National Consensus on Geriatric Immunization 2011

The Indonesian Society of Medical Gerontology

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ABSTRACT

As the growth of elderly population increases, the number of geriatric patients who may demand health care services is also increasing since the elderly are more vulnerable to various conditions of acute illnesses. Upper respiratory tract infections are the leading cause of death and the most significant cause that impairs quality of life in the elderly. Upper respiratory tract infections and influenza are common in the elderly and may develop into pneumonia.

Considering the high morbidity and mortality rates related to pneumonia in the elderly, it is important to have prevention strategies. A delay in diagnosis due to non-specific signs and symptoms of pneumonia in the elderly has demanded greater concern on the importance of pneumonia prevention strategies. Influenza and pneumonia impair quality of life in the elderly, resulted in decreased functional status (ADL scores) during infection and recovery period. With increasing antibiotic resistance, the management may be complicated as it may lead to conditions that reduce quality of life and cause high mortality rate. Therefore, immunization is very important as the prevention strategy against influenza and or pneumonia, reducing the incidence as well as the complication.

The consensus has been made in order to provide immunization against influenza and pneumonia for elderly population in Indonesia. It is expected that by 2025, about 60% of the elderly in Indonesia would have immunization against influenza and 50% of them would have immunization against pneumonia annually.

Key words: vaccination, virus, influenza, pneumonia, elderly.
INTRODUCTION

The number of elderly population in Indonesia is increasing and it will reach the highest acceleration in the world by 2020, i.e. 41.4% compared with the rate in 1996. By the year 2025, there will be 25.5 million octogenarians because of longer life expectancy and increasing number of older people in society. Increasing number of the elderly will be followed by greater number of geriatric patients who may demand health care services as they are more vulnerable to various conditions of acute illness. One of the illnesses includes respiratory tract infection, which is the leading cause of death and the most significant cause that impairs quality of life in the elderly.

The elderly is more vulnerable to infection as they own impaired physiological immune system and reduced lung function, i.e. suppression of the cough reflex and decreased function of mucocilliary epithelial in the respiratory tract; therefore, the risk of pneumonia in the elderly increases. Decreased cell-mediated immunity as shown by increasing anergic reaction, slower response of lymphocyte proliferation, as well as reduced function of helper T-cells and B- lymphocytes in the elderly will cause lower immune response against infections.

Upper respiratory tract infections and influenza are common in the elderly and may develop into pneumonia. The prevalence of influenza may reach 5-20% of population each year along with high mortality rate, especially among neonates and the elderly population. Therefore, vaccination may become a primary prevention strategy against the death and complication in the elderly.

In 2003, the mortality rate related to pneumonia is still as high as 30.3% of all hospitalized elderly patients. In 2000, a proportion of 54% hospitalization and 90% of death in the elderly over 65 years in the United States were caused by pneumonia. Until 2002, many elderly patients have died from pneumonia (200 out of 100,000 elderly).

Considering the high morbidity and mortality rates related to pneumonia in the elderly, it is important to have prevention strategies. A delay in diagnosis due to non-specific signs and symptoms of pneumonia in the elderly has demanded greater concern on the importance of pneumonia prevention strategies. Influenza and pneumonia may also impair quality of life in the elderly, resulted in decreased functional status (ADL scores) during infection and recovery period. With increasing antibiotic resistance, the management may be complicated as it may lead to conditions that reduce quality of life and cause high mortality rate. Therefore, immunization is very important as the prevention strategy against influenza and or pneumonia, reducing the incidence as well as the complication. The elderly in nursing home shall need greater special attention.

The consensus has been made in order to provide immunization against influenza and pneumonia for elderly population in Indonesia. It is expected that by 2025, about 60% of the elderly in Indonesia would have immunization against influenza and 50% of them would have immunization against pneumonia annually.

INFLUENZA IN ELDERLY

Influenza is acute upper respiratory tract infection, which may be caused by influenza virus, parainfluenza virus, adenovirus and respiratory syncytial virus (RSV). During seasonal epidemics or the rainy season, most cases are caused by influenza virus. The Flu Pandemic with extremely high death rate worldwide occurred in 1918. In Asia, there were reports on very high mortality rates in Iran, Indonesia and Singapore; it was estimated that approximately 3 million people died. At that time, approximately 114,000 (out of 3,250,000 people) in Madagascar died from influenza outbreak. The second pandemic (influenza virus A/H2N2) (1957) resulted in a sharp increase of death rate. In Europe, it reached 30% of population; while in Costa Rica and India, it affected 68% and 19% of population, respectively. The influenza virus A/H3N2 (1968-1969) also causes high morbidity and mortality rate around the world. The Asian reports indicated that 8.4% of total population in Madras, India had been infected by the disease, which was developed through the entry to sea harbor.

Influenza virus is a virus belonging to the family Orthomyxoviridae of RNA viruses. The structure of virus consists of a nucleus made of ribonucleic protein (to form helical structure of nucleocapsid) and covered by lipid and glycoprotein coat. Each virion contains 8 RNA molecules that accounts for encoding...
the synthesis of 10 different types of proteins. Among those are two glycoprotein expressed on the surface of virus particle, i.e. hemagglutinin and neuraminidase. Hemagglutinin, the antibody target of the available vaccine, has a role in attaching virus particle to neuraminic acid mucopolysaccharide (sialic acid) on the surface of respiratory epithelium. The location is a very important site of viral penetration and replication.

After the virus particle successfully penetrates into epithelium and the replication takes place, a new virion will be expressed on the surface of epithelial cells and bound to sialic acid. Neuroamidase, which is the target of antiviral agents, the anuroamidase inhibitors, subsequently breaks the bond between neuraminic acid and hemagglutinin resulting in the release of virion from epithelial cells and cause further infection to other epithelial cells.

M2 protein, which is unique to influenza virus A, is the active site that interact with M2 inhibitor agents such as amantadine, loratadin and rimantadin. It is the site where the virus replication is stopped.

Influenza viruses are classified into type A, B and C. Type C is non-virulent. Type B particularly causes infection in children and it has antigenic stability; therefore most adults, including the elderly, are not susceptible to the virus.

Type A influenza viruses attack people of all ages and easily alter its antigenic properties, either on the hemagglutinin or neuramidase site. The altered antigenic properties may appear as antigenic drift (due to nucleotide substitution) or antigenic shift (due to genetic recombination with other type A influenza viruses). The abovementioned antigenic change causes the virus remains undetected by immune response, both by memory T cell or antibody (immunoglobulin). Therefore, vaccination of one strain of type A influenza will not provide protection against other strain. Until now, there are three influenza A virus subtypes (strain), i.e. H1N1 strain (that cause the 1918 flu pandemic or Spanish influenza), H2N2 strain (the cause the pandemic of 1957) and H3N2 strain (that currently cause significant morbidity and mortality rate). Moreover, the strain of type B influenza viruses, both B/Victoria/2/87 and B/Yamagata/16/88 lineages are circulating strains in the environment.

For vaccination, WHO recommends two influenza type A subtypes (H1N1 and H3N2 strain) and one influenza type B subtype. The recommended vaccine composition for the 2008-2009 Northern Hemisphere (November 2008 – April 2009) and the 2008-2009 Southern Hemisphere (May – October 2009) influenza season includes the A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2)-like virus and B/Florida/4/2006-like virus.

Current data demonstrates that WHO recommend vaccine composition for northern hemisphere region in 2009, which begins in November 2009 to April 2010, i.e. A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2)-like virus, and B/Brisbane/60/2008 virus. The B/Malaysia/2506/2006 virus, B/Florida/4/2006 or B/Brisbane/60/2008 which is in the vaccine that now available in Indonesia were one of strain B/Victoria/2/87. Both the B/Malaysia/2506/2006 and B/Florida/4/2006, which is available vaccine in Indonesia, are of the B/Victoria/2/87 lineage.

**Epidemiology**

Type A influenza viruses have two patterns of spread. The first pattern is epidemics in certain geographical area during rainy/winter season, which occurs for several weeks. The second pattern has pandemic characteristic (occurs whole year round) and usually caused by virus that undergoes antigenic shift. Recognized host are pets and domestic animals (including birds) because of its closeness with human habitat, which highly facilitate genetic recombination resulting in genetic shift. The pandemic often occurs in Asian countries.

Documenting the morbidity, mortality and the impact of influenza is not easy; especially in tropical countries where the rainy season does not begin at fixed date like in subtropical countries. Data documentation in pandemic countries (such as Asia) is difficult because of the closeness with human habitat, which highly facilitate genetic recombination resulting in genetic shift. The pandemic often occurs in Asian countries.
influenza of certain period and the incidence of other period of time is the common method that has been utilized. In 2003, 82% of influenza outbreak in Thailand was dominated by H3N2 strain. In Indonesia, national data on the incidence of influenza has not been established. Hospital documentations and medical reports in the year of 2000 indicated that influenza was one of the top 10-common illnesses in Indonesia. National Health Survey 2001 demonstrated that upper respiratory tract infection was the third most common disease (24%) in Indonesia. About 97% of influenza outbreaks were caused by H3N2 strain. The prevalence of influenza may reach 5-20% of population each year along with high mortality rate, especially among neonates and the elderly population. In the population over 50 years of age, the mortality rate is increasing with age.

It has been reported that viral resistances to amantadine (when used for prophylaxis) were 76%, 27%, and 36% in 2005, 2006 and 2007, respectively. Amantadine resistance of H3N2 reached 99% in 2007-2008. The resistance to neuraminidase inhibitors used for influenza prophylaxis has also been reported; therefore, the use of both amantadine and neuraminidase for prophylaxis are not recommended. Initial spread begins through viral transmission of secreted droplet in the infected respiratory tract, with incubation period ranges from 1-5 days, before it becomes symptomatic after the average 2 days of incubation period. The first symptoms in the elderly usually are loss of appetite, weakness, fatigue, and malaise. Other symptoms may include symptoms of acute respiratory tract infection such as fever, myalgia, and headache. The fever may be extremely high and last for at least three days. Muscle pain may predominate in extremities, orbital area, and the trunk. The symptoms may be exaggerated by cough (initially appears as a non-productive cough), sore throat and coryza. On physical examination, the elderly will appear severely ill, had redness of the conjunctiva and sometimes accompanied with lymph node enlargement around neck (with tenderness); clear nasal secret (except when superimposed with bacterial/ secondary infection).

Complication

Respiratory tract hyperreactivity and pneumonia are the common complication of influenza. Signs and symptoms (usually appear 5-7 days after the initial symptoms) are worsened cough, dyspnea with wheezing, and unresolved fever along with productive purulent phlegm. It will result in reduced functional status, prolonged recovery time (post-influenza asthenia) with high dependency rate, or even sepsis and death. The manifested non-specific signs and symptoms (delirium syndrome, postural instability and fall) may cause further complication of influenza in the elderly. Microorganisms that may cause pneumonia as complication of influenza are opportunistic bacteria such as Streptococcus pneumonia, Haemophilus influenzae andStaphylococcus species. Although it is uncommon, other complications such as rhabdomyolysis, myoglobinuria, myocarditis, and pericarditis with tamponade may also occur.

Influenza complication in geriatric patient usually will also affect the patient’s dependency level. Barker et al (2004) reported that there was decreased ADL (activities of daily living) capacity in geriatric patient with type A influenza or respiratory syncytial virus infection. Dependency in taking a bath, mobility, performing household activity and personal drug management were increased from 25 to 31%; 7 to 11%; 18 to 26%; and from 3 to 12%, respectively. Comorbidity and reduced functional capacity of all body systems in the elderly with influenza infection will exaggerate their general condition resulting in weakness (which may include immobility and deconditioning). Immobility in the elderly due to infection will cause decreased mucus secretion, ineffective cilia movement, and inefficient cough mechanism, which may deteriorate the respiratory infection.

Complication of influenza in the elderly is more likely to be developed in patients with comorbidities such as diabetes, COPD (chronic obstructive pulmonary disease), bronchiectasis and coronary heart disease. Older age and poor oral hygiene are other important factors that may induce complications.

PNEUMONIA IN ELDERLY

Pneumonia Epidemiology

Until now, pneumonia is the leading cause of death in hospitalized geriatric patient. The prevalence of pneumonia at acute geriatric ward of Cipto Mangunkusumo Hospital in 2000 was
54.8% with mortality rate reached 32.5%. In 2001, the prevalence increased to 61.6% with mortality rate of 32.9%. In 2003, the prevalence of pneumonia in geriatric patients decreased into 52.2%, with mortality rate that remained high of 30.3%. In 2000, a proportion of 54% hospitalization and 90% of death in the elderly over 65 years in the United States were caused by pneumonia. Until 2002, many elderly patients have died from pneumonia (200 out of 100,000 elderly). In 1998, Niederman in New York reported community data that the death rate related to pneumonia in elderly patients was 9 out of 100,000 people (without comorbidity) and the death rate may increase into 217 patients out of 100,000 elderly people when there were 3 comorbidities.

Pneumococcal resistance to antibiotic is one of the other important issues. Parsons (2002) reported that the incidence of pneumococcal resistance to penicillin varied from country to country: Spain 65.6% (1999-2000), United States 23% (1998), England 9% (1998), and Australia 9% (1994). The resistance contributes to high mortality rate and the development of complications related to pneumonia such as meningitis and sepsis (invasive pneumococcal pneumonia = IPD). In Europe and United States, the incidence of invasive pneumococcal disease ranges between 25 and 100 per 100,000 cases with the highest age-specific incidence rate in the elderly. Mortality rate related to IPD may reach 40% in patients aged >85 years and 20% in patients aged >65 years. The issue of antimicrobial resistance apparently may not only restricted to penicillin, but also to other antimicrobial agents such as macrolides, chloramphenicol, trimetoprim-sulfametoxazol, and cephalosporin.

The transmission of pneumonia in the elderly patients is similar to the young adults. However, several aspects need to be concerned. First, oropharynx is the common site of microbial colonization that may increase the risk for pneumonia. Malnutrition, poor oral and dental hygiene also contribute as risk factors for recurrent pneumonia.

The elderly who lives in nursing home will carry greater probability to get pneumonia. It may occur since there is higher microbial density in the population and most of inhabitants are more vulnerable compared to those who live with their family in the community. Therefore, pneumococcal vaccination for the elderly is one of the prevention strategies recommended by WHO, CDCP and JVCI since 2003 up to now.

**Clinical Course**

Initial symptoms of pneumonia in the elderly are not specific. The common constitutional symptoms are weakness, loss of appetite and no eagerness to do activities. Frequently the families who live with them, or even the patient, do not realize that the infection has begun, which would developed into worse condition. The classic signs of cough and dyspnea with fever are hardly found, but it may be present. Patients are usually admitted to hospital due to fall, unconsciousness or exaggerated dyspnea. The non-specific clinical manifestations in elderly patients with pneumonia may lead to a delay in diagnosis, which may be misdiagnosed, resulting in unsatisfactory outcome.

Physical examination may reveal acute confusional state or delirium syndrome. Mild fever or even mild hypothermia may occur. It is not uncommon to find patients admitted to hospital without any fever. Tachypnea and altered consciousness may also be found. Auscultation examination may reveal rales or wheezing.

**Complication**

The aforementioned discussion has indicated that a delayed diagnosis or misdiagnosis of pneumonia in elderly patients is commonly occurs that may result in unsatisfactory outcomes. In many cases, the patient may experience various complications including respiratory failure, respiratory acidosis, sepsis and even death. Nevertheless, when the patient has managed to overcome the acute phase, the healing process may be prolonged causing high medical and hospitalization cost. Moreover, the patients usually have impaired functional state, which cause great dependency upon other people or having high dependency level to perform their activities of daily living.

As have been mentioned before, pneumonia in geriatric patients often has clinical presentation of postural instability, which may cause fall. Femoral fracture, immobilization, incontinence, contracture, decubitus and sepsis are conditions commonly found in geriatric patients with pneumonia. Such conditions may lead to impaired quality of life in the elderly patients.
INFLUENZA VACCINATION

Benefit

The vaccination is directed especially for high risk groups such as the elderly, who lives in the community or nursing homes and patients with chronic disease. The benefit of influenza vaccinations may be considered as medical and economic advantages. Medical advantages include lesser incidence of influenza complication (such as pneumonia), lower incidence of hospitalization due to respiratory tract infection and other diseases related to it and reduced hospital mortality rate related to respiratory tract infection. Economic advantages may be evaluated based on the lesser expense as a result of vaccination, including reduced hospitalization cost as well as reduced treatment cost in the outpatient unit. Various studies have demonstrated the benefit of immunization in decreasing morbidity and mortality.

Influenza vaccination can significantly decrease morbidity rate (the hospitalization rate related to pneumonia and influenza per 1000 elderly population are 4.8 vs 5.7 \( p < 0.02 \)) and reduce mortality rate (the mortality rate per 1000 elderly population are 3.4 vs 5.4 \( p < 0.001 \)) after controlled trials (controlled age, sex, comorbidity and previous access to health care provider).

A study in 1898 elderly patients with chronic pulmonary diseases reported that influenza vaccination has relatively good effect on outpatients rate (OR 0.64) and hospitalization rate (OR 0.48). The study also provided evidences that immunization may reduce mortality rate (OR 0.3) after demographic factors and comorbidities had been controlled. Similar result has also been demonstrated by Ikematsu et al (October 1999), who reported that influenza vaccination do not need booster injection on concurrent month since there was no significant benefit compared to once a year immunization. Voordouw et al. found that the first vaccination lowered mortality risk as much as 10% and revaccination in the following year will decrease mortality risk of 24%. Voordouw et al. found that the first vaccination lowered mortality risk as much as 10% and revaccination in the following year will decrease mortality risk of 24%.

Regarding the medical cost savings, Nichol et al (2003) reported that influenza vaccination may also lower the incidence of hospitalization caused by chronic respiratory disorder, heart failure, and stroke. Nichol et al (2003) reported that influenza vaccination
lowered morbidity rate of heart disease, CVD and pneumonia+influenza as much as 19%, 23% and 32%, respectively (p<0.001) and also reduced death from various causes as much as 50% (p < 0.001) after controlling the demographic characteristics and comorbidities (lung disease, stroke, diabetes, renal disease, rheumatism, vasculitis, malignancy, dementia, hypertension, atrial fibrillation and dyslipidemia).37

The result has also been supported by recent study conducted by Christenson in 2008, which reported that the incidence of hospitalization per 100,000 patients with heart failure has decreased as much as 62% (p<0.01) in elderly patients following the influenza vaccination. The elderly who had received influenza vaccination showed lower percentage of hospitalization due to heart failure compared to the elderly who got influenza and pneumonia vaccination. The incidence of hospitalization related to pneumonia has also decreased in the elderly who had only received influenza vaccination (49% decrease in pandemic season and 63% in non-pandemic season [p<0.001]).33

Although it was assumed that with increasing age, influenza vaccination in patients aged >80 years would not be as effective as vaccination in patients aged 65–79 years, but a study by Nichol (2004) in more than 567,000 subjects has found comparable effectiveness in both groups during influenza season in the year of 1996-1997, 1997 – 1998, 1998 – 1999, 1999 – 2000 (OR of influenza in patients aged 65-74 years were [0.44; 0.62; 0.58; and 0.61], respectively and OR in patients aged > 85 years were [0.40; 0.63; 0.48; and 0.51]).39

Similar study has also been reported by Wongsurakiat et al in Thailand (2004), where the incidence of upper respiratory tract infection related to influenza in 125 elderly with COPD was 6.8 per 100 people each year compared to the control group (28.1 per 100 people each year) (Relative Risk [RR] 0.24 [p<0.005]; vaccine effectiveness 76%).40 Similar effectiveness has also been reported in the interventional prospective study conducted by Chen et al in Taiwan (2004).41 The death rate per 100,000 elderly people due to chronic bronchitis, emphysema and asthma has been reduced from 93.62 in 1997 into 65.87 in 2002. It is consistent with the influenza immunization program, which has been implemented since 1997 until now.

There was a study providing evidences on effectiveness bias of influenza vaccination. It demonstrated lower mortality risk during the period prior to influenza season (RR = 0.39) and higher risk after the influenza season (RR=0.74), compared to the risk during the influenza season (RR=0.56).41 However, the study was comparing non-specific final result; thus, it has not been clear whether the working diagnosis was really caused by influenza virus or by other pathogen that may reduce the effectiveness and efficacy of vaccination (CDC MMWR 2008). It should be noted that difference on virus strains between those available in environment and virus strain contained in the vaccine during the given period may affect the efficacy and effectiveness of the vaccine. Center for Disease Control (CDC) also stated that the incidence of infection in the elderly is affected by the impaired immune response against the vaccination itself due to aging rather than incapacity of the vaccine in providing protection against influenza. The fact is supported by Skowronski et al who conducted review on various literatures and they concluded that there was no compelling evidence to support more rapid decline of the greater impairment of immunity in the elderly.42

The only double-blind controlled trial in the elderly of the community reported that efficacy of influenza prevention reached 58% when the vaccine and circulating virus strains were well-matched.43 However, the efficacy might be lower among those with older age (over 70 years). The vaccine effectiveness against respiratory infection in the elderly who lived in the nursing home reached 20-40%,44,45 and it might be not significant if the circulating and vaccine virus strains were different.46,47 Some studies have provided evidences on the effectiveness against death due to influenza as high as 80%.7

WHO reported reduced hospitalization rate up to 39% and decreased mortality rate of 39-75% in the elderly who lived in the community following the influenza vaccination. Hospitalization rate for elderly in nursing homes has also significantly reduced up to 50%.20 Crutchfeld (2001), reported that since WHO (World Health Organization) has published the recommendation of vaccination for elderly, the influenza immunization coverage in the United States is only about 58.5%. Therefore, in 2002, CDC (Center for Disease Control and Prevention)
and CMS (Center for Medicare and Medicaid Services) has issued an investigation protocol to increase influenza immunization coverage, with the target of 90% coverage by 2010. The protocol has become a standard health service in prevention strategies against influenza and pneumonia and a standard quality of health professional services.6,48

Until now, influenza vaccination has been extensively used in more than 50 developed and developing countries. One year following WHO recommendation on influenza vaccination for the elderly in 2000, there has been more than 350 doses of vaccine per 1000 elderly population in Canada. It is followed by the United States, where the vaccine reached 256 doses per 1000 elderly population, and Australia as well as Western European countries with 183-197 doses per 1000 elderly population. Korea and Japan have provided 147 and 109 vaccination doses per 1000 elderly population, respectively. Other Asian countries which already implemented the immunization program for elderly are: Taiwan, Lebanon, Hong Kong, Singapore and Un Arabi Arabian Emirates.49

**Table 1** contains a compilation of various studies conducted since 2001 that shows the benefit of influenza immunization.

**Risk**

Local side effects, which are found in less than one-third of cases, may present as local pain that usually will be alleviated in 2-3 days without any specific medication. Systemic side effects that may occur are fever, malaise, headache, myalgia, arthralgia, which may last for 6-12 hours following the vaccination and will be resolved in one to two days.

Individuals who have had allergic responses to egg protein may experience hypersensitivity reaction; therefore those who were allergic to eggs should not receive influenza vaccine (CDCP, 2004).

Chen (2004) reported that among 1,250,053 elderly subjects who had been vaccinated in 2002, 7.1% of them reported side effect of restlessness (fatigue). While the side effects of local pain and headache were reported of 4.9% and 4%, respectively. The side effects are temporary and will be resolved without any specific therapy.

<table>
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<th>Author (year)</th>
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<th>p/CI</th>
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<tr>
<td></td>
<td>n = 100.242 elderly</td>
<td>influenza vaccinated group ↓46%</td>
<td>Cl : 24;34</td>
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<td></td>
<td></td>
<td>pneumonia vaccinated group ↓29%</td>
<td>Cl : 3;58</td>
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<td></td>
<td></td>
<td>Incidence of pneumonia complication ↓36%</td>
<td>Cl : 1;77</td>
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<td></td>
<td></td>
<td>Invasive pneumococcal disease ↓52%</td>
<td>Cl : 55;60</td>
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<tr>
<td></td>
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<td>Total death in the group receiving immunization ↓57%</td>
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<tr>
<td>Nichol, et al (2003)</td>
<td>Cohort</td>
<td>Risk of heart disease hospitalization ↓19%</td>
<td>p&lt;0.001</td>
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<tr>
<td></td>
<td>n = 286.383</td>
<td>Risk of CVD hospitalization ↓32%</td>
<td>p&lt;0.001</td>
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<td></td>
<td>Death due to any causes ↓50%</td>
<td>p&lt;0.001</td>
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<tr>
<td>Vordouw, et al (2004)</td>
<td>6-year cohort</td>
<td>First vaccine → mortality risk ↓10%, HR 90%</td>
<td>Cl : 0.78;1.03</td>
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<td></td>
<td>n = 26,071</td>
<td>Revaccination in the next 1 year h mortality risk ↓24%, HR 0.76</td>
<td>Cl : 0.70;0.83</td>
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<td></td>
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<td>During epidemic → mortality risk ↓28%, HR 0.72</td>
<td>Cl : 0.53;0.96</td>
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<tr>
<td>Vordouw, et al (2004)</td>
<td>6-year cohort</td>
<td>Age ≥ 70 yr g mortality ↓</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>n = 26,071</td>
<td>Vaccination coverage 70% → prevent 1 death for every 302 vaccinations</td>
<td></td>
</tr>
<tr>
<td>Nichol, et al (2004)</td>
<td>Cohort (1996-2000)</td>
<td>Aged 65-74 yr: OR = 0.44; 0.62; 0.58; 0.61</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>n &gt; 567,000 elderly subjects</td>
<td>Aged ≥85 yrs: OR = 0.40; 0.63; 0.48; 0.51</td>
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<tr>
<td></td>
<td></td>
<td>Not significantly different between both groups</td>
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<tr>
<td>Wongsurakiat et al (2004)</td>
<td>Influenza vaccine benefit</td>
<td>Influenza vaccine group: incidence 6.8 per 100 individuals-year</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>n = 125 elderly patients with COPD</td>
<td>Control group: 28.1 per 100 individuals-year</td>
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<td></td>
<td></td>
<td>RR = 0.24</td>
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<td></td>
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<td>Vaccine effectiveness 76%</td>
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PNEUMONIAE VACCINATION

Benefit

Various studies have reported the benefits of pneumococcal polysaccharide vaccination, from the oldest serotype 2-valent vaccine to the latest serotype 23-valent vaccine. Christenson (2001) reported that the incidence of pneumonia in the group receiving vaccine has decreased as much as 29% compared to the non-vaccinated group; moreover, the incidence of invasive pneumococcal disease has been lowered up to 52%. Similar results have been reported by Wagner in 2003 who demonstrated lower risk for pneumonia in vaccinated group than non-vaccinated group (OR = 0.279; p<0.0001) after controlling demographic characteristics, body mass index and various comorbidities (COPD, coronary heart disease, heart failure, diabetes mellitus and malignancies). Mortality risk has also decreased in vaccinated group (OR = 0.331; p<0.0001). A double-blind trial by Koivula et al demonstrated that in the elderly subjects aged >60 years with comorbidities, there was lower risk for pneumonia in vaccinated group than those who had not receive vaccination (there was 59% protective efficacy). Gailat and Fedson (1999) have also reported that pneumonia vaccination in the elderly will provide a relatively great protection (77% protective efficacy). However, it should be noted that the critical appraisal of these studies showed that there was indistinct classification of diagnosis that may lead to misclassification and ascertainment bias.

<table>
<thead>
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<th>Author (year)</th>
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<th>p/CI</th>
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<tbody>
<tr>
<td>Christenson (2004)</td>
<td>Interventional prospective</td>
<td>Risk of hospitalization due to IPD and pneumonia in vaccinated group ↓ (OR = 0.67 vs OR = 0.79)</td>
<td>CI : 0.55;0.82</td>
</tr>
<tr>
<td></td>
<td>124.702 subjects receiving influenza/pneumonia vaccination</td>
<td>Risk of mortality in the group receiving influenza vaccination ↓ (OR = 0.88)</td>
<td>CI : 0.75;0.84</td>
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<tr>
<td></td>
<td>134.045 control group</td>
<td>Risk of mortality in the group receiving two or more vaccine ↓ (OR = 0.65)</td>
<td>CI : 0.69;1.11</td>
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<tr>
<td></td>
<td></td>
<td>Length of hospitalization in vaccinated group was shorter</td>
<td>CI : 0.54;0.78</td>
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<tr>
<td>Chen Y-H (2004)</td>
<td>Interventional prospective</td>
<td>Mortality rates due to chronic bronchitis, lung emphysema, and asthma decreased from 93.62/100.000 (in 1997) to 65.87/100.000 (in 2002)</td>
<td>OR 0.73 CI : 0.68;0.77</td>
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<tr>
<td></td>
<td>1.250.000 vaccination</td>
<td>- 27% lower risk for hospitalization due to pneumonia or influenza</td>
<td>OR 0.52 CI : 0.50-0.55</td>
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<tr>
<td></td>
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<td>- 48% lower mortality risk in groups of all age</td>
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<tr>
<td>Nichol KL et al (2007)</td>
<td>Cohort</td>
<td>Lower morbidity of 20-62% and lower hospitalization rate of 13-69% in subjects aged 65-79 yr</td>
<td>p&lt;0.001</td>
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<tr>
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<td>n = 713.059 elderly subjects in community</td>
<td>Lower hospitalization rate of 46% in subject aged &gt;80 yr</td>
<td>p&lt;0.01 CI : 0.43-0.69</td>
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<td>Greater decrease of hospitalization rate in subjects receiving influenza vaccination only (62%) compared to those receiving influenza + pneumonia vaccination (29%)</td>
<td>p&lt;0.001</td>
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<td>Lower morbidity and hospitalization rate in subjects with IPD (68% and 40%) and subjects with pneumococcal pneumonia (13% and 38%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Christenson B et al (2008)</td>
<td>Interventional prospective</td>
<td>Risk of mortality during epidemic season (OR = 0.58)</td>
<td>CI : 0.56-0.72</td>
</tr>
<tr>
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<td>n = 41,059 (in 2003), 14,799 (in 2004), 8,843 (2005)</td>
<td>Effectiveness in elderly subjects aged &gt;75 yrs ↓ (OR = 0.66)</td>
<td>CI : 0.50-0.86</td>
</tr>
<tr>
<td>Groenwold RHH et al (2009)</td>
<td>Interventional prospective</td>
<td>Risk of mortality during epidemic season (OR = 0.58)</td>
<td>CI : 0.56-0.72</td>
</tr>
<tr>
<td></td>
<td>n = 50,906 elderly subjects</td>
<td>Effectiveness in elderly subjects aged &gt;75 yrs ↓ (OR = 0.66)</td>
<td>CI : 0.50-0.86</td>
</tr>
</tbody>
</table>
are: Moore et al (1999), who reported that the response of antibody production and the effectiveness of vaccination are lower in elderly, especially in those aged >75 years; Mercola (2003) based on his study results indicated that there was no correlation between pneumonia vaccination and lowered risk for pneumonia of any etiology. Vaccine antigen will only stimulate B lymphocyte to produce antibody, but it has no effect on T lymphocyte.14

In January 2009, the Joint Committee on Vaccination and Immunization (JVCI) has proposed that pneumococcal conjugate vaccine (serotype 7-11) may provide greater promising results than pneumococcal polysaccharide vaccine, which has been used in elderly vaccination program around the world. While waiting for results of the study, JVCI recommended that pneumococcal polysaccharide vaccination is still relevant; however, it also has been considered to alter the implementation on type of conjugate vaccine. The use of 23-valent vaccine as a booster after conjugate vaccine injection may improve the vaccine effectiveness.53

Although the benefit of pneumonia immunization using the 23-valent vaccine is still being debated, WHO issued a stipulation that pneumonia vaccination in the elderly is quite effective to protect healthy elderly subjects against invasive diseases (pneumonia with complications such as meningitis, septicemia, and pneumococcal pneumonia). It is supported by an analysis on serotype distribution, which demonstrated that the greatest percentage of invasive disease is still caused by 23-valent serotype.54

Pneumococcal vaccination is still recommended in elderly vaccination program in the United States, 2009 and it has a priority on healthy elderly population who live in nursing home (CDCP, 2008). The study by Christenson et al (2004), which was a large scale prospective interventional study in Sweden with 124,702 elderly subjects who had received influenza and/or pneumonia vaccination (134,045 elderly subjects in control group) showed results supporting result on implementing vaccination.55 The study found that there was a lower risk of hospitalization due to influenza, pneumonia and IPD (invasive pneumococcal disease) in the vaccinated group compared to the non-vaccinated group. It also found that the mortality risk due to pneumonia was lower in the group receiving influenza vaccination, although it was not significant. However, in subjects who had received two kinds of vaccinations, the risk was significantly lower. The length of hospitalization of those who received vaccination was significantly shorter than those without vaccination. It is also important to notice that in order to control confounding factors, a survey in 10,000 elderly subjects has been conducted and the baseline data for vaccinated group are as follows: older mean age, more elderly lives in nursing homes, more comorbidities; overall, both group were not only comparable, but also at ‘lower’ starting point compared to the control group. Therefore, the results were underestimated from the true results. In conclusion, immunization for the elderly using influenza and pneumonia vaccine provides a relatively effective protection against morbidity and mortality related to influenza, pneumonia and IPD.

Meta-analysis on 11 blind-controlled trials and 2 non-blind controlled trials reported that the risk of systemic infection by pneumococcal reduced to 83% and the risk of infection caused by all types of pneumococci reached 73% of effectiveness.56 The current comprehensive meta-analysis by Morbeley in 2008, which evaluated 15 Randomized Controlled Trial (48,656 participants), and 7 non-RCT (62,294 participants) reported a strong evidence on the efficacy of polysaccharide vaccine against invasive pneumococcal disease (OR 0.25, CI 0.15-0.46, I2=0%); however, the efficacy against all-cause pneumonia cannot be concluded because of wide variation on statistical differences. It did not provide evidences on lower efficacy in the elderly or in patients group with chronic disease, which were statistically not significant in the study.57

Recent findings reported by Lamontagne et al in 2008 demonstrated that pneumococcal vaccination is associated with 50% lower incidence of myocardial infarction, especially in the group that has receive vaccination more than 2 years (OR after control 0.33, CI 0.29–0.46), which may occur through the mechanism of LDL oxidation and prevention of foam cells production, which act as precursors of atherosclerosis.58 However, a double-blind, controlled trial with greater power is still necessary since the study still has bias on greater number of healthy
subject in the control group. Another study conducted in 84 patients with chronic lung disease demonstrated a great increase of sera IgG level following the polysaccharide vaccination, especially the 23-valent. Such increase will remain until 3 years. It provide evidence that there is an increase of immunogenicity following the pneumococcal polysaccharide vaccination.

**Table 2.** Compilation of studies on the benefit of pneumonia polysaccharide immunization

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design and Methods</th>
<th>Results</th>
<th>p/CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koivula (1997)</td>
<td>Double blind trials</td>
<td>Elderly aged &gt;60 yr with comorbidity → pneumonia risk ↓ in vaccinated group (OR=0.41)</td>
<td>p&lt;0.05</td>
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<tr>
<td>Gailat &amp; Fedson (1999)</td>
<td></td>
<td>Pneumonia vaccine provides great benefit to elderly (77% protective efficacy)</td>
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<tr>
<td>Hutchinson BG, et al (1999)</td>
<td>Meta-analysis on 13 double-blind trials and double-blind quasi experimental studies</td>
<td>Effectiveness of 83% ↓ risk for pneumonia infection as much as 73% Lower efficacy was not statistically significant</td>
<td></td>
</tr>
<tr>
<td>Christenson (2001)</td>
<td>Prospective - n = 100,242 elderly subjects</td>
<td>841 pneumonia vaccine, 76,117 had received both influenza and pneumonia vaccine - The incidence of pneumonia: Pneumonia vaccine group decrease to 29% Invasive pneumococcal disease decrease 52%</td>
<td>CI : 24;34 Cl : 1;77</td>
</tr>
<tr>
<td>Wagner (2003)</td>
<td>Case control - 359 cases - 718 controls In subjects receiving vaccination: Pneumonia risk ↓ (OR=0.279) Mortality risk ↓ (OR=0.331)</td>
<td>p&lt;0.0001</td>
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<td>Mercola (2003)</td>
<td></td>
<td>There were no correlation between pneumonia vaccination lower risk of pneumonia</td>
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<tr>
<td>Christenson (2004)</td>
<td>Interventional prospective - 124,702 subjects receiving influenza/ pneumonia vaccination - 134,045 controls</td>
<td>Risk of hospitalization related to IPD and pneumonia in the vaccinated group was ↓ (OR=0.67 vs OR=0.79) Mortality risk in influenza vaccinated subjects was ↓ (OR=0.88) Mortality risk in the group receiving two or more vaccines ↓ (OR=0.65) Length of hospitalization was ↓</td>
<td>CI : 0.55;0.82 CI : 0.75;0.84 CI : 0.69;1.11 CI : 0.54;0.78</td>
</tr>
<tr>
<td>Córcoles AV et al (2005)</td>
<td>Cohort interventional 11,241 elderly subjects</td>
<td>Vaccination lowered mortality risk due to pneumonia Vaccination did not lower hospitalization risk or the incidence of pneumonia</td>
<td>HR 0.28 p&lt;0.018 HR 0.80 CI : 0.5-1.28</td>
</tr>
<tr>
<td>Lamontagne F et al (2008)</td>
<td>Hospital-based case control - n=43,209 adults with MCI risk; 999 subjects with MCI, 3996 controls</td>
<td>Greater number of MCI cases in non-vaccinated adults than the control Stronger association in adults with pneumococcal vaccination &gt;2 years</td>
<td>OR 0.53 CI : 0.40-0.70 p&lt;0.001 OR 0.33 CI : 0.20-0.46 p&lt;0.001</td>
</tr>
<tr>
<td>Huss A et al (2009)</td>
<td>Meta-analysis on 22 trials, either double-blind or non-blind trials - n = 101,507 - 23-valent vaccines were used in 8 studies.</td>
<td>Pneumococcal vaccination was less effective in pneumonia prevention strategy: The efficacy against pneumococcal pneumonia was low, but it was statistically not significant The relative risk for high mortality was high, but it was statistically not significant Vaccination was not effective in pneumonia prevention strategies at any causes</td>
<td>RR 1.04; p&gt;0.1 RR 1.00; p&gt;0.1 RR 0.99; p&lt;0.001</td>
</tr>
</tbody>
</table>

**Risk** Side effects of pneumonia vaccination includes local (20-30%) or systemic (<1%) reaction. Honkanen et al reported that 93% subjects experienced localized skin redness without tenderness after four days (284 subjects in the group receiving influenza vaccination only and 441 subjects in the group with influenza and
pneumococcal vaccination). Fever (37.5°C) was found in 10 subjects with influenza vaccination and there were more subjects who had received influenza and pneumococcal vaccination (24 subjects) who had fever. In conclusion, double immunization resulted in more localized side effects and fever; however the side effects are typically mild and will resolved without treatment.

INFLUENZA VACCINATION PROTOCOL

Indication
Elderly (age > 60 years)

Contraindication
History of hypersensitivity/allergic response to eggs and/or thimerosal.

Side Effects
Skin reaction (localized) such as local tenderness which occurs in 24 hours after injection; it is usually well-tolerated and resolved without any treatment in 2-3 days.

Systemic side effects include fever, malaise, headache, myalgia, and arthralgia that may occur in 6 – 12 hours following vaccination and will be resolved in one to two days.

Hypersensitivity reaction may occur in individuals who have had allergic responses to egg.

Managing Side Effects
When necessary, 500 mg paracetamol could be administered to reduce localized tenderness, fever, headache, myalgia and arthralgia. In severe hypersensitivity reaction, airway maintenance and cardiopulmonary resuscitation procedure should be performed according to the protocol. Introducing intravenous line (opening access to the vein) and subcutaneous or intramuscular epinephrine injection at dose of 0.2 – 1.0 ml and 200 mg of intravenous hydrocortisone injection in 30 seconds or methylprednisolone 62.5 – 125 mg (IM or IV in 30 minutes) could be administered as initial therapy in conjunction with resuscitation.

Virus Strain; Vaccine Type
The vaccine contains two different strains of influenza subtype A and one strain of influenza subtype B. Duration of protection is 1 year. The vaccine uses inactivated virus based on data of circulating virus in previous year since the type or antigenic configuration changes each year (based on the prevalent strain isolate of the one previous year). Split virus vaccine is administered since it is less immunogenic and has fewer side effects.

Posology
Suspension for injection; 0.5 mL vial.

Protocol
0.5 mL by subcutaneous or intramuscular injection; once a year.

PNEUMONIA VACCINE PROTOCOL

Indication
Healthy elderly subject (> 65 years old), especially those who lived in nursing homes.

The elderly who requires repeated vaccination are only individuals with impaired immunity (patients with diabetes, chronic renal failure and chronic liver disease) and individuals who have comorbidities or those who had received their first vaccination at the age less than 65 years.

Contraindication
History of allergy/hypersensitivity to the vaccine component(s).

Side Effects
Local skin redness, without tenderness or fever.

Managing Side Effects
500 mg paracetamol could be administered to reduce localized tenderness or fever.

More severe hypersensitivity reaction needs airway maintenance and cardiopulmonary resuscitation procedure according to the protocol. Introducing intravenous line (opening access to the vein) and subcutaneous or intramuscular epinephrine injection at dose of 0.2 – 1.0 ml and 200 mg of intravenous hydrocortisone injection in 30 seconds or methylprednisolone 62.5 – 125 mg (IM or IV in 30 minutes) could be administered as initial therapy in conjunction with resuscitation.

Vaccine Type
The available vaccine is Pneumo 23, which is purified polysaccharides of 23 serotype of Streptococcus pneumonia.

Posology
Solution for injection in a prefilled syringe (0.5 ml).
Protocol
Following aseptic and antiseptic procedure, the vaccine can be given subcutaneously or intramuscularly in the deltoid region. Pneumococcal vaccination can be given during the early influenza epidemic rather than before influenza season. Booster is not recommended for the elderly. Pneumococcal and influenza vaccination can be given together at the same day, but at different site of injection.

REFERENCES
42. CDCP (Center for Disease Control and Prevention). Prevention and control of influenza. MMWR. 2008;57:1-60.