Although influenza affects people of all ages, older adults often bear a greater proportion of the burden of severe influenza-associated morbidity and mortality. While individuals 65 years of age and older comprise only about 13% of the population in the United States (US), they represent more than 60% of influenza-related hospitalizations due to bacterial infections and pulmonary, cardiovascular, and cerebrovascular complications during a typical season, and about 90% of influenza-related deaths across all age groups. For each death due to influenza, there are approximately 8 hospitalizations. In all, adults 65 years of age and older account for about 40% of direct medical costs and 64% of the total economic burden of seasonal influenza in the US. As the population ages, these burdens will increase.

INFLUENZA-ASSOCIATED HOSPITALIZATIONS AND MORTALITY INCREASE WITH AGE

A study performed in England and Wales during 12 consecutive influenza seasons (1989-2001) quantified excess hospital admissions and average bed stay for respiratory conditions during influenza outbreaks and examined the importance of age. Excess admissions related to influenza were strongly age-related, with older adults accounting for the majority of hospitalizations. In all, adults 65 years of age and older account for about 40% of direct medical costs and 64% of the total economic burden of seasonal influenza in the US. As the population ages, these burdens will increase.

INFLUENZA: WHY THE HIGHER IMPACT IN OLDER ADULTS?

High-risk comorbidities

A number of factors influence the way in which older adults react to infection with influenza virus. Host factors, such as the accumulation of underlying disease conditions with age, play a role. The presence of high-risk comorbid conditions — such as diseases of the cardiovascular, pulmonary, renal, endocrine, or central nervous systems, and malignancy — dramatically increases the risk of influenza-related mortality in older adults.

For example, in one study conducted within a health maintenance organization during 2 influenza epidemics, the rate of pneumonia-and influenza-related deaths among adults 65 years of age and older increased sharply with the number of comorbid conditions. There were 9 deaths per 100,000 among those who had no comorbid high-risk conditions. For those with 1 comorbid condition, the mortality rate climbed to 217 per 100,000, and for those with 2 or more comorbid conditions, the rate was 306 per 100,000. In another study conducted in the United Kingdom during the 1989-1990 influenza season among nursing home residents.
65 years of age and older, the risk of influenza-associated mortality was increased nearly 8-fold among residents with at least 3 underlying conditions compared with those who had only 1 condition.9

Immune senescence: The immunologic context of aging and influenza

Changes occur with increasing age in both the innate and adaptive immune systems. This phenomenon, termed immune senescence, is generally defined as age-associated changes in the immune response and is a state of dysregulated immune function. Immune senescence increases susceptibility to some, but not all, infectious diseases.10

It is a common misconception that the immune system of the elderly becomes uniformly less responsive or generally nonfunctional with increasing age. Although many aspects of immunity do decline with age, the changes do not occur uniformly; some aspects of the aging immune response are preserved11 while others — such as pro-inflammatory cytokine production by macrophages — are actually enhanced.12

The age-related systemic chronic inflammation that results from increases in pro-inflammatory cytokines, called “inflammaging,” has been suggested as an important driver for frailty in the elderly and for the development and progression of common severe age-related diseases, including cardiovascular diseases, type 2 diabetes mellitus, and neurodegenerative diseases.12 In addition, the slower decline in inflammatory cytokines that also occur with inflamminging is associated with a pro-thrombotic state, which increases the risk for thromboembolic stroke and myocardial infarction in elderly patients following influenza infection.13 (Table)

These changes in the immune system with age affect both the clinical presentation and the consequences of influenza. Older people produce less interferon and interleukin, which may help explain the milder initial presentation of influenza (ie, reduced prevalence of fever and malaise) with age.13,14 Unfortunately, this lack of severe symptoms can delay the clinical diagnosis of influenza.13 Cell-mediated immune responses also decline with age, which may explain why influenza lasts longer in elderly patients.15

The response of elderly individuals to influenza vaccines is also impacted by immune senescence. (See page 3.)

Other biologic changes with age that affect the clinical presentation and consequences of influenza

In frail older patients, mucociliary function in the respiratory tract is impaired, leading to reduced cough and less efficient clearance of mucus and virus.13 Due to their poorer nutritional status, elderly patients often have depleted physiologic reserves, complicating their rehabilitation. In addition, cytokine storm secondary to influenza infection is more likely to induce delirium and other disturbances in the brains of elderly patients.13 (Table)

Influenza can also lead to functional decline in elderly patients

Especially among the most fragile elderly patients, influenza can lead to a decline in major physical functions, and therefore act as a trigger for catastrophic disability.16,17 More than a third of hospitalized patients 70 years of age or older in the US are discharged from the hospital less able to perform basic activities of daily living than when they were admitted.18 Because older patients often endure more frequent and longer influenza-related hospitalizations, influenza likely contributes significantly to this functional loss.

Table. Biologic changes with age related to clinical consequences of influenza10,12,15

<table>
<thead>
<tr>
<th>Biologic Change With Age</th>
<th>Clinical Implication With Infection</th>
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<tbody>
<tr>
<td>Reduced amplitude of cytokine response to infection</td>
<td>Fewer symptoms at disease onset; reduced fever — less efficient viral clearance</td>
</tr>
<tr>
<td>Impaired mucociliary function in respiratory tract</td>
<td>Reduced cough, less efficient viral clearance and mucus clearance</td>
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<tr>
<td>Reduced TNF-α*</td>
<td>Less malaise; delay in diagnosis</td>
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<tr>
<td>Delayed decline in inflammatory cytokines</td>
<td>Longer period during which inflammatory cytokines produce a prothrombotic state (increased risk for thromboembolic stroke, myocardial infarction)</td>
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<tr>
<td>Reduced T-cell function</td>
<td>Reduced protection from vaccine; reduced longevity of protection from vaccine</td>
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<tr>
<td>Poorer nutritional intake</td>
<td>Decreased physiologic reserve, more difficult rehabilitation</td>
</tr>
<tr>
<td>Brain aging</td>
<td>Cytokine storm more likely to produce delirium, sleep and appetite disturbances</td>
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*TNF-α = tumor necrosis factor alpha.
However, the role that influenza plays in these clinical consequences is often unrecognized. The typical clinical presentation of influenza and influenza-like illness—a brisk onset of fever, chills, myalgia, and headache, along with sore throat and cough—may be more subtle or even entirely absent in older patients. Instead, the frail elderly, including residents of nursing homes, may have a blunted febrile response to infection and exhibit mainly a decline in functional status, such as new or increasing confusion, incontinence, falling, deteriorating mobility, reduced food intake, or failure to cooperate with the staff.

Both a small case–control study of frail nursing home residents from a limited geographical location over 2 consecutive influenza seasons and a 6-year longitudinal analysis of nursing home residents from more than US 120 cities found that physical function outcome measures, such as the rate of decline in activities of daily living (Figure 2), weight loss, and pressure ulcers, exhibit a strong seasonal trend that corresponds to influenza mortality and severity.

Seasonal influenza may also be a factor in the pathogenesis of acute cardiovascular deaths and hospitalizations; vaccination against influenza may help prevent the infection–associated increase in acute coronary syndrome. See Part 1 of this monograph series for more information.

**INFLUENZA VACCINE AND PROTECTING THE ELDERLY**

Most studies suggest that the response to influenza vaccination in older adults is significantly reduced compared to that in young, healthy adults. For example, a study utilizing data from France’s Sentinel Network estimated vaccine effectiveness over a 7-year period at 62% to 76% in persons 15–64 years of age, but only between 26% and 52% among those 65 years of age and older. (Figure 3)

Nevertheless, a systematic review of studies of influenza vaccine in the elderly, including data from observational trials, found a 26% reduction in hospitalization from influenza and pneumonia, and a 42% reduction in all-cause mortality among community-dwelling elderly persons. A 2010 Cochrane review on influenza vaccine effectiveness and safety in the elderly found no convincing evidence for vaccine effectiveness against disease. However, a more recent study that utilized the same data as the Cochrane review but analyzed them according to “more clinically meaningful scenarios” found substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and influenza-related disease and death in the elderly.

According to the authors of this study, “vaccination of the elderly is efficacious in reducing infection, disease, and death caused by influenza virus infection; is worthwhile as a public health intervention; and … there is a sound scientific basis for the recommendations made by the World Health Organization, and multiple international and national bodies.”

Another recent retrospective cohort study conducted over a 15-year period among Ontario (Canada) residents 65 years of age and older linked weekly vaccination, hospitalization, and death records for 1.4 million community-dwelling persons. Excess pneumonia/influenza hospitalizations as well as excess deaths occurring within 30 days of a pneumonia/influenza hospitalization were significantly reduced by influenza vaccination, by 19% and 25%, respectively.

The effectiveness of influenza vaccine may reflect more than just the reduced risk of respiratory infection. Evidence suggests that influenza vaccines can contribute significantly to reducing mortality secondary to acute myocardial infarction and stroke among elderly adults. A recent meta-analysis of randomized controlled trials comparing influenza vaccine with placebo or control in patients at high risk of cardiovascular disease found that influenza vaccination was associated with a significantly lower risk of major adverse cardiovascular events. In fact, the greatest treatment effect was seen among the highest-risk patients, for example, those with recent acute coronary syndrome.

**AGING AND IMPAIRED IMMUNITY: IMPLICATIONS FOR INFLUENZA VACCINE DEVELOPMENT FOR OLDER ADULTS**

Because most influenza-related hospitalizations and the overwhelming majority of influenza-related deaths occur in elderly persons, vaccines with improved efficacy in this age group and continued efforts to increase vaccination rates are both needed to protect this vulnerable population.

In 2009, a higher-dose influenza vaccine with 4 times the hemagglutinin antigen content of standard inactivated influenza vaccine was licensed for use in persons 65 years of age and older based on studies demonstrating superior immunogenicity compared with a standard vaccine. The higher-dose vaccine also generated a significantly greater antibody response than did the standard vaccine in several studies that measured antibody titers at baseline and 28 days post vaccination. Efficacy studies comparing the higher-dose and the standard influenza vaccine have recently been completed.

In older adults, influenza can cause more than “just” pneumonia, hospitalization, and...
death, and the immune response to vaccine may be less robust. However, the severity of influenza and its sequelae can be reduced by immunization, even among the oldest and frailest persons, and even when vaccine fails to prevent infection.

 Armed with this knowledge, health care providers must continue to take an active role in ensuring that their elderly patients are immunized against influenza.

**REFERENCES:**


