

# Background Paper on Influenza Vaccines and Immunization

## SAGE Working Group

### TABLE OF CONTENTS

<b>Executive Summary</b> .....	<b>2</b>
<b>I. Context</b> .....	<b>6</b>
<b>II. Target Populations</b> .....	<b>9</b>
1. Pregnant women .....	9
2. Healthcare Workers .....	13
3. Children .....	16
4. Elderly .....	21
5. Individuals with underlying health conditions .....	24
<b>III. Considerations for Vaccination Programs</b> .....	<b>28</b>
1. Influenza surveillance and monitoring.....	28
2. Cost effectiveness of seasonal influenza vaccination .....	28
3. Prioritization of vaccination and coverage goals .....	29
4. Revaccination when vaccine strains have not changed from the previous year .....	29
5. Quadrivalent formulation of seasonal influenza vaccine .....	30
<b>IV. Recommendations</b> .....	<b>31</b>
<b>References</b> .....	<b>32</b>

## Executive Summary

This report reviews the available evidence supporting the use of influenza vaccines in target groups at risk of developing severe disease (hospitalization and death) and provides proposed updated recommendations. The target groups addressed are: children <5 years (with a special discussion of those <2 years and <6 months), the elderly, pregnant women, individuals with high-risk underlying conditions and healthcare workers. Data reviewed for each target group included disease burden and vaccine effectiveness, with a particular focus on low and middle-income countries where possible, as well as cost-effectiveness. The content reflects the key information and publications considered by the SAGE Working Group on Influenza Vaccines and Immunization.

### Findings and Recommendations

**Pregnant women** are at particularly high risk of severe complications and death from influenza, and the risk is exacerbated by co-morbidities and later trimester of pregnancy. Inactivated vaccines are safe and effective in reducing maternal morbidity due to respiratory disease. Infants less than 6 months of age have the highest rates of influenza-associated hospitalization. Maternal immunization against influenza prevents negative effects on fetal development due to maternal influenza infection and reduces rates of illness in infants for at least the first 6 months of life.

***Recommendation:** Pregnant women should be vaccinated against influenza at any stage of pregnancy. In countries considering initiating or expanding vaccination programs for influenza, SAGE recommends pregnant women as the highest priority group for vaccination. This recommendation is based on compelling evidence of a substantial risk of severe disease in pregnant women, evidence that vaccine is effective against severe disease, and the evidence supporting secondary protection of infants under 6 months, in whom disease burden is also high, as well as operational feasibility.*

**Healthcare workers** (HCWs) have an additional exposure risk for influenza, compared to the general population. Vaccinating HCWs is safe and effective and may reduce work absenteeism. HCWs can transmit virus to patients, who are at increased risk of severe disease due to influenza and may respond less well to vaccine. Vaccination of HCWs is likely to reduce morbidity and/or mortality in patients. However, vaccination rates of HCWs remain low in many places.

***Recommendation:** Healthcare workers are an important priority group for influenza vaccination. Vaccination of the healthcare worker not only protects the individual, but also maintains healthcare services during influenza epidemics and protects vulnerable patients.*

**Children** have a substantial disease burden associated with influenza with higher rates of clinic visits, hospitalizations and deaths compared to non-elderly adults. The effectiveness of influenza vaccines among children varies and vaccine effectiveness (VE) among children <2 is particularly affected by vaccine match to circulating strain but are generally similar to those in older children during seasons with a well-matched strain. Inactivated vaccines are the only choice for vaccination programs for children <2

years old. In children older than 2 years, either inactivated vaccine (IV) or live-attenuated vaccine (LAIV) is an appropriate choice for vaccination programs. Antibody responses among children with chronic medical conditions may be decreased compared with children without high-risk medical conditions.

***Recommendations:***

*Children under 2 years of age are recognized as a priority group for vaccination because of a high burden of severe disease. Preventing influenza disease in this influenza-naïve population is currently challenging as effective immunization requires two doses and is highly dependent on vaccine strain match to the circulating strains. Children under 2 years should be considered as an additional target group for influenza immunization when sufficient resources are available with due consideration for competing health priorities and operational feasibility. The future availability of vaccines which can be more effective at priming, whether adjuvanted or live-attenuated, will further increase the benefits and potentially reduce the need for two doses of influenza vaccine in this age group.*

*Children aged 2-5 years of age have a high burden of disease, but less than those younger than 2 years old. Children in this age group may respond better to vaccination with trivalent inactivated influenza vaccine than younger children. Live-attenuated influenza vaccine, when available, provides broader and higher levels of protection in this age group.*

*Children less than 6 months of age are not eligible to receive currently licensed influenza vaccines and should be protected through vaccination of their mothers during pregnancy and through ensuring vaccination of close contacts to limit transmission to the infant.*

For the **elderly**, influenza is a key contributor to increased mortality. Limited data suggest that influenza-associated mortality among the elderly in low and middle income countries may be higher than in high income countries. Inactivated vaccines have been shown to reduce the risk of morbidity and mortality in the elderly, although effectiveness decreases with increasing age and in those with underlying medical conditions.

***Recommendation:*** *Elderly persons have the highest risk of mortality, and vaccination of this high risk group has traditionally been a main focus of vaccine policy development. This continues to be an appropriate target group for vaccination. However, delivering annual immunization to this group requires considerable ongoing investment, and increasing evidence demonstrates that available influenza vaccines are less effective in this population, compared to younger adults.*

**Individuals with specific underlying health conditions**, such as chronic respiratory, cardiac disease, morbid obesity and compromised immune status, are more likely to develop severe or fatal disease due to influenza infection than healthy individuals of the same age group. Influenza vaccine effectiveness has been demonstrated among individuals with underlying health conditions in a number of settings.

***Recommendation:*** *Persons with specific chronic diseases are at high risk for severe influenza illness. These groups have often been targeted for influenza vaccination, and continue to be an appropriate target group for vaccination. However, identification of these individuals in many settings is often challenging and requires considerable ongoing effort and investment.*

### **Target Group Prioritization and vaccine coverage goals**

Although influenza immunization programs have traditionally targeted priority groups as outlined in the current WHO position paper on influenza immunization, accumulated evidence on disease burden, vaccine performance, and new vaccine developments have highlighted the need for both an updated global prioritization and the development of country-specific influenza vaccination policy and target group prioritization schemes. The following criteria are suggested for countries to consider in prioritizing target groups for vaccination:

- Contribution of risk group to the overall influenza disease burden in population
- Disease severity within individual risk group
- Vaccine effectiveness
- Feasibility of delivery
- Indirect effects of vaccination
- Cost-effectiveness
- Opportunity cost
- Existing recommendations and programs for use of influenza vaccine locally

Coverage goals are also essential elements of country-specific influenza vaccination program development. In order to accurately measure progress toward coverage goals, vaccination programs require integration with surveillance or monitoring systems that can evaluate vaccination levels in target groups, and show the impact of vaccination on influenza-associated morbidity and mortality.

### **Additional Considerations**

#### **Influenza surveillance programs**

Country-specific information about risk groups and disease burden is essential to aid policy makers and health program planners in making informed decisions about target groups for vaccination and appropriate timing of vaccination. Influenza surveillance platforms are also critical for monitoring the impact of vaccine introduction.

#### **Revaccination**

In determining whether to revaccinate individuals during years where vaccine strains have not changed, vaccine immunogenicity and antibody decay following immunization are important factors to be considered. Repeated vaccination will boost protective immune response especially among high-risk groups who may respond poorly to vaccination. Therefore annual vaccination (or re-vaccination if no change in vaccine strains) is recommended, particularly for high risk groups.

#### **Quadrivalent influenza vaccines (QIV)**

The WHO Global Influenza Surveillance and Response System (GISRS), which provides vaccine strains recommendation covering two influenza A viruses (H1N1 and H3N2) and an influenza B virus, had also recommended further research on inclusion of a fourth strain (another influenza B virus of different lineage). Further research and clinical evaluation of QIV is encouraged.

**Cost effectiveness**

Limited data are available on cost-effectiveness of influenza vaccination within each targeted population, and methodological variations between existing studies make direct comparisons difficult. However the majority of economic studies had found that vaccination is cost-effective.

## I. Context

In 2010, the WHO Strategic Advisory Group of Experts on immunization (SAGE) requested the establishment of the Working Group on Influenza Vaccines and Immunization (WGIVI) with the primary objective to prepare for a SAGE evidence-based review and updating of WHO recommendations on the use of seasonal influenza vaccine (e.g. priority target groups) with a particular focus on low and middle-income countries (LMIC) and with a view to update the 2005 WHO influenza vaccine position paper. The activities of the WGIVI build on the work of the SAGE H5N1 Working Group and the SAGE H1N1 Working Group and relate to issues of seasonal and pandemic influenza vaccines.

To facilitate the development of a work plan for the WGIVI to achieve its objectives, a conceptual matrix was built to outline key issues on seasonal influenza vaccines that are associated with targeted populations (Table 1). The WGIVI had regular face-to-face meetings since its establishment and such meetings were supplemented with teleconferences to discuss outstanding issues.

This background document outlines the evidence gathered and reviewed by the WGIVI in support of recommendations to SAGE on updating the WHO position paper on influenza vaccine. The information provided in this document reflects the important information and publications reviewed with support from various systematic reviews performed for specific topics (see below). When reviewing evidence on vaccine efficacy the WGIVI relied, where possible, on studies with laboratory confirmed influenza as an endpoint. Studies reporting efficacy against influenza like illness (ILI) or other acute respiratory infection (ARI) are difficult to compare, as the proportion of ILI or ARI attributable to influenza infection will vary between populations and at different time periods in the same population. As data on the effect of comorbidities on outcome of seasonal influenza was incomplete for LMICs, the WG took the view that extrapolation of risk factor data from developed countries was appropriate. Immunogenicity data was also used as necessary as an adjunct to efficacy data.

The following systematic reviews of literature were assessed:

1. The efficacy and effectiveness of seasonal and pandemic (H1N1) 2009 influenza vaccines in low and middle income countries: a systematic review and meta-analysis. *Performed by* Department of Methodology and Applied Biostatistics, Faculty of Earth and Life Sciences, VU University Amsterdam, The Netherlands.
2. A systematic review of economic evaluations of seasonal and pandemic (H1N1) 2009 influenza vaccines in low and middle income countries. *Performed by* Department of Methodology and Applied Biostatistics, Faculty of Earth and Life Sciences, VU University Amsterdam, The Netherlands.
3. The effectiveness of vaccination of healthcare workers for the protection of patients at higher risk of acute respiratory disease: a systematic review. *Performed by* Health Protection Research Group, Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, UK.
4. Nair, H., et al., Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*, 2011. 378(9807): p. 1917-30. [1]
5. Jefferson, T., et al., Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews*, 2008(2): p. CD004879. [2]
6. Osterholm, M.T., et al., Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 2012. 12(1): p. 36-44. [3]
7. Jefferson, T., et al., Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews*, 2010(2): p. CD004876. [4]

8. Rivetti, D., et al., Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews*, 2006. 3: p. CD004876. [5]
9. Mosby, L.G., S.A. Rasmussen, and D.J. Jamieson, 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. *American Journal of Obstetrics and Gynecology*, 2011. 205(1): p. 10-8. [6]
10. Ortiz, J.R., J.A. Englund, and K.M. Neuzil, Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. *Vaccine*, 2011. 29(27): p. 4439-52. [7]
11. Lin, J.C. and K.L. Nichol, Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Archives of Internal Medicine*, 2001. 161(3): p. 441-6. [8]
12. Cates, C.J., T.O. Jefferson, and B.H. Rowe, Vaccines for preventing influenza in people with asthma. *Cochrane Database of Systematic Reviews*, 2008(2): p. CD000364. [9]
13. Keller, T., et al., Influenza vaccines for preventing coronary heart disease. *Cochrane Database of Systematic Reviews*, 2008(3): p. CD005050. [10]
14. Michiels, B., et al., A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. *Vaccine*, 2011. 29(49): p. 9159-70. [11]
15. Anema, A., et al., Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. *HIV Medicine*, 2008. 9(1): p. 57-61. [12]
16. Atashili, J., L. Kalilani, and A.A. Adimora, Efficacy and clinical effectiveness of influenza vaccines in HIV-infected individuals: a meta-analysis. *BMC Infectious Diseases*, 2006. 6: p. 138. [13]
17. Kuster, S.P., et al., Incidence of influenza in healthy adults and healthcare workers: a systematic review and meta-analysis. *PLoS One*, 2011. 6(10): p. e26239. [14]
18. Jefferson, T.O., et al., Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews*, 2007(2): p. CD001269. [15]
19. Ng, A.N. and C.K. Lai, Effectiveness of seasonal influenza vaccination in healthcare workers: a systematic review. *Journal of Hospital Infection*, 2011. 79(4): p. 279-86. [16]
20. Burls, A., et al., Vaccinating healthcare workers against influenza to protect the vulnerable--is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation. *Vaccine*, 2006. 24(19): p. 4212-21. [17]
21. Hollmeyer, H.G., et al., Influenza vaccination of health care workers in hospitals--a review of studies on attitudes and predictors. *Vaccine*, 2009. 27(30): p. 3935-44. [18]
22. Postma, M.J., et al., Further evidence for favorable cost-effectiveness of elderly influenza vaccination. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2006. 6(2): p. 215-27. [19]
23. Mullooly, J.P., et al., Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. *Annals of Internal Medicine*, 1994. 121(12): p. 947-52. [20]

**Table 1. Conceptual matrix of necessary information for SAGE WGIVI**

Key Issue	Target Populations				
	Children (<5 years) (<2 years)	Elderly	Pregnant Women	Other High-risk Groups	Healthcare Workers
Burden of Disease					
Vaccine performance (efficacy, effectiveness, safety and impact)					
Cost-effectiveness					
Operational issues					

For each category of work, the following information was gathered:

- What data exist?
- What data are needed?
- What are the gaps?
- What infrastructure or technology could address these issues in the future?



## II. Target Populations

### 1. Pregnant women

#### **Key Points: Pregnant Women**

- Pregnant women are at particularly high risk of severe complications and death from influenza; this risk is exacerbated by the presence of co-morbidities and later trimester of pregnancy.
- Inactivated vaccines are effective in reducing maternal morbidity due to respiratory disease.
- Inactivated vaccines had been shown to be safe in pregnant women and their offspring when given at any trimester.
- Infection of pregnant women leads to complications in the fetus, such as stillbirth, infant death, preterm delivery, decreased birth weight and emergency caesarean delivery.
- Infants <6 months of age have the highest rates of influenza-associated hospitalizations of any age groups. Maternal immunization against influenza is likely to prevent negative effects on fetal development due to maternal influenza infection and reduces rates of illness in infants for up to 6 months of life.

#### **Disease burden**

Influenza is responsible for substantial morbidity and mortality in pregnant women. In the US, half of hospitalizations for healthy pregnant women in their third trimester during the influenza season have been attributed to seasonal influenza viruses.[21] Risk of hospitalization is even higher in women with other risk factors; among pregnant women with asthma, it has been estimated as ten-fold higher than among pregnant women with no other risk factors (odds ratio of 10.63).[22] Additional analyses of mortality data among pregnant women in the US from 1998-2005 documented excess mortality due to seasonal influenza particularly in the 3rd trimester.[23]

During the 2009 pandemic, pregnant women were documented as an important risk group for severe disease across the globe. In Canada, pregnant women accounted for 3% of community cases, but comprised 20% of hospitalized cases and 12% of intensive care unit (ICU) cases.[24] Similar trends in rates of hospitalization and ICU admission of influenza infected pregnant women were seen in Australia and New Zealand, where a study of 722 ICU patients reported pregnancy accounts for 9.1% of cases, as compared to the proportion of pregnancy (1%) of the overall population.[25] Additional data from the US and Australia found hospitalization rates among pregnant women infected with influenza to be high compared to the general population (Risk ratio 4.3; 95% CI: 2.3-7.8)[26] and to women of child-bearing age.[27] In the US, 13% of total influenza A(H1N1)pdm deaths reported from April to June 2009 occurred in pregnant women.[26] In South Africa, pregnancy was the second most frequent risk factor among fatalities.[28] A global review of pandemic influenza virus infection in high risk groups found the unadjusted relative risk of hospitalization among pregnant women, compared to women of childbearing age in the general population, ranged from 3.5 in Germany to 25.3 in France (median: 6.8, n=10 countries).[29] The unadjusted relative risk of death, while elevated in pregnant women as compared to non-pregnant women in more than half of the studied countries, was generally lower than that for hospitalization, with a median of 1.9 (n=11 countries), with a relative risk of one in four countries/territories (Japan, the Netherlands, Singapore and Hong Kong SAR ).

Pregnancy alone is a risk factor for severe disease. During the 2009 H1N1 pandemic, pregnant women without other “high risk” co-morbidities were approximately twice as likely to be hospitalized for

influenza infection as compared to non-pregnant women (71% vs. 32%).[30] The risk for pregnant women for severe infection is exacerbated by the presence of co-morbid conditions. An extensive review of the global literature on influenza A(H1N1)pdm infection among pregnant women estimated that 30.3% of hospitalized pregnant women had either additional identified risk factors for severe disease or unspecified co-morbidities.[6] The most common additional risk factor reported was asthma, followed by diabetes mellitus of any type. Obesity was also commonly reported.

The negative effects of maternal influenza virus infection on fetal health are primarily due to complications, such as stillbirth, infant death, preterm delivery and emergency caesarean delivery, rather than viral infection of the fetus.[31-34] During the 2009 pandemic, few infants of infected mothers had evidence of infection with influenza A(H1N1)pdm virus. However, a large number of neonates required neonatal ICU admission and extended hospital stays were primarily due to their preterm birth. Delivery complications also resulted in neonatal morbidity and mortality.[6] Severe neonatal outcomes (ICU admission or death) resulted from 83.3% of severe maternal infections, as opposed to 12.5% among mothers with moderate illness.[30] The primary impacts on neonates from severe maternal infection with seasonal or pandemic influenza virus are preterm birth, low birth weight, and decreased weight for gestational age.[6, 35, 36]

### **Vaccine performance**

Immunization with trivalent inactivated influenza vaccine (TIV) is shown to generate a robust immune response in pregnant women, similar to non-pregnant healthy young adults. Immunogenicity analyses in the US and Bangladesh have found significantly higher geometric mean titer (GMT) of antibodies against influenza vaccine strains [37] and higher proportions of individuals with serological protective titers for all vaccine strains [38] among pregnant vaccine recipients. Earlier analyses conducted comparing antibody responses among pregnant versus non-pregnant women in the US found no significant differences, indicating that pregnant women do not respond differently to vaccine from non-pregnant women.[39-41] Studies from the US, UK, and Bangladesh looking at serological protective antibody titers in cord blood and infant sera show significantly higher proportion of serological protection among vaccinated versus unvaccinated mothers.[38, 41, 42] These levels of protective antibody wane over time among infants of vaccinated mothers, with titers (defined in the US study as  $\geq 1:20$ ) decreasing from 7/18 infants at 3 months of age to 1/7 infants at 6 months.[41] However, data from a study of MF-59 adjuvanted vaccine in Italy found that the elevated infant antibody titers observed at birth did not decrease at 2 months or 5 months of follow up.[43]

The available data suggest that TIV is effective in reducing maternal morbidity due to respiratory disease, although there are gaps in the data on laboratory-confirmed influenza outcomes among vaccinated pregnant women. A recent systematic review of maternal immunization found that none of published studies compared the risk of laboratory-confirmed influenza among immunized versus non-immunized women.[7] Results from the studies were mixed; a retrospective cohort study from the US from 1997-2002 did not find a decreased risk of ILI visits, [44] while a similar study from 1962-1963 found a decrease in the number of episodes of febrile upper respiratory tract infection among women receiving vaccine.[45] Outside of the US, the Mother's Gift Trial in Bangladesh (2004-2005), a prospective randomized control trial (RCT) of TIV, showed an overall 36% reduction of maternal febrile respiratory illness.[46]

Maternal infection with influenza virus may negatively impact fetal development, [35, 36, 39] an effect which can be prevented by vaccination. Data from the 2004-2005 Bangladesh trial found maternal immunization during pregnancy to be associated with a lower proportion of infants who were small for gestational age and an increase in mean birth weight.[47] An analysis of birth weight data among newborns born to mothers vaccinated with TIV or pneumococcal polysaccharide vaccine during periods of high and low influenza virus circulation found that vaccination with TIV was associated with a 200

gram increase in birth weight for neonates who were *in utero* during periods of peak influenza virus circulation. These data suggest that maternal influenza virus infection may lead to decreased fetal growth.

Maternal immunization with TIV reduces laboratory-confirmed influenza infection in neonates. Recent data on the neonatal effects of immunization from the US and Bangladesh showed TIV vaccine effectiveness ranged from 36%-92%, depending on the infant outcome studied.[7] The Bangladesh study followed infants for 24 weeks after delivery and estimated the vaccine's effectiveness (VE) against respiratory illness with fever at 36% in this population, with a VE of 69% against laboratory-confirmed influenza.[46] In a multi-site study in the US from 2002-2009, infants of vaccinated mothers were 45-48% less likely to have laboratory-confirmed influenza hospitalization than infants of unvaccinated mothers.[48] A maternal immunization study in Apache and Navajo populations from 2002-2005 estimated a VE of 41% against laboratory-confirmed influenza in infants, [49] while a case control study of US infants with laboratory-confirmed influenza found an effectiveness of 92% against influenza-associated hospitalization in the first 6 months of life.[50]

The American College of Obstetricians and Gynecologists recommends that TIV be considered an essential element of prenatal care, based on the increased risk of serious influenza illness facing pregnant women and notes no study to date has shown an adverse consequence of inactivated influenza vaccine in pregnant women or their offspring.[51]

### **Vaccine safety**

Safety evaluations of influenza vaccine in pregnancy dated back to the late 1950's. Early prospective cohort studies from the US found no significant increase in adverse outcomes of vaccination in mothers or infants.[45, 52, 53] RCTs from the US and Bangladesh analyzing the effects of vaccine in all trimesters as compared to unvaccinated pregnant women, influenza-vaccinated non-pregnant women, and pregnant women vaccinated with tetanus toxoid found no significant adverse reactions, and no fetal, perinatal, or infant complications among offspring of vaccinated women.[37, 40, 41, 46] Post-marketing surveillance of 2009 Influenza A(H1N1)pdm vaccine has been carried out in the US, Europe, and South Korea, including non-adjuvanted TIV (US, S. Korea) and ASO3- and MF59-adjuvanted vaccines (Europe). To date, these vaccines have demonstrated a safety profile comparable to seasonal influenza vaccine in non-pregnant adults, with only mild self-limited reactogenicity and no evidence of teratogenicity or impact on pregnancy outcomes.[54-59] Likewise, retrospective studies of seasonal TIV from the US found no severe adverse events within 42 days of vaccination or any differences in pregnancy outcomes or infant health status.[44, 60, 61]

### **Special considerations**

Experience with pandemic influenza vaccine indicates an increased acceptability of vaccine in pregnant women. Efforts are needed to improve awareness of influenza vaccine and its safety profile to women and their medical providers. Surveys of pregnant women in North America showed moderate rates of influenza A(H1N1)pdm vaccine coverage that represented an increase from previous years' seasonal influenza vaccine coverage.[62, 63] However, among those women not receiving either seasonal or pandemic vaccine, safety concerns and lack of knowledge of the vaccine were frequently cited as reasons for not receiving the vaccine.[62, 64] Questions regarding attitudes toward vaccination identify medical providers as the primary and most trusted information source for influenza and vaccination. Lack of provider recommendation was a key barrier to immunization, [65] while 87% of women report they would accept influenza vaccine if recommended by their attending medical provider.[66] One additional possibility for influenza immunization programs for pregnant women is the integration of influenza vaccination with existing maternal-child health initiatives, such as tetanus toxoid vaccination.

### **For future research**

- Duration of protection from influenza infection for infants conferred by maternal immunization

- Safety and effectiveness of adjuvanted IV and LAIV among pregnant women
- Optimal timing of vaccination relative to virus circulation and trimester of pregnancy

**Recommendation: Pregnant Women**

- Pregnant women should be vaccinated against influenza at any stage of pregnancy. In countries considering initiating or expanding vaccination programs for influenza, SAGE recommends pregnant women as the highest priority group for vaccination.
- This recommendation is based on compelling evidence of a substantial risk of severe disease in pregnant women, evidence that vaccine is effective against severe disease, and the evidence supporting secondary protection of infants under 6 months, in whom disease burden is also high, as well as operational feasibility.

## 2. Healthcare Workers

### Key Points: Healthcare Workers

- Healthcare workers (HCWs) have an additional exposure risk for influenza, compared to the general population.
- Vaccinating HCWs is safe and effective in reducing their own risk of developing disease and may also reduce work absenteeism.
- HCWs can transmit virus to patients, who are at increased risk of severe disease due to influenza and may respond less well to vaccine.
- Vaccination of HCWs should reduce morbidity and/or mortality in patients.
- Vaccination rates of HCWs remain low in many places.

### Disease burden

Healthcare workers are at increased risk of infection with influenza compared to the general adult population. A 2011 systematic review of the incidence of influenza in healthy adults and healthcare workers [14] calculated a pooled annual incidence of infection of 18.7 per 100 HCW per season in unvaccinated HCWs and 6.5 per 100 HCW per season in vaccinated HCWs. These estimates were significantly higher than the incidence rates in adults working in non-healthcare settings. A review of influenza attack rates among HCW populations found that attack rates can reach up to 59% during an outbreak.[67] Further, risk of infection is not evenly distributed to all HCWs; those in emergency departments and other clinical settings have been shown to have significantly higher attack rates as compared to those in other hospital locations.[68] Nurses have also been found to have increased risk of infection, as compared to other healthcare professionals.[69]

Healthcare workers frequently come to work despite being sick, which can result in nosocomial transmission of influenza and other viruses to patients. A survey of nursing personnel and physicians in California found that 35.3% of HCWs developed influenza-like illness during the influenza season, and 76.6% of them cared for patients while ill.[70] Further, a survey of Glasgow HCWs found serological evidence of infection among 23% of HCWs during the 1993-1994 influenza season, with 28-59% of these cases not associated with a self-reported influenza-like illness.[71] These findings suggest subclinical infection in HCWs could spread influenza virus within a healthcare facility.

Transmission of influenza virus between HCWs has been documented. Reports of HCW infection with influenza A(H1N1)pdm virus indicate that 14% likely acquired infection from another HCW.[72] An investigation of an outbreak of influenza A (H1N1)pdm in a Chicago hospital found that 13/20 (65%) HCWs with laboratory confirmed infection were healthcare-associated.[73] The majority of these cases were attributed to transmission between staff, many of whom reported working for 1 or more days after illness onset. However, other studies suggest that risk of infection with seasonal influenza viruses among HCWs is higher from household than occupational exposures. A prospective study from Berlin found that HCWs were not at increased risk of serologically-confirmed influenza virus infection, compared to non-healthcare workers, although living with children resulted in significantly increased risk of infection.[74]

There is also evidence of transmission of influenza viruses from healthcare workers to patients. Transmission of influenza virus from HCWs to patients was cited as a principal source of infection for patients in a review of nosocomial influenza infection.[67] This is particularly important for patients that are at increased risk of severe infection, including those that do not produce a sufficient immune response to influenza vaccination (e.g., infants, the elderly, and those with immunosuppressive conditions). Among infants, a study in a neonatal intensive care unit (NICU) with low influenza vaccine coverage among staff

(15%) found that 19 NICU infants were infected with influenza A, including 6 symptomatic cases and 1 death.[75] A nosocomial outbreak of influenza A(H1N1)pdm in a pediatric oncology ward in Italy also linked transmission to HCWs.[76] In the elderly, a prospective survey of an institutionalized population identified an outbreak of influenza A(H3N2) with symptomatic attack rate of 45.5% among the elderly population despite a 97% vaccination coverage. The attack rate among HCWs, who were mainly unvaccinated, was 47.5%, suggesting that they played a role in transmission.[77]

### **Vaccine performance**

A recent meta-analysis found that efficacy of TIV in adults aged 18-65 was shown in 8 of the 12 seasons analyzed in ten RCTs, with a pooled efficacy of 59%.[3] A previous meta-analysis of 38 VE studies in adults that included findings by vaccine match to circulating strains indicated a point estimate of 80% efficacy for TIV during well-matched years and 50% efficacy during years with poor match.[15] This review estimated an overall efficacy of 62% for LAIV, with less evidence of a difference in vaccine performance between vaccine-matched and non-matched years.

Absenteeism of HCWs due to influenza (either as a direct result of infection of the HCW, or as a result of caregiving for an infected household member) can have negative effects on patient health. The effect of staff shortages can be seen on patient health outcomes, particularly in the ICU, where fewer nurses per patient can result in increased mortality.[78] Studies specifically looking at populations of healthcare workers have also found evidence of vaccine effectiveness, as well as a possible decrease in absenteeism among vaccine recipients. A 3-year RCT of TIV in young healthy HCWs in Baltimore, using serologically confirmed influenza infection as an outcome measure, estimated a VE of 88% for influenza A and 89% for influenza B.[79] This study did not identify a significant difference in absenteeism among vaccinated versus unvaccinated HCPs. However, a study in Europe on the impact of vaccination in HCWs with TIV found a small but significant decrease in the number of days of work lost due to respiratory infections over a single winter season (1.0 days among vaccinated vs. 1.4 days among unvaccinated,  $p = 0.02$ ).[80] An observer-blinded observational study in Singapore found a significant difference in influenza-like illness rates between vaccinated and unvaccinated HCWs when data were stratified by vaccine match to circulating virus.[81] A systematic review of seasonal influenza vaccination in HCWs was recently conducted, which identified only 3 randomized controlled trials, noting a lack of strong evidence for effectiveness of vaccination to prevent disease in HCWs, and suggested that programs highlight the role of vaccination in reducing disease among patients, rather than the providers themselves. [16]

Limited evidence suggests that vaccinating healthcare workers reduces morbidity and/or mortality in patients. Studies exploring the effect of HCW vaccination on the number of ILI outbreaks among US, UK, and Japanese long-term care facility patient populations have indicated a protective effect of HCW vaccination.[82-85] Studies evaluating the effect of HCW vaccination on inpatient mortality (including all-cause, respiratory, laboratory-confirmed influenza mortality) consistently found a decrease in total mortality among patients in facilities where HCWs received influenza vaccine.[83, 86-88] A Cochrane meta-analysis of the effect of HCW vaccination on health outcomes in elderly patients found significant protective effects against pneumonia mortality and all-cause mortality rates. This review's pooled estimates for VE of HCWs against laboratory-confirmed influenza or lower respiratory tract infections in patients were in the direction of a protective effect, but were not significant due to the limited amount of data available.[89]

Two modeling studies suggest that, in both acute and long term care settings, HCW vaccination coverage levels are directly correlated with patient protection against influenza infection.[90, 91] These models simulated virus transmission in a 30-bed facility with different levels of HCW vaccine uptake, examining the resulting attack rates among patients, did not detect a herd immunity threshold.

### **Vaccine safety**

Influenza vaccines are safe and effective in healthy working adults, including healthcare workers. [11, 92-94]

### **Special considerations**

Vaccination coverage among HCWs remains low, despite the relative accessibility of this target population, as well as a number of efforts to increase coverage (recommendations from major health care organizations, educational campaigns, free and easily available vaccines).[17, 95-99] A systematic review of HCW attitudes toward influenza vaccine identified two critical reasons for lack of vaccine uptake. These were: misconceptions/lack of knowledge (about influenza virus infection, its risks for patients, vaccine safety and effectiveness); and lack of convenient access to vaccine.[18] The review also found that self-protection was the most important reason provided by HCWs for accepting influenza vaccination.

Mandatory vaccination programs, requiring that all individuals employed by a specific healthcare provider receive influenza vaccination as a criterion for employment, are utilized by some employers and are effective in increasing HCW vaccination coverage. During the 2010-11 influenza season, vaccination coverage was 98.1% for US medical centers that mandated influenza vaccination, compared to 58.3% for those that did not.[100] For facilities using mandates, exemptions for medical or religious reasons were possible and very few employees were terminated or left (< 0.2%). However, mandatory vaccination of HCWs remains controversial; there are multiple publications that discuss ethical issues regarding the use of mandates, with most reviews in favor of their use.[101-103]

### **For future research**

- Impact of HCW vaccination in different settings
- Vaccine efficacy of aTIV and LAIV in HCW populations

#### **Recommendation: Healthcare Workers**

- Healthcare workers are an important priority group for influenza vaccination. Vaccination of the healthcare worker not only protects the individual, but also maintains healthcare services during influenza epidemics and protects vulnerable patients.

### 3. Children

#### **Key Points: Children <5, with special consideration for children <2**

- The disease burden associated with influenza is substantial in children, with higher rates of infection and illness as compared to adults. Compared with non-elderly adults, children have higher rates of clinic visits, hospitalizations and deaths. The highest rates of severe disease are in children <2 years.
- The effectiveness of influenza vaccines among children varies from year to year as the result of changes in circulating viruses; with effectiveness among children <2 particularly affected by vaccine match to circulating strains. VE estimates are generally similar to those in older children during seasons with well-matched vaccine strains.
- In children older than 2 years, either TIV or live-attenuated influenza vaccine (LAIV) is an appropriate choice for vaccination programs. Data indicate that LAIV may be more effective than TIV in healthy preschool and school-aged children, but there is currently limited availability of LAIVs.
- Inactivated vaccines are the current choice for vaccination programs that will target children < 2 years, because other vaccine approaches are not currently available in this age group.
- Limited data indicated that adjuvanted vaccines are likely safe and effective in this age group. However, these vaccines are not yet available for this age group.
- Children < 9 years of age who had not previously received influenza vaccine require two doses of vaccine to help to ensure that they generate a protective immune response. Some data suggest that a single dose of LAIV may provide sufficient protection in this immunologically naïve population.
- Antibody responses among children with chronic medical conditions may be decreased compared with children without chronic medical conditions.

#### **Disease burden**

The global disease burden associated with influenza in children <5 years of age is substantial. A recent meta-analysis concluded that, in 2008, 90 million cases of influenza occurred among children < 5 years. [1] These infections resulted in 20 million cases of acute lower respiratory illness (ALRI), one million cases of severe ALRI and 28,000-111,500 deaths. The authors estimated that 7% of all severe pediatric ALRI was due to influenza and that 99% of these severe outcomes and deaths occurred in developing countries. Finally, with very limited data, the case-fatality proportion associated with influenza in developing countries was as much as 15 times higher in developing countries compared with developed countries.

Children generally have higher rates of infection and illness compared with adults. Illness rates are highest among pre-school and school-aged children, likely due to their relative lack of pre-existing immunity to circulating influenza viruses and their propensity for being in crowded settings, such as schools or daycares, where viral transmission is facilitated.[104] Data from serologic surveys have demonstrated that 15-45% of children are infected with an influenza virus each year, [105] and by the age of 6, most children have been infected with influenza viruses at least once.[106] Children infected with influenza will shed higher titers of virus during their illness and shed virus for longer periods of time compared with adults. [107, 108] This finding, together with high rates of illness, suggests children are critical source in the transmission of influenza in communities and households, and sustain annual epidemics.[104, 109-112]



Influenza has been demonstrated to be an important cause of medical visits and hospitalizations in children. In the US and Europe, 10-15% of children seek medical care for influenza-associated disease each year.[104, 113-118] While data are more limited in tropical countries, influenza has been demonstrated to be an important cause of clinic visits in these settings as well.[119-121] In a large population-based study in Thailand, 1.4% of children had clinic visits for influenza-associated illness in the study year, and children < 14 years of age accounted for 80% of all influenza-associated clinic visits. [121]

Influenza among school-aged children can lead to high rates of school absenteeism and lost days of work among parents. In one US study, for every 100 children followed during an influenza season, 28 illnesses among the children resulted in 68 missed school days, 20 work days missed by parents and 22 secondary illness among household members.[112] In Thailand, influenza-associated illnesses were estimated to account for 1,701,450 missed days of school annually among children <14 years of age.[121]

Etiologic studies of pediatric hospitalizations for acute lower respiratory tract infections have identified influenza to be associated with 2-23% of admissions, with most large studies identifying influenza virus in 5-10% of hospitalized children in both developed and developing countries.[122-140] Rates of influenza-associated hospitalizations are primarily available from developed countries, where approximately 1-3 hospitalizations per 1000 child-years have been observed.[113, 114, 117, 141-145] Influenza-associated hospitalization rates are higher among children with cardiac and pulmonary conditions than among healthy children.[143, 145]

Deaths from influenza among children < 18 years old in developed countries are rare. In the United States, mortality due to influenza in children ranges from 45-268/year from 2004-2010, with 153 deaths in 2003-4, and 115 deaths in 2010.[146] While children with underlying diseases are more likely to die than those without underlying diseases, most deaths in the US occurred among children with no risk factors due to the low prevalence of risk factors among young children in this population.

Children under 5 years of age are at particularly high risk of severe disease. Rates of hospitalization [114, 141, 143] among pre-school aged children are comparable to those observed for persons 50-64 years of age.[147] Children <2 years are at even higher risk. In one study, hospitalization rates among children < 6 months of age were 240 per 100,000 children, while rates among children 2 to 5 years of age were 20 per 100,000 children. Among infants < 6 months of age, estimated rate of 9-104 hospitalizations occur per 10,000 children. [114, 148-150]

## **Vaccine performance**

### ***Inactivated influenza vaccines***

As in other groups, the effectiveness of influenza vaccines among children varies by season, but estimates are generally similar to those among adults. Two meta-analyses on VE of TIV, [2, 151] including both RCTs and observational studies, found pooled VE estimates of 65% (45-77%) in children 6 months - 16 years of age [151] and 59% (41-71%) in children <18 years.[2] RCTs conducted in children during years when the vaccine strains are well-matched to circulating strains have generally found the vaccines to confer significant efficacy.[152-156] However, like in other populations, in settings where the vaccine is less matched against circulating strains or where low rates of influenza infection are observed, decreased or non-significant estimates of VE have been measured.[153, 156, 157] Several observational studies of TIV VE among children less than 5 years of age have found a VE of 60-85% in seasons where vaccine strains are well-matched to circulating strains, but a VE of 0-60% when vaccines are poorly matched to circulating strains.[158-164] In addition to the direct protection of children conferred by influenza immunization, limited data indicate that protection of unvaccinated household [165, 166] and community contacts [154] may be conferred by immunization of children.

Young children who have not previously received influenza vaccine require two doses of vaccine to generate a protective immune response.[167-169] Observational studies have demonstrated that children who had not previously received vaccine and who received only one dose of vaccine had no statistically significant protection while children who received two doses had significant protection.[159, 163, 170, 171] As a result of these data, all children aged 6 months to 8 years who are being vaccinated for the first time should receive 2 vaccine doses separated by  $\geq 4$  weeks. Once a child has been primed, either with vaccine or natural infection, a single dose of vaccine should elicit protective antibodies.

Antibody responses among children with high-risk medical conditions may be decreased compared with children without high-risk medical conditions.[172] No RCTs of influenza VE have been conducted in children with chronic diseases or immunosuppression, as these children have long been recommended to receive vaccine due to the high risk of severe disease. In one nonrandomized controlled trial of vaccine among pediatric asthma clinic patients in Japan, effectiveness estimates were 67.5% against laboratory-confirmed influenza A infection and 43.7% against laboratory-confirmed influenza B infection.[173] Antibody responses among children with asthma are similar to those of healthy children, and are not significantly different during asthma exacerbations requiring short-term prednisone treatment.[174]

#### ***Live attenuated influenza vaccines (LAIV)***

Randomized, placebo controlled trials of LAIV in children have uniformly demonstrated significant effectiveness against laboratory-confirmed outcomes. Two meta-analyses, using RCTs, found pooled VEs of LAIV against laboratory-confirmed influenza of 80% (53-91%) and 82% (71-89%).[2, 151] Individual RCTs of LAIVs have found VEs of 51% - 96%. [152, 155, 175-180] While Negri, et al. [151] found no significant differences in effectiveness of LAIV and TIV in children, other reviews have concluded that vaccination with LAIV results in superior effectiveness compared with TIVs.[2, 3, 181] In addition, some trials have indicated that a single dose of LAIV is as effective as 2 doses in naïve children, [176, 177] and that LAIV may be more effective than TIV against antigenically drifted strains.[182, 183] LAIV has also been found to provide indirect protection to children <12 years when delivered through school-based clinics.[184]

#### ***Adjuvanted vaccines***

Although data on adjuvanted vaccines are limited, results from a recent study indicate that such vaccines may also provide improved protection in children compared with TIV. A large-scale study of European children aged 6 to 72 months compared adjuvanted TIV containing MF-59 (a proprietary oil-in-water adjuvant) (aTIV) to unadjuvanted TIV and placebo.[156] This study found an efficacy of 79% in children 6 to 36 months of age and 92% in children 36-72 months of age with aTIV, approximately twice as efficacious as unadjuvanted TIV in these populations, in which TIV had a VE of 40% and 45%, respectively. This study also found that antibody responses to aTIV were higher than those to TIV.

#### **Vaccine effectiveness in children younger than 2 years**

Inactivated vaccines are the best choice at the present time for protecting children <2 years, but their effectiveness is lower in this age group than among older children. Only two RCTs of TIV have enrolled children <2 years of age and included a virologically confirmed influenza outcome.[153, 180] Hoberman et al.[153] found that an overall efficacy against influenza culture-confirmed febrile illness of 66% [34-82%] during the first year when illness rates among study participants were high, but no significant protection during the second study year when illness rates were low. Vesikari et al. [180] found no significant protection from PCR-confirmed illness with TIV among children <24 months of age, compared with 45% VE measured in children 36-71 months of age enrolled in the same study. Similar trends of decreasing VE by age were observed in other studies.[155, 185]

While data from observational trials demonstrate that TIVs can be effective in this age group, the level of effectiveness is clearly related to how closely vaccines are matched against circulating strains.[158, 159, 161-164, 170, 171, 186] In effectiveness studies where vaccine strains were antigenically similar to circulating strains, effectiveness was generally high among even the youngest infants.[158, 161, 162, 186] However, when a sub-optimal match was present, effectiveness was relatively low or not significant. [158, 159, 163, 164]

While RCTs of LAIV mostly have also demonstrated significant efficacy in children aged 2 to 5 years of age, few data are available on efficacy in the <2 years old children. One study of LAIV in children 6-35 months found an efficacy of 84-85%.[180] However, live vaccines are not licensed for children <2 years due to concerns about adverse events.

Adjuvanted vaccines have shown promise to overcome poor immune responses and efficacy in naïve children. One recent RCT of MF-59 aTIV found a VE of 79% in children 6-36 months;[156] unadjuvanted TIV failed to confer significant protection in the same study. However, adjuvanted TIV are not yet available for use in this age group.

Although the high burden of disease in this age group supports the need for vaccination, and inactivated vaccines are the only choice at the present time for protecting children < 2 years, there is some evidence that initial priming with inactivated vaccines may limit the breadth of subsequent immune responses to influenza. Concerns have been raised from animal data that early and repeated vaccination with non-adjuvanted inactivated vaccines may interfere with heterosubtypic immunity and therefore increase susceptibility to illness with heterotypic strains.[187, 188] This might be of particular concern in the setting of the emergence of pandemic influenza viruses. However, the theoretical dangers of early and repeated vaccination of children are outweighed by the disease reduction associated with protection against currently circulating subtypes.

Current vaccines are not licensed for children <6 months of age. Protection of these children relies on vaccinating household and other close contacts to limit transmission to these children, or by immunizing the mother during pregnancy to protect the newborn via transplacentally-acquired antibodies against influenza (see “Pregnant Women” section).

### **Vaccine safety**

Like any other injected vaccine, TIV may cause local reactions but such reactions are usually mild and short-lived. Review of studies on safety of TIV in children did not reveal any evidence for important safety concerns [157], in particular no evidence of an increased risk of febrile convulsion.[78] In clinical trials, an increased risk for wheezing post-vaccination was observed in LAIV recipients aged <24 months. [182, 189] An increase in hospitalizations also was observed in children aged <24 months after vaccination with LAIV. As a result, LAIV is currently not recommended for children younger than 2 years old in countries where these vaccines are licensed. The safety profile of non-adjuvanted TIV showed that no true safety concerns exist when used in children of different ages.[157] Similar conclusions can be drawn for LAIV in children older than 2 years of age.[157, 182] Studies of MF59-adjuvanted TIV have also provided comparable safety data in children.[156] However, there are uncertainties on the safety of an AS03-adjuvanted pandemic vaccine with reports of increased incidence of narcolepsy in some countries.

### **Special considerations**

Additional considerations for vaccination of children include integration of influenza vaccines with existing immunization programs, the development of vaccines that provide more than a single year of protection, and protection of neonates against influenza virus infection through vaccination of pregnant women. The WHO Expanded Programme on Immunization (EPI) targets young children for basic

immunizations, providing a standard schedule and creating an infrastructure that can be utilized for additional interventions, including influenza vaccination. An important consideration for adding influenza to an existing childhood immunization program is the need for immunologically naïve children to receive two doses in order to mount a protective response to the virus. However, evidence suggests that the timing of the second dose is not critical to this response, and can be given up to a year following the first dose, allowing for some flexibility in vaccination program strategies. Influenza vaccines that could protect individuals for more than one year with a single dose, simplifying vaccine delivery and administration programs and improving the cost-effectiveness of the vaccine, are active areas of research. By delivering vaccines to pregnant women through existing maternal-child health programs, infants could be protected from influenza virus infection during their first 6 months of life due to transfer of maternal antibodies. (See “Pregnant Women” section.)

**For future research**

- Vaccine effectiveness in children in low income counties and countries with year-round circulation of influenza viruses.
- Mortality due to influenza among children in low and middle-income countries
- Safety of adjuvanted vaccines in children and LAIVs in young children under 2 years

**Recommendation: Children**

- Children under 2 years of age are recognized as a priority group for vaccination because of a high burden of severe disease. Preventing influenza disease in this influenza-naïve population is currently challenging as effective immunization requires two doses and is highly dependent on vaccine strain match to the circulating strains. Children under 2 years should be considered as an additional target group for influenza immunization when sufficient resources are available with due consideration for competing health priorities and operational feasibility. The future availability of vaccines which can be more effective at priming, whether adjuvanted or live-attenuated, will further increase the benefits and potentially reduce the need for two doses of influenza vaccine in this age group.
- Children aged 2-5 years have a high burden of disease, but less than those younger than 2 years old. Children in this age group may respond better to vaccination with trivalent inactivated influenza vaccine than younger children. Live-attenuated influenza vaccine, when available, provides broader and higher levels of protection in this age group.
- Children less than 6 months of age are not eligible to receive currently licensed influenza vaccines and should be protected through vaccination of their mothers during pregnancy and through ensuring vaccination of close contacts to limit transmission to the infant.

## 4. Elderly

### Key Points: Elderly

- Influenza is a key contributor to mortality in the elderly.
- Limited recent data suggest that influenza-associated mortality in low and middle income countries may be higher than in high income countries.
- Institutionalized elderly are at risk of disease due to outbreaks of influenza viruses.
- Inactivated vaccines have been shown to reduce the risk of morbidity and mortality in the elderly, although effectiveness decreases with increasing age and in those with underlying medical conditions.
- Limited data on LAIV in elderly populations suggest that LAIV may provide comparable protection to TIV.

### Disease burden

Influenza is a key contributor to mortality in the elderly. In the US from 1976-2007, adults aged  $\geq 65$  years consistently accounted for approximately 90% of all influenza-related deaths during this period.[190] In the UK from 1999-2010, an estimated 2.5-8.1% of deaths among individuals  $\geq 75$  years were due to influenza.[191] Risk of influenza-associated death is highest among older elderly; those  $\geq 85$  years have been found to be 16 times more likely to die from influenza-associated illness than those aged 65-69 years.[192] Estimates using all-cause excess mortality models in Portugal [193] and all-cause, respiratory, and circulatory mortality in Australia [194] also identified a distinct increased burden of influenza-associated mortality in this age group, well above that estimated through direct laboratory confirmation of influenza virus. In Singapore, influenza-associated deaths were 11.3 times more likely among individuals  $\geq 65$  years than among the general population[195], and rates of influenza-associated deaths in Hong Kong, estimated at 136 deaths/100,000 person-years, are also similar to estimates in the US and elsewhere.[196] Excess mortality data from tropical regions also indicated multiple peaks throughout the year.[197]

The burden of hospitalization among the elderly is also high; estimated rates from the US are 125-228 hospitalizations per 100,000 persons without high-risk conditions [198] and 399-528 hospitalizations per 100,000 persons with high-risk conditions among those  $\geq 65$  years of age.[199] These rates are four to ten-fold higher than hospitalizations among younger adults with and without high-risk conditions.[198, 199]

Recent data suggest that influenza-associated mortality among elderly populations in LMIC may be several times higher than in high income countries. Excess mortality modeling estimates for those  $\geq 65$  years in South Africa from 1998-2005 suggested 545 influenza-attributable deaths per 100,000 population for all causes and 63 per 100,000 population for pneumonia and influenza mortality. These estimates were 5 times and 3 times higher, respectively, than those from the US during this time period, with an observed increase in influenza-associated deaths during the winter months 2-4 times higher than that seen in the US.[200] In addition to direct fatalities from pneumonia, influenza can also precipitate death from non-respiratory causes, which can be detected through analyzing trends in excess cardiovascular and all-cause mortality.[201]

Institutionalized elderly are also at risk for infection due to outbreaks of influenza throughout the year. Influenza outbreaks have been regularly documented in long-term care facilities, including outbreaks of vaccine-matched influenza strains among highly vaccinated institutional populations.[202-205] Summer outbreaks of influenza also occur among elderly populations in long-term care facilities, [206-208] highlighting the year-round risk of transmission in institutionalized settings.

### **Vaccine performance**

Influenza vaccines have been shown to reduce the risk of morbidity and mortality in the elderly, although VE estimates varied between 20-80%, depending on the study, the population, vaccine strains match and the outcome measured. Generally, data have indicated that VE in the elderly is lower than VE among healthy, non-elderly persons. Four RCTs measure the effect of inactivated vaccine on ILI or laboratory-confirmed influenza in this age group.[209-212] Their findings were summarized in a recent Cochrane review, [4] and their pooled effectiveness against ILI was estimated to be 41%, with an efficacy against laboratory-confirmed influenza of 58%. These results included multiple settings (community and institution-based) and populations (healthy and those with co-morbidities). Overall, the studies summarized in this review did not show a significant effect of vaccination against all-cause mortality. However, an earlier meta-analysis of influenza vaccine in community-dwelling adults  $\geq 65$  years of age found an effectiveness of 35% against ILI, 33% against pneumonia and influenza hospitalizations, 47% against pneumonia and influenza mortality, and 50% against all-cause mortality.[213] Also in contrast to the Cochrane findings, several studies have reported that vaccination can be up to 80% effective in preventing influenza-related mortality.[211, 214-216] Additionally, a study looking at the population-level impact of a vaccination program in Sao Paulo, Brazil detected a 26% reduction in age-specific influenza-attributable mortality following the introduction in 1998 of funding for annual mass vaccination campaigns for adults aged  $\geq 65$  years.[217]

The effects of vaccination may vary between community-dwelling and institutionalized elderly populations. A 2006 Cochrane review noted a modest effect of vaccine among the community-dwelling elderly in preventing hospitalization (25%) as compared to 45% effectiveness among individuals in long-term care facilities.[5] The most recent estimates for TIV efficacy among non-institutionalized elderly are from a large European study, which found a 60% efficacy in those  $>60$  years of age.[218] Limited data from tropical settings have comparable findings: a RCT conducted in Thailand of adults  $\geq 60$  years living in the community detected a relative risk reduction of ILI of 56% (decreased incidence from 11% to 5% during the study period).[219] Among institutionalized elderly, observational study on estimates of influenza VE in preventing medically-attended acute illness were slightly lower than the Cochrane review estimate, ranging from 20%–40%.[211, 220] A RCT among elderly nursing home residents in Malaysia found a relative risk reduction of ILI during the 6-month study period between 55-76%, [221] similar to the 56% risk reduction seen in the community-based population study in Thailand.

An additional factor that associates with variability in the VE findings from observational studies among elderly populations is “healthy vaccinee” effect. This bias, described by Jackson et al., [222] occurs due to the differences in overall health status between individuals who seek influenza vaccines and those who are hospitalized for severe disease (or have other non-specific severe outcomes), and can result in overestimated VE. Several recent observational studies have corrected for this effect, with VE of 8.5-12.4% against pneumonia hospitalizations [223, 224] and 4.6% against all-cause mortality.

Limited data on LAIV in elderly populations suggest that LAIV provides comparable protection to TIV. A 2011 review of studies comparing TIV and LAIV concluded that the two vaccines have a similar relative efficacy in the elderly, based on the currently available data.[225] In South Africa, a randomized placebo-controlled trial in 2001 estimated LAIV efficacy against vaccine-matched influenza viruses to be 42.3%, with highest efficacy against influenza A(H3N2) viruses (52.5%), no efficacy against influenza B viruses, and no increase of severe adverse events for LAIV recipients compared to placebo.[226] A superiority trial in South Africa in 2002 found no significant difference in relative efficacy between LAIV and TIV, although this was due in part to the small number of laboratory-confirmed infections in the two study arms.[227] Finally, a study among Russian adults aged 60 and over who received either TIV or LAIV alone or a combination of the two, found a similar efficacy when TIV or LAIV was administered alone, at 50% and 51% respectively.[228] This study also observed a slightly increased efficacy of 67%

among participants receiving a combination of both vaccines, which could be explored for future vaccination strategies.

Several studies were conducted on adjuvanted influenza A(H1N1)pdm vaccine safety and effectiveness among elderly populations. One study from Italy found MF-59 adjuvanted vaccine to be well-tolerated in this population, [229] and another study from the Netherlands found only a moderate VE due to the occurrence of a number of breakthrough infections in elderly vaccine recipients.[230] In England, a study of AS03-adjuvanted monovalent influenza A(H1N1)pdm vaccine estimated an effectiveness among those  $\geq 50$  of 41%, lower than what was found in those  $< 10$  and 10-24 years of age (77% and 100%, respectively) but higher than the effectiveness among adults aged 25-49 (22%).[231]

Preliminary data for high dose (HD) TIV, a formulation developed specifically for elderly populations, show that it elicits an elevated antibody response compared to standard dose (SD) TIV. Falsey et al. [232] randomized adults  $\geq 65$  years old in the US to HD TIV (containing 60 micrograms of hemagglutinin per strain) or SD TIV (15 micrograms per strain). They then measured serological responses, finding a statistically significant increase in serological conversion rates and mean HI titers among recipients of HD TIV that met superiority criteria for both influenza A strains, as well as non-inferiority criteria for the influenza B strain. These findings suggest that HD TIV may provide improved protection against infection in this age group, although vaccine efficacy data are needed. HD TIV was licensed in the US in 2009, and US CDC's Advisory Committee on Immunization Practices (ACIP) has not expressed a preference for HD TIV over SD TIV formulations based on current data.[233]

#### **Vaccine safety**

Systematic review of seasonal influenza vaccine in the elderly showed that vaccine induces systematic and local side effects more frequently in vaccinated persons than controls but not statistically significant. [4] Safety of seasonal influenza vaccine does not appear to be of major concern in elderly populations.

#### **Special considerations**

As elderly individuals are at especially high risk of severe disease due to influenza infection, and vaccination has been shown to reduce this risk, vaccination recommendations are in place in many countries that target this population. Appropriate clinical endpoints that document morbidity and mortality due to influenza virus in the elderly are also a challenge; identification of influenza virus infections, particularly in the context of VE studies, can be difficult due to the wide clinical spectrum in this population.

#### **For future research**

- Burden of influenza disease among elderly populations in tropical countries, and in low and middle income countries
- Relative vaccine effectiveness of high-dose inactivated, adjuvanted inactivated, and live-attenuated vaccine formulations in the elderly populations

#### **Recommendation: Elderly**

- Elderly persons have the highest risk of mortality, and vaccination of this high risk group has traditionally been a main focus of vaccine policy development. This continues to be an appropriate target group for vaccination. However, delivering annual immunization to this group requires considerable ongoing investment, and increasing evidence demonstrates that available influenza vaccines are less effective in this population, compared to younger adults.

## 5. Individuals with underlying health conditions

### Key Points: Individuals with Underlying Health Conditions

- Individuals with underlying health conditions, such as chronic respiratory or cardiac disease or compromised immune status, are more likely to develop severe or fatal disease due to influenza infection than healthy individuals of the same age group.
- Influenza vaccine effectiveness has been demonstrated among individuals with underlying health conditions in a number of settings.

**Table 2. List of high-risk underlying health conditions**

1. Respiratory disease <ol style="list-style-type: none"> <li>a. Asthma</li> <li>b. Chronic bronchitis and emphysema</li> <li>c. Other pulmonary diseases</li> </ol>
2. Cardiac disease <ol style="list-style-type: none"> <li>a. Atherosclerotic heart disease</li> <li>b. Cardiomyopathy/chronic congestive heart failure</li> <li>c. Congenital heart disease</li> </ol>
3. Neurodevelopmental disorders <ol style="list-style-type: none"> <li>a. cerebral palsy</li> <li>b. musculodystrophy</li> <li>c. cognitive disorders</li> </ol>
4. Metabolic disorders <ol style="list-style-type: none"> <li>a. Diabetes</li> </ol>
5. Immunocompetency disorders <ol style="list-style-type: none"> <li>a. HIV/AIDS</li> <li>b. Chemotherapy</li> <li>c. Transplant patients on immunosuppressive agents</li> <li>d. Chronic corticosteroid therapy</li> </ol>
6. Chronic renal insufficiency on dialysis
7. Chronic liver disease especially with cirrhosis.
8. Morbid obesity
9. Hematological diseases <ol style="list-style-type: none"> <li>a. Sickle cell anemia</li> <li>b. Thalassemia major</li> </ol>
10. Chronic aspirin therapy in children (risk of Reye's syndrome)
Other groups to consider (not necessarily with a chronic illness): <ol style="list-style-type: none"> <li>1. Members of socially disadvantaged minority groups.</li> <li>2. Residents of long term care facilities.</li> </ol>



### **Disease burden**

Individuals with underlying medical conditions have higher rates of severe disease (hospitalization and death) from influenza virus infection than healthy individuals. This elevated risk is observed in children and adults, including pregnant women, and has been found for all groups listed in Table 2. Within each group, there is a range of elevated risk, driven by age, severity of the condition, and other factors.

A study of children with medically treated asthma or other chronic medical conditions in the US found that hospitalization rates ranged from two to four times the rate seen in children without medical conditions, with the highest burden in infants 0-11 months (1900 per 100,000 high-risk population) and the greatest increase in risk compared to those without medical conditions in children 1-2 years of age. [145] US hospitalization surveillance data confirmed this finding: 40% of hospitalized children in the Emerging Infections Program (laboratory-confirmed influenza in 10 states) have one or more underlying medical conditions (predominantly asthma, followed by prematurity or developmental delay).[234] Underlying conditions also put children at risk for longer hospitalization stays, compared to children without underlying conditions, [235] and are frequently present among fatal cases of influenza virus infection among children.[236] Among adults with acute exacerbations of chronic obstructive pulmonary disease (COPD), a systematic review found that RT-PCR-confirmed influenza was associated with 7% of cases, and with highest number of respiratory viruses detected in Europe, but a highest proportion of influenza relative to other viruses in Asia.[237]

A global meta-analysis of risk factors for severe disease from pandemic influenza found that the proportion of patients with at least one chronic medical condition who were infected with influenza A(H1N1)pdm increased with increasing severity: from 31% of hospitalized, to 52% of ICU-admitted and 62% of fatal cases, although there were small variations in this pattern by country. Chronic respiratory conditions (excluding asthma) and asthma were the risk factors most often reported among severe cases, followed closely by diabetes and chronic cardiac conditions. This review also found morbid obesity to be associated with ICU admission or fatal outcome.[29]

The risk of severe infection by influenza in cases with morbid obesity is demonstrated in a case series from the first pandemic wave in California, 51% of hospitalized cases had a BMI  $\geq 30$ , twice the average BMI among California adults, and BMI  $\geq 40$  (observed in 30% of cases) was associated with increased likelihood of a fatal outcome (odds ratio of 4.2).[238]

Among pregnant women with underlying medical conditions, there is also an observed increased risk of hospital admission from infection with influenza virus, irrespective of stage of pregnancy during the influenza season [239] although the 3<sup>rd</sup> trimester is frequently reported as an independent risk factor for severe disease.[21]

Among adolescents and adults with HIV infection in the US, influenza-associated excess mortality can be 7 to 14 times higher than that in the general population, comparable to or sometimes higher than excess mortality rates among those  $\geq 65$  years.[8] Data have also shown that those with HIV infection have a longer duration and increased severity of illness, compared to the general population.[240-243]

Cancer patients and transplant recipients are also at high risk of infection with influenza virus, including nosocomial acquisition of influenza.[244-246] In addition, immunosuppressed individuals are at elevated risk of developing an antiviral resistant influenza infection in response to an antiviral treatment regimen; high rates of resistant infection have been documented in this group for seasonal [247-249] and influenza A(H1N1)pdm virus.[250, 251]

## **Vaccine performance**

### **Individuals with respiratory/cardiovascular conditions**

Influenza vaccine effectiveness has been demonstrated in some populations with asthma, COPD, and chronic lung diseases. Among children with asthma, two observational studies found that VE varied by age and by virus type and subtype. A retrospective cohort study of asthmatic children  $\leq 12$  years found a VE against ARI of 55% in children  $<6$  years old and 5% in children  $>6$  years old.[252] A prospective cohort of children with moderate to severe asthma aged 2-14 years estimated the following VE estimates by age group: 54% in 2-6 year olds and 78% in  $>6$  year olds against influenza A(H3N2), and 22% in 2-6 year olds and 60% in  $>6$  year olds against influenza B.[173] Among patients with COPD, a randomized controlled trial found a vaccine efficacy of 76% against influenza-related ARI with no difference by severity of COPD.[253] A Cochrane review of vaccine performance among COPD patients concluded that the limited available data suggested that vaccines reduce acute exacerbations among COPD patients.[254] Among individuals  $>65$  years old with chronic lung disease, additional analyses suggest that influenza vaccine reduces the rates of pneumonia and influenza hospitalizations and all-cause mortality in this risk group.[255, 256]

Influenza vaccine effectiveness has also been evaluated among individuals with underlying cardiac diseases. A RCT of optimally treated coronary artery disease patients found a significant reduction in risk of 12-month cumulative cardiovascular death among those who were vaccinated (hazard ratio of 0.54). [257] A prospective cohort study of influenza vaccination in individuals with cardiac disease obtained similar findings, with a 0.34 hazard ratio for cardiovascular death at 1 year.[258] A recent study with similar methods among patients with acute coronary syndrome looked at a broader outcome of combined major cardiovascular events and found a significant hazards ratio of 0.70, but found no significant difference in cardiovascular deaths between the vaccine and control groups.[259] A 2008 Cochrane review of vaccine effects on patients with coronary heart disease included 2 trials and concluded that the small numbers of outcomes of interest, such as cardiovascular death and myocardial infarction, resulted in imprecise estimates and insufficient data to evaluate this association.[10]

Compared to healthy populations, vaccine performance may be decreased in populations with underlying respiratory and/or cardiovascular diseases, and meta-analyses indicate that there is insufficient evidence to conclude that vaccines are adequately effective in these groups. A 2003-04 case control study of high risk (with reported underlying medical conditions) and non-high risk 50-64 year olds found a decreased vaccine efficacy against laboratory confirmed influenza among high risk compared to non-high risk individuals (48% vs. 60%).[260] A 2011 systematic review of the available data on vaccine performance among different vaccine target groups found limited good-quality evidence of vaccine effectiveness in COPD patients and elderly individuals with comorbid conditions.[11]

### **Immunocompromised individuals**

Certain immunocompromised groups, such as HIV patients with low CD4-count, do not respond as robustly to vaccines as healthy individuals. TIV is immunogenic among HIV-infected persons with normal CD4 counts.[261-264] However, data show TIV to be less immunogenic, with a possible reduced vaccine efficacy, in persons with low CD4 counts.[262, 265, 266] Further, a second dose does not improve immune responses in this group.[265] Studies on the performance of monovalent inactivated influenza A(H1N1)pdm vaccine have similar findings with reduced immunogenicity (60%) among HIV-positive individuals, particularly those with lower CD4 counts.[267, 268] These findings of reduced immunogenicity extend to adjuvanted vaccines (AS03 and MF-59) among HIV-positive compared to HIV-negative individuals.[269-271] Two systematic reviews conducted on the effectiveness of influenza vaccines among HIV-positive populations showed limited evidence of VE in this population and called for more data from RCT settings.[12, 13] However, a recent RCT of TIV among HIV-infected adults in South Africa showed a vaccine efficacy of 76% and high levels of serological conversion.[272] Data from

this study also suggested that the serological conversion rate for influenza A(H1N1)pdm underestimated efficacy of the vaccine strain for this subtype.

Among other immunocompromised populations, primarily cancer patients and transplant recipients (individuals receiving hematopoietic stem cell or solid organ transplants), single doses of both unadjuvanted and adjuvanted inactivated influenza vaccines have solicited only moderate immunological responses in adults [269, 273-279] and children.[280-282] Many of these studies found that a second dose significantly improved the proportion achieving serological protection. Despite decreased levels of protective antibodies, several analyses have found evidence of reduced risk of death following vaccination in immunocompromised cohorts.[283, 284] Additional studies among immunosuppressed pediatric populations on the effect of LAIV found only a moderate level of immunogenicity, but no prolonged viral shedding, suggesting that this vaccine is well-tolerated in this group.[285, 286]

### **Special considerations**

As individuals with one or more high-risk medical conditions are a heterogeneous population, there are a number of challenges to targeted vaccination campaigns. Among those with a given type of medical condition, there is a range of risk for severe influenza disease. In addition, the prevalence of high-risk conditions such as HIV is high in some LMICs, while the prevalence of other medical conditions is not always well documented. Further, high-risk individuals may obtain vaccines through multiple sources, making estimates of vaccination coverage difficult.

### **For future research**

- Prevalence of underlying illnesses common in low and middle-income countries (e.g. TB and HIV) as well as malnutrition
- Relative importance of various chronic conditions for severe complications of influenza, particularly in LMIC
- Unidentified environmental and clinical risk conditions
- Safety of LAIV in HIV-positive populations

### **Recommendation: Individuals with Underlying Health Conditions**

- Persons with specific chronic diseases are at high risk for severe influenza illness. These groups have often been targeted for influenza vaccination, and continue to be an appropriate target group for vaccination. However, identification of these individuals in many settings is often challenging and requires considerable ongoing effort and investment.

## **II. Considerations for Vaccination Programs**

### **1. Influenza surveillance and monitoring**

The overarching goal of influenza surveillance is to minimize the impact of the disease by providing information to public health authorities for planning appropriate control and intervention measures, health resource allocation, and for making case management recommendations.

Specifically, the goal of influenza surveillance is to provide timely, high quality data, in order to:

- Describe the seasonality of influenza.
- Identify and monitor groups at high risk of severe disease.
- Establish baseline levels of activity for influenza and severe influenza-related disease with which to evaluate the impact and severity of each season.
- Determine influenza burden.
- Provide a platform for evaluation of intervention effectiveness.
- Identify locally circulating types and subtypes and their relationship to global and regional patterns and matching of vaccine strains.
- Facilitate vaccine strain selection.
- Provide candidate viruses for vaccine production.

For programs considering introduction of influenza vaccination, country-specific information about risk groups and disease burden will provide information on vaccine demands to aid policy makers and health program planners in making informed decisions about target groups for vaccination and resource allocation. In addition, knowledge of the transmission patterns, the timing of seasons, and the relationship of these to other countries will allow health officials to better choose which vaccine to use and the most appropriate timing of vaccination. Finally, a surveillance system can provide a platform on which to monitor the impact of vaccine introduction particularly when combined with information on vaccination coverage rates. WHO has recommended a strategy for influenza surveillance that includes both surveillance for mild, outpatient-managed influenza-like illness (ILI) and for hospitalized severe acute respiratory infections (SARI).

### **2. Cost effectiveness of seasonal influenza vaccination**

Regardless of the methodology used, the majority of economic studies of influenza vaccine have found that vaccination is cost-effective. Systematic reviews of cost-effectiveness analyses among elderly populations found that almost all studies determined vaccination to be cost-effective or cost saving, [19, 287] although variations in methodology between studies made comparisons difficult. However, vaccination of persons over 65 years old was found to result in cost savings from both the societal perspective [20, 256] and from the perspective of health programs.[288]

Vaccination of adults <65 years old has been found to reduce direct and indirect costs from work absenteeism in two US studies, [289, 290] although these findings were not replicated in a third study. [291] This study did, however, find vaccination of children to be cost saving, with maximum cost savings reached by vaccination of children with medical conditions. Economic evaluations of vaccinating children have demonstrated a wide range of cost estimates, but have generally found this strategy to be either cost-saving or cost-beneficial.[292-295] A comparison of the economics of vaccinating children with TIV or LAIV found similar cost savings between the two vaccines, with an increased cost for both vaccines for older versus younger children.[296] Analyses of vaccination programs targeting pregnant women show

that it is cost-effective.[297-299] Vaccination of pregnant women with additional comorbidities was found to be cost-saving.[299]

Cost effectiveness also varies by the location where the vaccine is given, with lower estimated costs for vaccination in nonmedical settings, such as pharmacies, as compared to medical settings, particularly doctors' offices, [300] and that cost-effectiveness is maximized by vaccination as early in the influenza season as possible (as soon as vaccine is available), to minimize the likelihood of infection.[298] Although almost all cost-effectiveness analyses to date have focused on high-income countries and may not apply to low and middle countries, studies evaluating the economic impact of vaccinating healthcare workers have been conducted in Thailand and Colombia.[301, 302] Both studies demonstrated cost-effectiveness of targeting HCWs in Thailand using a combined intervention package (including vaccination, anti-viral access, and awareness campaigns) and in Colombia vaccinating HCWs in contact with high-risk cancer patients.

### **3. Prioritization of vaccination and coverage goals**

Although traditionally influenza immunization programs have targeted priority groups as outlined in the 2005 WHO position paper on influenza immunization, accumulated evidence on disease burden, vaccine performance and new vaccine developments have highlighted different prioritization needs. Country-specific policy development regarding influenza vaccination and prioritization of targeted risk groups should account for both vaccine effectiveness in such groups and concerns such as local disease burden assessment, ease of implementation and the available resources. Criteria for countries to consider in prioritizing target groups for influenza vaccination include:

- Contribution of risk group to the overall influenza disease burden in population
- Disease severity within individual risk group
- Vaccine effectiveness
- Feasibility of delivery
- Indirect effects of vaccination
- Cost-effectiveness
- Opportunity cost
- Existing recommendations and programs for use of influenza vaccine locally

Coverage goals are also an essential element of country-specific influenza vaccination program development. WHO currently provides vaccination coverage goals at 75% for those 65 years and older, and has developed guidance for countries in the process of setting coverage goals. In order to accurately measure progress toward coverage goals, vaccination programs require integration with surveillance or monitoring systems that can evaluate vaccination levels in target groups, and show the impact of vaccination on influenza-associated morbidity and mortality.

### **4. Revaccination when vaccine strains have not changed from the previous year**

The question of whether to revaccinate in years in which vaccine strains have not been changed from previous years was discussed. It was felt by the WGIVI that the occurrence of vaccine strains unchanged from previous year had been rare. In this respect, vaccine immunogenicity and post-immunization antibody decay are important factors to be considered and such data are highly vaccine and age group specific (LAIV vs. TIV, adults vs. children, elderly etc.). Therefore, annual vaccination (including re-

vaccination with unchanged vaccine strains) is recommended, particularly for high-risk groups who may respond poorly to influenza vaccination, for whom repeated vaccination would boost immune response for protection from severe infection.

## **5. Quadrivalent formulation of seasonal influenza vaccine**

The development of quadrivalent (QIV) formulation for seasonal influenza vaccine is of interest in providing comprehensive protection against influenza B viruses. Current vaccine strains recommendation comes from the WHO Global Influenza Surveillance and Response System (GISRS) which covers two influenza A viruses (H1N1 and H3N2) and an influenza B virus. GISRS also recommended there be further research on the fourth strain (another influenza B virus of different lineage). To assess the effectiveness of QIV, information on the global co-circulation of influenza B strains is required. It was noted that for 4 of the previous 8 seasons, use of QIV instead of TIV would have had substantially improved match of global circulating strains and there is potential public health benefit for QIV. A quadrivalent LAIV has recently been licensed in the US. Further research and clinical evaluation of different QIVs are encouraged.

### III. Recommendations

- **Pregnant women** should be vaccinated against influenza at any stage of pregnancy. In countries considering initiating or expanding vaccination programs for influenza, SAGE recommends pregnant women as the highest priority group for vaccination. This recommendation is based on compelling evidence of a substantial risk of severe disease in pregnant women, evidence that vaccine is effective against severe disease, and the evidence supporting secondary protection of infants under 6 months, in whom disease burden is also high, as well as operational feasibility.
- **Healthcare workers** are an important priority group for influenza vaccination. Vaccination of the healthcare worker not only protects the individual, but also maintains healthcare services during influenza epidemics and protects vulnerable patients
- **Children under 2 years of age** are recognized as a priority group for vaccination because of a high burden of severe disease. Preventing influenza disease in this influenza-naïve population is currently challenging as effective immunization requires two doses and is highly dependent on vaccine strain match to the circulating strains. Children under 2 years should be considered as an additional target group for influenza immunization when sufficient resources are available with due consideration for competing health priorities and operational feasibility. The future availability of vaccines which can be more effective at priming, whether adjuvanted or live-attenuated, will further increase the benefits and potentially reduce the need for two doses of influenza vaccine in this age group.
- **Children aged 2-5 years of age** have a high burden of disease, but less than those younger than 2 years old. Children in this age group may respond better to vaccination with trivalent inactivated influenza vaccine than younger children. Live-attenuated influenza vaccine, when available, provides broader and higher levels of protection in this age group.
- **Children less than 6 months of age** are not eligible to receive currently licensed influenza vaccines and should be protected through vaccination of their mothers during pregnancy and through ensuring vaccination of close contacts to limit transmission to the infant.
- **Elderly persons** have the highest risk of mortality, and vaccination of this high risk group has traditionally been a main focus of vaccine policy development. This continues to be an appropriate target group for vaccination. However, delivering annual immunization to this group requires considerable ongoing investment, and increasing evidence demonstrates that available influenza vaccines are less effective in this population, compared to younger adults.
- **Persons with specific chronic diseases** are at high risk for severe influenza illness. These groups have often been targeted for influenza vaccination, and continue to be an appropriate target group for vaccination. However, identification of these individuals in many settings is often challenging and requires considerable ongoing effort and investment.

## References

1. Nair, H., et al., *Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis*. Lancet, 2011. **378**:1917-30.
2. Jefferson, T., et al., *Vaccines for preventing influenza in healthy children*. Cochrane Database of Systematic Reviews, 2008:CD004879.
3. Osterholm, M.T., et al., *Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis*. The Lancet Infectious Diseases, 2012. **12**:36-44.
4. Jefferson, T., et al., *Vaccines for preventing influenza in the elderly*. Cochrane Database of Systematic Reviews, 2010:CD004876.
5. Rivetti, D., et al., *Vaccines for preventing influenza in the elderly*. Cochrane Database of Systematic Reviews, 2006. **3**:CD004876.
6. Mosby, L.G., S.A. Rasmussen, and D.J. Jamieson, *2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature*. American Journal of Obstetrics and Gynecology, 2011. **205**:10-18.
7. Ortiz, J.R., J.A. Englund, and K.M. Neuzil, *Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions*. Vaccine, 2011. **29**: 4439-52.
8. Lin, J.C. and K.L. Nichol, *Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome*. Archives of Internal Medicine, 2001. **161**:441-6.
9. Cates, C.J., T.O. Jefferson, and B.H. Rowe, *Vaccines for preventing influenza in people with asthma*. Cochrane Database of Systematic Reviews, 2008:CD000364.
10. Keller, T., et al., *Influenza vaccines for preventing coronary heart disease*. Cochrane Database of Systematic Reviews, 2008:CD005050.
11. Michiels, B., et al., *A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups*. Vaccine, 2011. **29**:9159-70.
12. Anema, A., et al., *Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis*. HIV Medicine, 2008. **9**:57-61.
13. Atashili, J., L. Kalilani, and A.A. Adimora, *Efficacy and clinical effectiveness of influenza vaccines in HIV-infected individuals: a meta-analysis*. BMC infectious diseases, 2006. **6**: p. 138.
14. Kuster, S.P., et al., *Incidence of influenza in healthy adults and healthcare workers: a systematic review and meta-analysis*. PLoS One, 2011. **6**:e26239.
15. Jefferson, T.O., et al., *Vaccines for preventing influenza in healthy adults*. Cochrane Database of Systematic Reviews, 2007:CD001269.
16. Ng, A.N. and C.K. Lai, *Effectiveness of seasonal influenza vaccination in healthcare workers: a systematic review*. Journal of Hospital Infection, 2011. **79**:279-86.
17. Burls, A., et al., *Vaccinating healthcare workers against influenza to protect the vulnerable--is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation*. Vaccine, 2006. **24**:4212-21.
18. Hollmeyer, H.G., et al., *Influenza vaccination of health care workers in hospitals--a review of studies on attitudes and predictors*. Vaccine, 2009. **27**:3935-44.
19. Postma, M.J., et al., *Further evidence for favorable cost-effectiveness of elderly influenza vaccination*. Expert Review of Pharmacoeconomics and Outcomes Research, 2006. **6**:215-27.



20. Mullooly, J.P., et al., *Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization*. *Annals of Internal Medicine*, 1994. **121**:947-52.
21. Neuzil, K.M., et al., *Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women*. *American Journal of Epidemiology*, 1998. **148**:1094-102.
22. Hartert, T.V., et al., *Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season*. *American Journal of Obstetrics and Gynecology*, 2003. **189**:1705-12.
23. Callaghan, W.M., S.Y. Chu, and D.J. Jamieson, *Deaths from seasonal influenza among pregnant women in the United States, 1998-2005*. *Obstetrics and Gynecology*, 2010. **115**:919-23.
24. Zarychanski, R., et al., *Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection*. *Canadian Medical Association Journal*, 2010. **182**:257-64.
25. Webb, S.A. and I.M. Seppelt, *Pandemic (H1N1) 2009 influenza ("swine flu") in Australian and New Zealand intensive care*. *Critical care and resuscitation : Journal of the Australasian Academy of Critical Care Medicine*, 2009. **11**:170-2.
26. Jamieson, D.J., et al., *H1N1 2009 influenza virus infection during pregnancy in the USA*. *Lancet*, 2009. **374**:451-8.
27. Ward, K.A., P.J. Spokes, and J.M. McAnulty, *Case-control study of risk factors for hospitalization caused by pandemic (H1N1) 2009*. *Emerging Infectious Diseases*, 2011. **17**:1409-16.
28. Archer, B., et al., *Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases*. *Eurosurveillance*, 2009. **14**:pii=19369.
29. Van Kerkhove, M.D., et al., *Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis*. *PLoS medicine*, 2011. **8**:e1001053.
30. Creanga, A.A., et al., *Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women*. *Obstetrics and Gynecology*, 2010. **115**:717-26.
31. ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. *Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study*. *BMJ*, 2010. **340**:c1279.
32. *2009 pandemic influenza A (H1N1) in pregnant women requiring intensive care - New York City, 2009*. *Morbidity and Mortality Weekly Report*, 2010. **59**:321-6.
33. Hewagama, S., et al., *2009 H1N1 influenza A and pregnancy outcomes in Victoria, Australia*. *Clinical Infectious Diseases*, 2010. **50**:686-90.
34. Louie, J.K., et al., *Severe 2009 H1N1 influenza in pregnant and postpartum women in California*. *The New England Journal of Medicine*, 2010. **362**:27-35.
35. McNeil, S.A., et al., *Effect of respiratory hospitalization during pregnancy on infant outcomes*. *American Journal of Obstetrics and Gynecology*, 2011. **204**(Suppl 1):S54-7.
36. Omer, S.B., et al., *Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study*. *PLoS Medicine*, 2011. **8**:e1000441.
37. Englund, J.A., et al., *Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants*. *The Journal of Infectious Diseases*, 1993. **168**:647-56.

38. Steinhoff, M.C., et al., *Influenza immunization in pregnancy--antibody responses in mothers and infants*. The New England Journal of Medicine, 2010. **362**:1644-6.
39. Deinard, A.S. and P. Ogburn, Jr., *A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome*. American Journal of Obstetrics and Gynecology, 1981. **140**:240-5.
40. Murray, D.L., et al., *Antibody response to monovalent A/New Jersey/8/76 influenza vaccine in pregnant women*. Journal of Clinical Microbiology, 1979. **10**:184-7.
41. Sumaya, C.V. and R.S. Gibbs, *Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant*. The Journal of Infectious Diseases, 1979. **140**:141-6.
42. Puleston, R.L., et al., *Observational study to investigate vertically acquired passive immunity in babies of mothers vaccinated against H1N1v during pregnancy*. Health Technology Assessment, 2010. **14**:1-82.
43. Zuccotti, G., et al., *Transplacental antibody transfer following maternal immunization with a pandemic 2009 influenza A(H1N1) MF59-adjuvanted vaccine*. Journal of the American Medical Association, 2010. **304**:2360-1.
44. Black, S.B., et al., *Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants*. American Journal of Perinatology, 2004. **21**:333-9.
45. Hulka, J.F., *Effectiveness of Polyvalent Influenza Vaccine in Pregnancy. Report of a Controlled Study during an Outbreak of Asian Influenza*. Obstetrics and Gynecology, 1964. **23**:830-7.
46. Zaman, K., et al., *Effectiveness of maternal influenza immunization in mothers and infants*. The New England Journal of Medicine, 2008. **359**:1555-64.
47. Steinhoff, M.C., et al., *Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial*. Canadian Medical Association Journal, 2012. **184**:645-53.
48. Poehling, K.A., et al., *Impact of maternal immunization on influenza hospitalizations in infants*. American Journal of Obstetrics and Gynecology, 2011. **204**(6 Suppl 1):S141-8.
49. Eick, A.A., et al., *Maternal influenza vaccination and effect on influenza virus infection in young infants*. Archives of Pediatrics & Adolescent Medicine, 2011. **165**:104-11.
50. Benowitz, I., et al., *Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants*. Clinical Infectious Diseases, 2010. **51**:1355-61.
51. ACOG Committee on Obstetric Practice, *ACOG committee opinion number 305, November 2004. Influenza vaccination and treatment during pregnancy*. Obstetrics and Gynecology, 2004. **104**:1125-6.
52. Hall, C.B., et al., *Trial of bivalent influenza A vaccine in high-risk infants*. The Journal of Infectious Diseases, 1977. **136** Suppl:S648-51.
53. Heinonen, O.P., et al., *Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy*. International journal of epidemiology, 1973. **2**(3): p. 229-35.
54. Girard, M.P., et al., *Report of the 7th meeting on Evaluation of Pandemic Influenza Vaccines in Clinical Trials, World Health Organization, Geneva, 17-18 February 2011*. Vaccine, 2011. **29**:7579-86.
55. Folkenberg, M., et al., *Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark November 2009-March 2010*. Vaccine, 2011. **29**:1180-4.

56. Lim, S.H., et al., *Adverse reaction of influenza A (H1N1) 2009 virus vaccination in pregnant women and its effect on newborns*. *Vaccine*, 2010. **28**:7455-6.
57. Parretta, E., et al., *Italian post-marketing surveillance for adverse event reports after MF59-adjuvanted H1N1v vaccination*. *Vaccine*, 2011. **29**:3708-13.
58. Tavares, F., et al., *Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study*. *Vaccine*, 2011. **29**:6358-65.
59. Tsai, T., et al., *Exposure to MF59-adjuvanted influenza vaccines during pregnancy--a retrospective analysis*. *Vaccine*, 2010. **28**:1877-80.
60. France, E.K., et al., *Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants*. *Archives of Pediatrics & Adolescent Medicine*, 2006. **160**:1277-83.
61. Munoz, F.M., et al., *Safety of influenza vaccination during pregnancy*. *American Journal of Obstetrics and Gynecology*, 2005. **192**:1098-106.
62. Goldfarb, I., et al., *Uptake of influenza vaccine in pregnant women during the 2009 H1N1 influenza pandemic*. *American Journal of Obstetrics and Gynecology*, 2011. **204**(6 Suppl 1):S112-5.
63. Gracie, S., et al., *Utilization of the 2009 H1N1 vaccine by pregnant women in a pandemic year*. *Journal of Obstetrics and Gynaecology Canada*, 2011. **33**:127-33.
64. Fisher, B.M., et al., *Behaviors and perceptions regarding seasonal and H1N1 influenza vaccination during pregnancy*. *American Journal of Obstetrics and Gynecology*, 2011. **204**(6 Suppl 1):S107-11.
65. Kharbanda, E.O., et al., *Exploring pregnant women's views on influenza vaccination and educational text messages*. *Preventive Medicine*, 2011. **52**:75-7.
66. Vitek, W.S., et al., *Vaccine eligibility and acceptance among ambulatory obstetric and gynecologic patients*. *Vaccine*, 2011. **29**:2024-8.
67. Salgado, C.D., et al., *Influenza in the acute hospital setting*. *Lancet Infectious Diseases*, 2002. **2**:145-55.
68. Balkhy, H.H., A. El-Saed, and M. Sallah, *Epidemiology of H1N1 (2009) influenza among healthcare workers in a tertiary care center in Saudi Arabia: a 6-month surveillance study*. *Infection Control and Hospital Epidemiology*, 2010. **31**:1004-10.
69. Chen, M.I., et al., *Risk factors for pandemic (H1N1) 2009 virus seroconversion among hospital staff, Singapore*. *Emerging Infectious Diseases*, 2010. **16**:1554-61.
70. Weingarten, S., et al., *Barriers to influenza vaccine acceptance. A survey of physicians and nurses*. *American Journal of Infection Control*, 1989. **17**:202-7.
71. Elder, A.G., et al., *Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993-4 epidemic: results of serum testing and questionnaire*. *British Medical Journal*, 1996. **313**:1241-2.
72. Srinivasan, A. and T.M. Perl, *Respiratory protection against influenza*. *Journal of the American Medical Association*, 2009. **302**:1903-4.
73. Magill, S.S., et al., *Investigation of an outbreak of 2009 pandemic influenza A virus (H1N1) infections among healthcare personnel in a Chicago hospital*. *Infection Control and Hospital Epidemiology*, 2011. **32**:611-5.
74. Williams, C.J., et al., *Seasonal influenza risk in hospital healthcare workers is more strongly associated with household than occupational exposures: results from a*

- prospective cohort study in Berlin, Germany, 2006/07*. BMC Infectious Diseases, 2010. **10**:8.
75. Cunney, R.J., et al., *An outbreak of influenza A in a neonatal intensive care unit*. Infection Control and Hospital Epidemiology, 2000. **21**:449-54.
  76. Chironna, M., et al., *A nosocomial outbreak of 2009 pandemic influenza A(H1N1) in a paediatric oncology ward in Italy, October-November 2009*. Eurosurveillance, 2010. **15**:pii: 19454.
  77. Ruel, N., et al., *[Outbreaks due to respiratory syncytial virus and influenza virus A/H3N in institutionalized aged. Role of immunological status to influenza vaccine and possible implication of caregivers in the transmission]*. Presse Médicale, 2002. **31**:349-55.
  78. Cho, S.H., J.H. Hwang, and J. Kim, *Nurse staffing and patient mortality in intensive care units*. Nursing Research, 2008. **57**:322-30.
  79. Wilde, J.A., et al., *Effectiveness of influenza vaccine in health care professionals: a randomized trial*. Journal of the American Medical Association, 1999. **281**:908-13.
  80. Saxen, H. and M. Virtanen, *Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers*. The Pediatric Infectious Disease Journal, 1999. **18**:779-83.
  81. Kheok, S.W., et al., *The efficacy of influenza vaccination in healthcare workers in a tropical setting: a prospective investigator blinded observational study*. Annals Academic Medicine Singapore, 2008. **37**:465-9.
  82. Oshitani, H., et al., *Influenza vaccination levels and influenza-like illness in long-term-care facilities for elderly people in Niigata, Japan, during an influenza A (H3N2) epidemic*. Infection Control and Hospital Epidemiology, 2000. **21**:728-30.
  83. Potter, J., et al., *Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients*. Journal of Infectious Diseases, 1997. **175**:1-6.
  84. Shugarman, L.R., et al., *The influence of staff and resident immunization rates on influenza-like illness outbreaks in nursing homes*. Journal of the American Medical Directors Association, 2006. **7**:562-7.
  85. Stevenson, C.G., et al., *Prevention of influenza and pneumococcal pneumonia in Canadian long-term care facilities: how are we doing?* Canadian Medical Association Journal, 2001. **164**:1413-9.
  86. Carman, W.F., et al., *Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial*. Lancet, 2000. **355**:93-7.
  87. Hayward, A.C. and J. Watson, *Effectiveness of influenza vaccination of staff on morbidity, and mortality of residents of long term care facilities for the elderly*. Vaccine, 2011. **29**:2357-8.
  88. Lemaitre, M., et al., *Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial*. Journal of the American Geriatrics Society, 2009. **57**:1580-6.
  89. Thomas, R.E., T. Jefferson, and T.J. Lasserson, *Influenza vaccination for healthcare workers who work with the elderly*. Cochrane Database Systemtic Review, 2010. (2):CD005187.
  90. van den Dool, C., et al., *The effects of influenza vaccination of health care workers in nursing homes: insights from a mathematical model*. PLoS Medicine, 2008. **5**:e200.
  91. van den Dool, C., et al., *Modeling the effects of influenza vaccination of health care workers in hospital departments*. Vaccine, 2009. **27**:6261-7.

92. Belshe, R., et al., *Safety, immunogenicity and efficacy of intranasal, live attenuated influenza vaccine*. Expert Review of Vaccines, 2004. **3**:643-54.
93. Vellozzi, C., et al., *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring*. Vaccine, 2009. **27**:2114-20.
94. Baxter, R., et al., *A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in adults 18-49 years of age*. Vaccine, 2012. **30**:3053-60.
95. Caban-Martinez, A.J., et al., *Sustained low influenza vaccination rates in US healthcare workers*. Preventive Medicine, 2010. **50**:210-2.
96. Christini, A.B., K.A. Shutt, and K.E. Byers, *Influenza vaccination rates and motivators among healthcare worker groups*. Infection Control and Hospital Epidemiology, 2007. **28**:171-7.
97. Pearson, M.L., C.B. Bridges, and S.A. Harper, *Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP)*. MMWR Recommendations and Reports, 2006. **55**(RR-2):1-16.
98. Polgreen, P.M., et al., *Relationship of influenza vaccination declination statements and influenza vaccination rates for healthcare workers in 22 US hospitals*. Infection Control Hospital Epidemiology, 2008. **29**:675-7.
99. Song, J.Y., et al., *Effect of a hospital campaign for influenza vaccination of healthcare workers*. Infection Control Hospital Epidemiology, 2006. **27**:612-7.
100. *Influenza vaccination coverage among health-care personnel --- United States, 2010-11 influenza season*. MMWR Morbidity Mortality Weekly Report, 2011. **60**:1073-7.
101. Caplan, A., *Time to mandate influenza vaccination in health-care workers*. Lancet, 2011. **378**:310-1.
102. Steckel, C.M., *Mandatory influenza immunization for health care workers--an ethical discussion*. AAOHN Journal, 2007. **55**:34-9.
103. van Delden, J.J., et al., *The ethics of mandatory vaccination against influenza for health care workers*. Vaccine, 2008. **26**:5562-6.
104. Glezen, W.P., et al., *Acute respiratory disease associated with influenza epidemics in Houston, 1981-1983*. Journal of Infectious Diseases, 1987. **155**:1119-26.
105. Monto, A.S. and F. Kioumeh, *The Tecumseh Study of Respiratory Illness. IX. Occurrence of influenza in the community, 1966--1971*. American Journal of Epidemiology, 1975. **102**:553-63.
106. Sauerbrei, A., et al., *Seroprevalence of influenza A and B in German infants and adolescents*. Medical Microbiology and Immunology, 2009. **198**:93-101.
107. Frank, A.L., et al., *Patterns of shedding of myxoviruses and paramyxoviruses in children*. The Journal of Infectious Diseases, 1981. **144**:433-41.
108. Hall, C.B., et al., *Viral shedding patterns of children with influenza B infection*. The Journal of Infectious Diseases, 1979. **140**:610-3.
109. Glezen, P.F. and R.B. Couch, *Interpandemic influenza in the Houston area, 1974-76*. The New England Journal of Medicine, 1978. **298**:587-92.
110. Glezen, W.P., *Considerations of the risk of influenza in children and indications for prophylaxis*. Reviews of Infectious Diseases, 1980. **2**:408-20.
111. Longini, I.M., Jr., et al., *Estimating household and community transmission parameters for influenza*. American Journal of Epidemiology, 1982. **115**:736-51.

112. Neuzil, K.M., C. Hohlbein, and Y. Zhu, *Illness among schoolchildren during influenza season: effect on school absenteeism, parental absenteeism from work, and secondary illness in families*. *Archives of Pediatrics and Adolescence Medicine*, 2002. **156**:986-91.
113. Mullooly, J.P. and W.H. Barker, *Impact of type A influenza on children: a retrospective study*. *American Journal of Public Health*, 1982. **72**:1008-16.
114. Neuzil, K.M., et al., *The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children*. *The New England Journal of Medicine*, 2000. **342**:225-31.
115. Neuzil, K.M., et al., *Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study*. *Journal of Infectious Diseases*, 2002. **185**:147-52.
116. Paget, W.J., et al., *Assessing the burden of paediatric influenza in Europe: the European Paediatric Influenza Analysis (EPIA) project*. *European Journal of Pediatrics*, 2010. **169**:997-1008.
117. Poehling, K.A., et al., *The underrecognized burden of influenza in young children*. *The New England Journal of Medicine*, 2006. **355**:31-40.
118. O'Brien, M.A., et al., *Incidence of outpatient visits and hospitalizations related to influenza in infants and young children*. *Pediatrics*, 2004. **113**:585-93.
119. Brooks, W.A., et al., *Influenza is a major contributor to childhood pneumonia in a tropical developing country*. *The Pediatric Infectious Disease Journal*, 2010. **29**:216-21.
120. Niang, M.N., et al., *Viral etiology of respiratory infections in children under 5 years old living in tropical rural areas of Senegal: The EVIRA project*. *Journal of Medical Virology*, 2010. **82**:866-72.
121. Simmerman, J.M., et al., *The cost of influenza in Thailand*. *Vaccine*, 2006. **24**:4417-26.
122. Ahn, K.M., et al., *Clinical characteristics of acute viral lower respiratory tract infections in hospitalized children in Seoul, 1996-1998*. *Journal of Korean Medical Science*, 1999. **14**:405-11.
123. Banerji, A., et al., *Risk factors and viruses associated with hospitalization due to lower respiratory tract infections in Canadian Inuit children : a case-control study*. *The Pediatric Infectious Disease Journal*, 2009. **28**:697-701.
124. Berkley, J.A., et al., *Viral etiology of severe pneumonia among Kenyan infants and children*. *The Journal of the American Medical Association*, 2010. **303**:2051-7.
125. Cilla, G., et al., *Viruses in community-acquired pneumonia in children aged less than 3 years old: High rate of viral coinfection*. *Journal of Medical Virology*, 2008. **80**:1843-9.
126. Forster, J., et al., *Prospective population-based study of viral lower respiratory tract infections in children under 3 years of age (the PRI.DE study)*. *European Journal of Pediatrics*, 2004. **163**:709-16.
127. Johnson, A.W., et al., *Etiologic agents and outcome determinants of community-acquired pneumonia in urban children: a hospital-based study*. *Journal of the National Medical Association*, 2008. **100**:370-85.
128. Michelow, I.C., et al., *Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children*. *Pediatrics*, 2004. **113**:701-7.
129. Nakayama, E., et al., *Rapid optimization of antimicrobial chemotherapy given to pediatric patients with community-acquired pneumonia using PCR techniques with serology and standard culture*. *Journal of Infection and Chemotherapy*, 2007. **13**:305-13.

130. Nascimento-Carvalho, C.M., et al., *The role of respiratory viral infections among children hospitalized for community-acquired pneumonia in a developing country*. The Pediatric Infectious Disease Journal, 2008. **27**:939-41.
131. O'Callaghan-Gordo, C., et al., *Viral acute respiratory infections among infants visited in a rural hospital of southern Mozambique*. Tropical Medicine and International Health, 2011. **16**:1054-60.
132. Olsen, S.J., et al., *Incidence of respiratory pathogens in persons hospitalized with pneumonia in two provinces in Thailand*. Epidemiology and Infection, 2010. **138**:1811-22.
133. Samransamruajkit, R., et al., *Prevalence, clinical presentations and complications among hospitalized children with influenza pneumonia*. Japanese Journal of Infectious Diseases, 2008. **61**:446-9.
134. Simmerman, J.M., et al., *Incidence, seasonality and mortality associated with influenza pneumonia in Thailand: 2005-2008*. PloS One, 2009. **4**:e7776.
135. Singleton, R.J., et al., *Viral respiratory infections in hospitalized and community control children in Alaska*. Journal of Medical Virology, 2010. **82**:1282-90.
136. Thomazelli, L.M., et al., *Surveillance of eight respiratory viruses in clinical samples of pediatric patients in southeast Brazil*. Jornal de Pediatria, 2007. **83**:422-8.
137. Tsolia, M.N., et al., *Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections*. Clinical Infectious Diseases, 2004. **39**:681-6.
138. Virkki, R., et al., *Radiographic follow-up of pneumonia in children*. Pediatric Pulmonology, 2005. **40**:223-7.
139. Wasem, S., et al., *Lower respiratory tract disease in children: constant pathogens - constant management?!* Klinische Padiatrie, 2008. **220**:291-5.
140. Yu, C.M., et al., *[Analysis of viral etiology of severe pneumonia in infants and young children in Chongqing area]*. Chinese Journal of Pediatrics, 2010. **48**:143-7.
141. Chiu, S.S., et al., *Virologically confirmed population-based burden of hospitalization caused by influenza A and B among children in Hong Kong*. Clinical Infectious Diseases, 2009. **49**:1016-21.
142. Iwane, M.K., 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.
143. Izurieta, H.S., et al., *Influenza and the rates of hospitalization for respiratory disease among infants and young children*. The New England journal of medicine, 2000. **342**(4): p. 232-9.
144. Munoz, F.M., *The impact of influenza in children*. Seminars in Pediatric Infectious Diseases, 2002. **13**:72-8.
145. Neuzil, K.M., et al., *The burden of influenza illness in children with asthma and other chronic medical conditions*. The Journal of Pediatrics, 2000. **137**:856-64.
146. Finelli, L., et al., *Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection*. Pediatrics, 2008. **122**:805-11.
147. Thompson, W.W., et al., *Influenza-associated hospitalizations in the United States*. The Journal of the American Medical Association, 2004. **292**:1333-40.
148. Ampofo, K., et al., *Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection*. Pediatrics, 2006. **118**:2409-17.

149. Dawood, F.S., et al., *Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008*. The Journal of Pediatrics, 2010. **157**:808-14.
150. Griffin, M.R., et al., *Epidemiology of respiratory infections in young children: insights from the new vaccine surveillance network*. The Pediatric Infectious Disease Journal, 2004. **23**(Suppl):S188-92.
151. Negri, E., et al., *Influenza vaccine in healthy children: a meta-analysis*. Vaccine, 2005. **23**:2851-61.
152. Clover, R.D., et al., *Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses*. The Journal of Infectious Diseases, 1991. **163**:300-4.
153. Hoberman, A., et al., *Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial*. The Journal of the American Medical Association, 2003. **290**:1608-16.
154. Loeb, M., et al., *Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial*. The Journal of the American Medical Association, 2010. **303**:943-50.
155. Neuzil, K.M., et al., *Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience*. The Pediatric Infectious Disease Journal, 2001. **20**:733-40.
156. Vesikari, T., et al., *Oil-in-water emulsion adjuvant with influenza vaccine in young children*. The New England Journal of Medicine, 2011. **365**:1406-16.
157. Heikkinen, T. and S. Heinonen, *Effectiveness and safety of influenza vaccination in children: European perspective*. Vaccine, 2011. **29**:7529-34.
158. Cochran, L.W., et al., *Vaccine effectiveness against laboratory-confirmed influenza in infants: A matched case control study*. Human Vaccines, 2010. **6**:729-735.
159. Eisenberg, K.W., et al., *Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003-2004 and 2004-2005 influenza seasons*. Pediatrics, 2008. **122**:911-9.
160. Joshi, A.Y., et al., *Effectiveness of inactivated influenza vaccine in children less than 5 years of age over multiple influenza seasons: a case-control study*. Vaccine, 2009. **27**(33): p. 4457-61.
161. Katayose, M., et al., *The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons*. Vaccine, 2011. **29**:1844-9.
162. Kelly, H., et al., *Vaccine Effectiveness Against Laboratory-confirmed Influenza in Healthy Young Children: A Case-Control Study*. The Pediatric Infectious Disease Journal, 2011. **30**:107-11.
163. Shuler, C.M., et al., *Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004*. Pediatrics, 2007. **119**:e587-95.
164. Szilagyi, P.G., et al., *Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study*. Archives of Pediatrics and Adolescent Medicine, 2008. **162**:943-51.
165. Esposito, S., et al., *Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households*. Vaccine, 2003. **21**:3162-8.



166. Hurwitz, E.S., et al., *Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts*. The Journal of the American Medical Association, 2000. **284**:1677-82.
167. Englund, J.A., et al., *Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers*. Pediatrics, 2006. **118**:e579-85.
168. Neuzil, K.M., et al., *Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naive 5-8-year-old children*. The Journal of Infectious Diseases, 2006. **194**:1032-9.
169. Walter, E.B., et al., *Influenza vaccine immunogenicity in 6- to 23-month-old children: are identical antigens necessary for priming?* Pediatrics, 2006. **118**:e570-8.
170. Allison, M.A., et al., *Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season*. The Journal of Pediatrics, 2006. **149**:755-762.
171. Ritzwoller, D.P., et al., *Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses*. Pediatrics, 2005. **116**:153-9.
172. Groothuis, J.R., M.V. Lehr, and M.J. Levin, *Safety and immunogenicity of a purified haemagglutinin antigen in very young high-risk children*. Vaccine, 1994. **12**:139-41.
173. Sugaya, N., et al., *Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B*. The Journal of the American Medical Association, 1994. **272**:1122-6.
174. Park, C.L., et al., *Influenza vaccination of children during acute asthma exacerbation and concurrent prednisone therapy*. Pediatrics, 1996. **98**:196-200.
175. Alexandrova, G.I., et al., *Study of live recombinant cold-adapted influenza bivalent vaccine of type A for use in children: an epidemiological control trial*. Vaccine, 1986. **4**:114-8.
176. Belshe, R.B., et al., *Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine*. The Journal of Pediatrics, 2000. **136**:168-75.
177. Belshe, R.B., et al., *The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children*. The New England Journal of Medicine, 1998. **338**:1405-12.
178. Gruber, W.C., et al., *Evaluation of live attenuated influenza vaccines in children 6-18 months of age: safety, immunogenicity, and efficacy*. National Institute of Allergy and Infectious Diseases, Vaccine and Treatment Evaluation Program and the Wyeth-Ayerst ca Influenza Vaccine Investigators Group. The Journal of Infectious Diseases, 1996. **173**:1313-9.
179. Tam, J.S., et al., *Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia*. The Pediatric Infectious Disease Journal, 2007. **26**:619-28.
180. Vesikari, T., et al., *Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care*. Pediatrics, 2006. **118**:2298-312.
181. Ambrose, C.S., et al., *The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta-analysis of 8 randomized controlled studies*. Vaccine, 2012. **30**:886-92.
182. Belshe, R.B., et al., *Live attenuated versus inactivated influenza vaccine in infants and young children*. The New England Journal of Medicine, 2007. **356**:685-96.

183. Belshe, R.B., et al., *Efficacy of live attenuated influenza vaccine in children 6 months to 17 years of age*. *Influenza and Other Respiratory Viruses*, 2010. **4**:141-5.
184. Glezen, W.P., et al., *Direct and indirect effectiveness of influenza vaccination delivered to children at school preceding an epidemic caused by 3 new influenza virus variants*. *The Journal of Infectious Diseases*, 2010. **202**:1626-33.
185. Maeda, T., et al., *Prophylactic effect of inactivated influenza vaccine on young children*. *Pediatrics International*, 2002. **44**:43-6.
186. Heinonen, S., et al., *Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study*. *The Lancet Infectious Diseases*, 2011. **11**:23-9.
187. Bodewes, R., et al., *Annual vaccination against influenza virus hampers development of virus-specific CD8 T cell immunity in children*. *Journal of Virology*, 2011. **85**:11995-2000.
188. Bodewes, R., J.H. Kreijtz, and G.F. Rimmelzwaan, *Yearly influenza vaccinations: a double-edged sword?* *The Lancet Infectious Diseases*, 2009. **9**:784-8.
189. *FluMist [Package insert]*. Gaithersburg, MD: MedImmune Vaccines, Inc.; 2007.
190. *Estimates of deaths associated with seasonal influenza --- United States, 1976-2007*. *Morbidity and Mortality Weekly Report*, 2010. **59**:1057-62.
191. Hardelid, P., R. Pebody, and N. Andrews, *Mortality caused by influenza and respiratory syncytial virus by age group in England and Wales 1999-2010*. *Influenza and Other Respiratory Viruses*, 2012. Mar 9. doi: 10.1111/j.1750-2659.2012.00345.x. [Epub ahead of print]
192. Thompson, W.W., et al., *Mortality associated with influenza and respiratory syncytial virus in the United States*. *The Journal of the American Medical Association*, 2003. **289**:179-86.
193. Nunes, B., et al., *Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004*. *PloS One*, 2011. **6**:e20661.
194. Newall, A.T., J.G. Wood, and C.R. Macintyre, *Influenza-related hospitalisation and death in Australians aged 50 years and older*. *Vaccine*, 2008. **26**:2135-41.
195. Chow, A., et al., *Influenza-associated deaths in tropical Singapore*. *Emerging Infectious Diseases*, 2006. **12**:114-21.
196. Wong, C.M., et al., *Influenza-associated hospitalization in a subtropical city*. *PLoS Medicine*, 2006. **3**:e121.
197. Yang, L., et al., *Seasonal effects of influenza on mortality in a subtropical city*. *BMC Infectious Diseases*, 2009. **9**:133.
198. Simonsen, L., et al., *The impact of influenza epidemics on hospitalizations*. *The Journal of Infectious Diseases*, 2000. **181**:831-7.
199. Barker, W.H. and J.P. Mullooly, *Impact of epidemic type A influenza in a defined adult population*. *American Journal of Epidemiology*, 1980. **112**:798-811.
200. Cohen, C., et al., *Elevated influenza-related excess mortality in South African elderly individuals, 1998-2005*. *Clinical Infectious Diseases*, 2010. **51**:1362-9.
201. Alling, D.W., W.C. Blackwelder, and C.H. Stuart-Harris, *A study of excess mortality during influenza epidemics in the United States, 1968-1976*. *American Journal of Epidemiology*, 1981. **113**:30-43.
202. Burette, P., et al., *Influenza outbreak in a well-vaccinated nursing home population in Belgium*. *Acta Clinica Belgica*, 2009. **64**:324-8.

203. Camilloni, B., et al., *An influenza B outbreak during the 2007/2008 winter among appropriately immunized elderly people living in a nursing home*. *Vaccine*, 2010. **28**:7536-41.
204. Iorio, A.M., et al., *An influenza A/H3 outbreak during the 2004/2005 winter in elderly vaccinated people living in a nursing home*. *Vaccine*, 2006. **24**:6615-9.
205. Win, M.K., et al., *Influenza B outbreak among influenza-vaccinated welfare home residents in Singapore*. *Annals of the Academy of Medicine, Singapore*, 2010. **39**:448-52.
206. Ferson, M.J., et al., *Concurrent summer influenza and pertussis outbreaks in a nursing home in Sydney, Australia*. *Infection Control and Hospital Epidemiology*, 2004. **25**:962-6.
207. Gaillat, J., et al., *Summer influenza outbreak in a home for the elderly: application of preventive measures*. *Journal of Hospital Infection*, 2008. **70**:272-7.
208. Kohn, M.A., et al., *Three summertime outbreaks of influenza type A*. *The Journal of Infectious Diseases*, 1995. **172**:246-9.
209. Allsup, S.J., et al., *Can a short period of micronutrient supplementation in older institutionalized people improve response to influenza vaccine? A randomized, controlled trial*. *Journal of the American Geriatrics Society*, 2004. **52**:20-4.
210. Edmondson, W.P., Jr., et al., *A comparison of subcutaneous, nasal, and combined influenza vaccination. II. Protection against natural challenge*. *American Journal of Epidemiology*, 1971. **93**:480-6.
211. Govaert, T.M., et al., *The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial*. *The Journal of the American Medical Association*, 1994. **272**:1661-5.
212. Stuart, W.H., et al., *Evaluation of monovalent influenza vaccine in a retirement community during the epidemic of 1965-66*. *The Journal of the American Medical Association*, 1969. **209**:232-8.
213. Vu, T., et al., *A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community*. *Vaccine*, 2002. **20**:1831-6.
214. Coles, F.B., G.J. Balzano, and D.L. Morse, *An outbreak of influenza A (H3N2) in a well immunized nursing home population*. *Journal of the American Geriatrics Society*, 1992. **40**:589-92.
215. Kelly, H. and A.T. Newall, *Mortality benefits of influenza vaccination in elderly people*. *The Lancet Infectious Diseases*, 2008. **8**:462-3; author reply 463-5.
216. Libow, L.S., et al., *Sequential outbreak of influenza A and B in a nursing home: efficacy of vaccine and amantadine*. *Journal of the American Geriatrics Society*, 1996. **44**:1153-7.
217. Antunes, J.L., et al., *Effectiveness of influenza vaccination and its impact on health inequalities*. *International Journal of Epidemiology*, 2007. **36**:1319-26.
218. Kissling, E., et al., *I-MOVE Multi-Centre Case Control Study 2010-11: Overall and Stratified Estimates of Influenza Vaccine Effectiveness in Europe*. *PloS One*, 2011. **6**:e27622.
219. Praditsuwan, R., et al., *The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community*. *Journal of the Medical Association of Thailand*, 2005. **88**:256-64.
220. Patriarca, P.A., et al., *Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic*. *The Journal of the American Medical Association*, 1985. **253**:1136-9.

221. Isahak, I., A.A. Mahayiddin, and R. Ismail, *Effectiveness of influenza vaccination in prevention of influenza-like illness among inhabitants of old folk homes*. The Southeast Asian Journal of Tropical Medicine and Public Health, 2007. **38**:841-8.
222. Jackson, L.A., et al., *Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors*. International Journal of Epidemiology, 2006. **35**:345-52.
223. Baxter, R., G.T. Ray, and B.H. Fireman, *Effect of influenza vaccination on hospitalizations in persons aged 50 years and older*. Vaccine, 2010. **28**:7267-72.
224. Fireman, B., et al., *Influenza vaccination and mortality: differentiating vaccine effects from bias*. American Journal of Epidemiology, 2009. **170**:650-6.
225. Ambrose, C.S., M.J. Levin, and R.B. Belshe, *The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults*. Influenza and Other Respiratory Viruses, 2011. **5**:67-75.
226. De Villiers, P.J., et al., *Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older*. Vaccine, 2009. **28**:228-34.
227. Forrest, B.D., et al., *A prospective, randomized, open-label trial comparing the safety and efficacy of trivalent live attenuated and inactivated influenza vaccines in adults 60 years of age and older*. Vaccine, 2011. **29**:3633-9.
228. Rudenko, L.G., et al., *Immunogenicity and efficacy of Russian live attenuated and US inactivated influenza vaccines used alone and in combination in nursing home residents*. Vaccine, 2000. **19**:308-18.
229. Cristiani, C., et al., *Safety of MF-59 adjuvanted vaccine for pandemic influenza: results of the vaccination campaign in an Italian health district*. Vaccine, 2011. **29**:3443-8.
230. Steens, A., et al., *Effectiveness of a MF-59-adjuvanted pandemic influenza vaccine to prevent 2009 A/H1N1 influenza-related hospitalisation; a matched case-control study*. BMC Infectious Diseases, 2011. **11**:196.
231. Andrews, N., et al., *Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England*. The Journal of Infectious Diseases, 2011. **203**:32-9.
232. Falsey, A.R., et al., *Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older*. The Journal of Infectious Diseases, 2009. **200**:172-80.
233. *Licensure of a high-dose inactivated influenza vaccine for persons aged  $\geq$  65 years (Fluzone High-Dose) and guidance for use - United States, 2010*. Morbidity and Mortality Weekly Report, 2010. **59**:485-6.
234. Dawood, F.S., et al., *Children with asthma hospitalized with seasonal or pandemic influenza, 2003-2009*. Pediatrics, 2011. **128**:e27-32.
235. Coffin, S.E., et al., *Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza*. Pediatrics, 2007. **119**:740-8.
236. Bhat, N., et al., *Influenza-associated deaths among children in the United States, 2003-2004*. The New England Journal of Medicine, 2005. **353**:2559-67.
237. Mohan, A., et al., *Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review*. Respiriology, 2010. **15**:536-42.
238. Louie, J.K., et al., *A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1)*. Clinical Infectious Diseases, 2011. **52**:301-12.

239. Dodds, L., et al., *Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women*. Canadian Medical Association Journal, 2007. **176**:463-8.
240. Couch, R.B., *Influenza, influenza virus vaccine, and human immunodeficiency virus infection*. Clinical Infectious Diseases, 1999. **28**:548-51.
241. Radwan, H.M., et al., *Influenza in human immunodeficiency virus-infected patients during the 1997-1998 influenza season*. Clinical Infectious Diseases, 2000. **31**:604-6.
242. Safrin, S., J.D. Rush, and J. Mills, *Influenza in patients with human immunodeficiency virus infection*. Chest, 1990. **98**:33-7.
243. Tasker, S.A., et al., *Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial*. Vaccine, 1998. **16**:1039-42.
244. Couch, R.B., J.A. Englund, and E. Whimbey, *Respiratory viral infections in immunocompetent and immunocompromised persons*. The American Journal of Medicine, 1997. **102**:2-9; discussion 25-6.
245. Greenberg, S.B., *Respiratory viral infections in adults*. Current Opinion in Pulmonary Medicine, 2002. **8**:201-8.
246. Ison, M.G. and F.G. Hayden, *Viral infections in immunocompromised patients: what's new with respiratory viruses?* Current Opinion in Infectious Diseases, 2002. **15**:355-67.
247. Boivin, G., N. Goyette, and H. Bernatchez, *Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient*. Clinical Infectious Diseases, 2002. **34**:E23-5.
248. Englund, J.A., et al., *Common emergence of amantadine- and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults*. Clinical Infectious Diseases, 1998. **26**:1418-24.
249. Memoli, M.J., et al., *Rapid selection of a transmissible multidrug-resistant influenza A/H3N2 virus in an immunocompromised host*. The Journal of Infectious Diseases, 2010. **201**:1397-403.
250. Couturier, B.A., et al., *Oseltamivir-resistant influenza A 2009 H1N1 virus in immunocompromised patients*. Influenza and Other Respiratory Viruses, 2010. **4**:199-204.
251. Graitcer, S.B., et al., *Characteristics of patients with oseltamivir-resistant pandemic (H1N1) 2009, United States*. Emerging Infectious Diseases, 2011. **17**:255-7.
252. Smits, A.J., et al., *Clinical effectiveness of conventional influenza vaccination in asthmatic children*. Epidemiology and Infection, 2002. **128**:205-11.
253. Wongsurakiat, P., et al., *Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study*. Chest, 2004. **125**:2011-20.
254. Poole, P.J., et al., *Influenza vaccine for patients with chronic obstructive pulmonary disease*. Cochrane Database of Systematic Reviews, 2006(1):CD002733.
255. Nichol, K.L., L. Baken, and A. Nelson, *Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease*. Annals of Internal Medicine, 1999. **130**:397-403.
256. Nichol, K.L., J. Wuorenma, and T. von Sternberg, *Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens*. Archives of Internal Medicine, 1998. **158**:1769-76.

257. Ciszewski, A., et al., *Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study*. European Heart Journal, 2008. **29**:1350-8.
258. Gurfinkel, E.P., et al., *Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study*. European Heart Journal, 2004. **25**:25-31.
259. Phrommintikul, A., et al., *Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome*. European Heart Journal, 2011. **32**:1730-5.
260. Herrera, G.A., et al., *Influenza vaccine effectiveness among 50-64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003-2004*. Vaccine, 2007. **25**:154-60.
261. Chadwick, E.G., et al., *Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children*. The Pediatric Infectious Disease Journal, 1994. **13**:206-11.
262. Fine, A.D., et al., *Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City*. Clinical Infectious Diseases, 2001. **32**:1784-91.
263. Huang, K.L., et al., *Antibody responses after influenza and pneumococcal immunization in HIV-infected homosexual men*. The Journal of the American Medical Association, 1987. **257**:2047-50.
264. Miotti, P.G., et al., *The influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine*. The Journal of the American Medical Association, 1989. **262**:779-83.
265. Kroon, F.P., et al., *Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study*. Vaccine, 2000. **18**:3040-9.
266. Staprans, S.I., et al., *Activation of virus replication after vaccination of HIV-1-infected individuals*. The Journal of Experimental Medicine, 1995. **182**:1727-37.
267. Crum-Cianflone, N.F., et al., *Durability of antibody responses after receipt of the monovalent 2009 pandemic influenza A (H1N1) vaccine among HIV-infected and HIV-uninfected adults*. Vaccine, 2011. **29**:3183-91.
268. Tebas, P., et al., *Poor immunogenicity of the H1N1 2009 vaccine in well controlled HIV-infected individuals*. AIDS, 2010. **24**:2187-92.
269. Fabbiani, M., et al., *Immune response to influenza A (H1N1)v monovalent MF59-adjuvanted vaccine in HIV-infected patients*. Vaccine, 2011. **29**:2836-9.
270. Kajaste-Rudnitski, A., et al., *Induction of protective antibody response by MF59-adjuvanted 2009 pandemic A/H1N1v influenza vaccine in HIV-1-infected individuals*. AIDS, 2011. **25**:177-83.
271. Manuel, O., et al., *Humoral response to the influenza A H1N1/09 monovalent AS03-adjuvanted vaccine in immunocompromised patients*. Clinical Infectious Diseases, 2011. **52**:248-56.
272. Madhi, S.A., et al., *Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety*. Clinical Infectious Diseases, 2011. **52**:128-37.
273. Avetisyan, G., et al., *Evaluation of immune responses to seasonal influenza vaccination in healthy volunteers and in patients after stem cell transplantation*. Transplantation, 2008. **86**:257-63.

274. de Lavallade, H., et al., *Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host*. *Haematologica*, 2011. **96**:307-14.
275. Lagler, H., et al., *Pandemic influenza A H1N1 vaccine in recipients of solid organ transplants: immunogenicity and tolerability outcomes after vero cell derived, non-adjuvanted, whole-virion vaccination*. *Vaccine*, 2011. **29**:6888-93.
276. Ortqvist, A., et al., *Effectiveness of an adjuvanted monovalent vaccine against the 2009 pandemic strain of influenza A(H1N1)v, in Stockholm County, Sweden*. *Clinical Infectious Diseases*, 2011. **52**:1203-11.
277. Rousseau, B., et al., *Immunogenicity and safety of the influenza A H1N1v 2009 vaccine in cancer patients treated with cytotoxic chemotherapy and/or targeted therapy: the VACANCE study*. *Annals of Oncology*, 2012. **23**:450-7.
278. Saad, C.G., et al., *Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases*. *Annals of the Rheumatic Diseases*, 2011. **70**:1068-73.
279. Soesman, N.M., et al., *Efficacy of influenza vaccination in adult liver transplant recipients*. *Journal of Medical Virology*, 2000. **61**:85-93.
280. Haller, W., et al., *Immune response to pandemic H1N1 2009 influenza a vaccination in pediatric liver transplant recipients*. *Liver Transplantation*, 2011. **17**:914-20.
281. Meier, S., et al., *Antibody responses to natural influenza A/H1N1/09 disease or following immunization with adjuvanted vaccines, in immunocompetent and immunocompromised children*. *Vaccine*, 2011. **29**:3548-57.
282. Shahgholi, E., et al., *Immunogenicity of trivalent influenza vaccine in children with acute lymphoblastic leukemia during maintenance therapy*. *Pediatric Blood and Cancer*, 2010. **54**:716-20.
283. Hurst, F.P., et al., *Outcomes associated with influenza vaccination in the first year after kidney transplantation*. *Clinical Journal of the American Society of Nephrology*, 2011. **6**:1192-7.
284. Langley, J.M., et al., *Pneumococcal and influenza immunization in asplenic persons: a retrospective population-based cohort study 1990-2002*. *BMC Infectious Diseases*, 2010. **10**:219.
285. Carr, S., et al., *Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer*. *The Journal of Infectious Diseases*, 2011. **204**:1475-82.
286. Halasa, N., et al., *Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer*. *Vaccine*, 2011. **29**:4110-5.
287. de Waure, C., et al., *Economic value of influenza vaccination*. *Human Vaccines and Immunotherapeutics*, 2012. **8**:119-29.
288. Maciosek, M.V., et al., *Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older*. *American Journal of Preventive Medicine*, 2006. **31**:72-9.
289. Nichol, K.L., *Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza*. *Archives of Internal Medicine*, 2001. **161**:749-59.
290. Nichol, K.L., K.P. Mallon, and P.M. Mendelman, *Cost benefit of influenza vaccination in healthy, working adults: an economic analysis based on the results of a clinical trial of trivalent live attenuated influenza virus vaccine*. *Vaccine*, 2003. **21**:2207-17.
291. Meltzer, M.I., et al., *An economic analysis of annual influenza vaccination of children*. *Vaccine*, 2005. **23**:1004-14.

292. Cohen, G.M. and M.D. Nettleman, *Economic impact of influenza vaccination in preschool children*. Pediatrics, 2000. **106**:973-6.
293. Dayan, G.H., et al., *Cost-effectiveness of influenza vaccination in high-risk children in Argentina*. Vaccine, 2001. **19**:4204-13.
294. Luce, B.R., et al., *Cost-effectiveness analysis of an intranasal influenza vaccine for the prevention of influenza in healthy children*. Pediatrics, 2001. **108**:E24.
295. White, T., S. Lavoie, and M.D. Nettleman, *Potential cost savings attributable to influenza vaccination of school-aged children*. Pediatrics, 1999. **103**:e73.
296. Prosser, L.A., et al., *Health benefits, risks, and cost-effectiveness of influenza vaccination of children*. Emerging Infectious Diseases, 2006. **12**:1548-58.
297. Jit, M., et al., *The cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales*. Vaccine, 2010. **29**:115-22.
298. Myers, E.R., D.A. Misurski, and G.K. Swamy, *Influence of timing of seasonal influenza vaccination on effectiveness and cost-effectiveness in pregnancy*. American Journal of Obstetrics and Gynecology, 2011. **204**(Suppl 1):S128-40.
299. Skedgel, C., et al., *An incremental economic evaluation of targeted and universal influenza vaccination in pregnant women*. Canadian Journal of Public Health, 2011. **102**:445-50.
300. Prosser, L.A., et al., *Non-traditional settings for influenza vaccination of adults: costs and cost effectiveness*. Pharmacoeconomics, 2008. **26**:163-78.
301. Apisarnthanarak, A., et al., *Reduction of seasonal influenza transmission among healthcare workers in an intensive care unit: a 4-year intervention study in Thailand*. Infection Control and Hospital Epidemiology, 2010. **31**:996-1003.
302. Chicaiza-Becerra, L.A., et al., *[Economic evaluation of influenza vaccine applied to health personnel attending hospitalised oncological patients]*. Revista de Salud Pública (Bogota), 2008. **10**:756-66.