time.

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

¶ Two doses administered at least 6 weeks apart are recommended for children aged 5–<9 years who are receiving influenza vaccine for the first time.

** One dose equals 0.5 mL, divided equally between each nostril.

適応評価分野（第３分野）

厚生労働科学研究費補助金（新興・再興感染症研究事業）
分担研究報告書

65歳以上高齢者における肺炎球菌ワクチン接種の臨床経済的分析

分担研究者　大久保一郎　筑波大学人間総合科学研究科教授
研究協力者　星　淑玲　筑波大学博士課程人間総合科学研究科
分担研究者　小島原　典子　東京女子医大衛生学・公衆衛生第2講座講師

研究要旨

抗菌剤の開発が目覚ましい今日においても肺炎による入院や死亡は毎年世界各国で多数報告されている。肺炎の起因菌は様々あるが、なかでも肺炎球菌による肺炎が市中肺炎の約30-50%と報告されている。これまで、肺炎球菌による疾患の治療にペニシリン系抗生物質が使われてきたが、抗生物質耐性の肺炎球菌の増加で治療が難しくなってきた。一部の欧米諸国では侵襲性肺炎球菌感染症の予防を目的に、65歳以上高齢者の肺炎球菌ワクチンの無料接種を導入した。

わが国における肺炎の諸相は欧米諸国と同様であるため、近年、一部の地方自治体が高齢者に対する一部公費負担の接種プログラムを実施し始めた。こうした背景を踏まえて、本研究は、わが国における高齢者に対する肺炎球菌ワクチンの費用対効果分析を行った。

A. 研究目的

抗菌剤の開発が目覚ましい今日においても肺炎による入院や死亡は毎年世界各国で多数報告されている[1-5]。肺炎の起因菌は様々あるが、なかでも肺炎球菌による肺炎が市中肺炎の約30-50%と報告されている[1-5]。肺炎球菌は肺以外にも、血液、髄液、関節内腔などに侵入し、侵襲性肺炎球菌感染症（invasive pneumococcal disease、以下IPDとする）になる場合がある[1-3]。IPDになると症状が重篤化し、死に至る確率が高くなる[1-3]。これまで、肺炎球菌による疾患の治療にペニシリン系抗生物質が使われてきたが、抗生物質耐性の肺炎球菌の増加で治療が難しくなってきたため、ワクチンによる予防が注目される様になってきた[1-3]。近年では、IPDの予防を目的として、いち早く65歳以上高齢者の無料接種を導入した米国[3]に加え、カナダ[6]、オーストラリア[7]およびイギリス[8]などの国も65歳以上高齢者を対象に公的接種プログラムの実施を始めた。

一方、わが国では、肺炎は死亡原因の第4位を占めており、死亡者の95%以上が65歳以上の高齢者である[9]。わが国における肺炎の諸相、例えば、社会的負担の度合い、または市中肺炎の中の肺炎球菌性肺炎が起因の割合、更にペニシリン耐性肺炎球菌（PRSP）の増加による治療抵抗性の状況などは欧米諸国と同様である[1-2]。これらのことから、近年、高齢者に対する一部公費負担の接種プログラムの実施を始めた地方自治体もある[10]。

肺炎球菌ワクチンが注目されていることを背景に、本研究は、65から79歳までの高齢者に対する肺炎球菌ワクチン予防接種の費用効果分析を行うことにした。この結果は現在、盛んに論議されている高齢者への肺炎球菌ワクチンの効率的な接種を考える上で有用であろう。