Influenza among the elderly in the Americas: a consensus statement

Ricardo W. Rüttimann,[1] *Pablo E. Bonvehí,*[2] *Diana Vilar-Compte,*[3] *Raúl E. Isturiz,*[4] *Jaime A. Labarca,*[5] *and Edison I. Vidal*[6]

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ABSTRACT *Influenza exacts a heavy burden on the elderly, a segment of the population that is estimated to experience rapid growth in the near future. In the past decade most developed and several developing countries have recommended influenza vaccination for those > 65 years of age. The World Health Organization (WHO) set a goal of 75% influenza vaccination coverage among the elderly by 2010, but it was not achieved. In 2011, the Technical Advisory Group at the Pan American Health Organization, Regional Office of WHO for the Americas, reiterated the influenza vaccine recommendation for older adults.*

Relatively little information has been compiled on the immunological aspect of aging or on reducing its impact, information particularly relevant for clinicians and gerontologist with firsthand experience confronting its effects. To fill this data gap, in 2012 the Americas Health Foundation (Washington, D.C., United States) and the nonprofit, Fighting Infectious Diseases in Emerging Countries (Miami, Florida, United States), convened a panel of Latin American clinicians and gerontologists with expertise in influenza to discuss key issues and develop a consensus statement. The major recommendations were to improve influenza surveillance throughout Latin America so that its impact can be quantified; and to conduct laboratory confirmation of influenza for all patients who have flu-like symptoms and are frail, immunosuppressed, have comorbidities, are respiratory compromised, or have been admitted to a hospital. The panel also noted that: since evidence for antivirals in the elderly is unclear, their use should be handled on a case-by-case basis; despite decreased immunological response, influenza vaccination in older adults is still crucial; indirect immunization strategies should be encouraged; and traditional infection control measures are essential in long-term care facilities.

Key words Influenza, human; health of the elderly; aged; aged, 80 and over; immunization; influenza vaccines; consensus development conferences as topic; Latin America.

[1] Fighting Infectious Diseases in Emerging Countries (FIDEC), University of Miami, Miami, Florida, United States of America. Send correspondence to: Ricardo W. Rüttimann, rruttimann@fidec-online.org
[2] Sección Infectología, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina.
[3] Departamento de Infectología, Instituto Nacional de Cancerología, Mexico City, Mexico.
[4] Centro Médico de Caracas and Centro Médico Trinidad, Caracas, Venezuela.
[5] Departamento de Enfermedades Infecciosas, Escuela de Medicina de la Pontíficia Universidad Católica de Chile, Santiago, Chile.
[6] Universidade Estadual Paulista (UNESP), Botucatu, Brazil.

Influenza is caused by highly infectious viruses that result in acute febrile illness and respiratory symptoms; it is associated with high morbidity and mortality, particularly among high-risk groups. Each year, seasonal epidemics of influenza cause serious illness and death throughout the world. The World Health Organization (WHO) estimates that the global disease burden from influenza is 1 billion individuals infected, 3–5 million cases of severe disease, and 300 000–500 000 deaths annually, mostly from respiratory complications (1).

This consensus report focuses on the impact of influenza on the elderly in Latin America; and because most of influenza-related data and recommendations refer to the elderly as those ≥ 65 years of age, the authors arbitrarily used this definition, making exceptions when the data referred to a different age group. This segment of the population, whose numbers are estimated to

experience the most rapid growth in the near future, is at high risk of developing influenza complications. It has been estimated that each year in the United States, there are 300 000 hospitalizations and 23 000 deaths associated with influenza among those ≥ 65 years of age (2). An excess of mortality and pneumonia in the elderly was also associated with influenza virus in Mexico during a 5-year study period (3).

During the last decade, the majority of developed and several developing countries recommended influenza vaccination for individuals ≥ 65 years of age. WHO posited the goal of achieving 75% vaccination coverage in the elderly by 2010, but not all countries achieved it. By December 2008, a total of 35 of the 43 countries in the Americas had developed immunization policies targeting this population (4).

To address influenza among the elderly in Latin America, the Americas Health Foundation (Washington, D.C, United States; AHF) and Fighting Infectious Diseases in Emerging Countries (FIDEC) convened a conference with a panel of the Region's clinicians and scientists with expertise in influenza. Prior to this conference, the 'Panel' conducted a review of the literature to identify articles that: (a) were published from 2000–2012; (b) covered aspects of elderly-onset influenza in Latin America and/or national and international guidelines for disease prevention; (c) were based on clinical trials or observational studies; and (d) identified the study design and population. Over 200 papers met these criteria. The Panel discussed the scientific evidence as it related to questions posed by the attendees. It then drafted responses that underwent a review process based on group discussion, until unanimous consensus was reached. After the conference, the Panel continued to review and fine-tune the responses.

The present report details the Panel's consensus in its final responses to the following five questions posed by conference attendees:

1. What is the burden and epidemiology of influenza in the elderly?
2. Does an impaired immune response in the elderly require a different approach to the prevention and management of influenza?
3. Is the clinical course of influenza in the elderly different than in other age groups?
4. What steps should be taken for the diagnosis and treatment of influenza in the elderly?
5. What measures should be taken to prevent influenza in the elderly?

1. What is the burden and epidemiology of influenza in the elderly?

Influenza viruses have worldwide distribution. Influenza is most commonly caused by two RNA viruses: A and B. The B viruses are relatively antigenically stable compared to the A viruses, which are characterized by frequent changes in two dominant antigenic proteins, Hemaglutinin (H) and Neuraminidase (N). These surface proteins incur mild to dramatic changes, which result in new immunologic challenges to the human host. Antigenic *drifts* are due to small alterations in H and N proteins resulting in slight changes that occur every year and are responsible for seasonal epidemics. Antigenic *shifts* are the consequence of novel combinations of H and N resulting in major changes that can carry a high risk for epidemic or pandemic spread.

Influenza is a seasonal disease occurring from late autumn to early spring in temperate areas of both hemispheres. Over 80% of the cases arise during a period of 9–10 weeks. In tropical areas, transmission and cases occur throughout the year. The recent pandemic of A(pH1N1) generated an important impact on public health that changed the way the infection is handled. Today, the A(pH1N1) is circulating along with the A(H3N2) and B, and is considered one of the seasonal strains. In addition, avian A(H5N1) is considered a candidate for another pandemic.

Whereas upper respiratory infections in children are often due to a variety of respiratory viruses, among the elderly influenza is predominantly detected. The burden of influenza in the elderly is high; about 90% of seasonal deaths occur in this population (5). Age-specific risk of influenza-related mortality increases exponentially after 65 years of age. In the United States, individuals ≥ 80 years of age have a risk of death due to influenza-related complications 11 times greater than that of those 65–69 years of age.

Furthermore, the impact of influenza on the elderly will increase with the aging of the population. In Latin America, the population ≥ 65 years of age is predicted to increase from 4.2% (11.5 million) in 1970 to 17.4% (106.3 million) by 2050. Inevitably, the prevalence of comorbidities that increase the risk and severity of influenza, and related deaths, will increase (6).

Residents of long-term care facilities are among the elderly with the most comorbidities; therefore, they have more frequent and prolonged influenza-related hospitalizations and a higher rate of influenza-related mortality. In addition, they have greater exposure to viruses from other residents, visitors, and caregivers, and thus have higher transmission (7).

The entire burden of influenza in the elderly is difficult to quantify, particularly in Latin America. This is because laboratory confirmation is not done routinely, and the complications—both infectious and non-infectious—frequently exacerbate existing medical conditions that can necessitate hospitalization and cause death, well beyond the infectious period. Nevertheless, current evidence is substantial enough to affirm that age constitutes a significant risk factor for increased severity, complications, hospitalizations, and death from influenza.

In Latin America, the rate of influenza-related death among those ≥ 65 years of age has also increased, but underreporting is a significant problem. In Mexico, the influenza-related mortality rate ranged from 149.6–205.8 deaths per 100 000 inhabitants in 1999–2005, with a decreasing trend through the years (3). Although the data from Latin America supports the fact that influenza is a serious and debilitating disease, much better surveillance is needed in all countries to better quantify the problem and identify areas for improvement.

2. Does an impaired immune response in the elderly require a different approach to the management and prevention of influenza?

Normal aging is associated with several changes in the immune system that produce a declining immune response; this process is called immunosenescence (8). Immunosenescence impacts how the older adult responds to infectious insults and how effective vaccines are at provid-

ing protection. However, the degree to which the immune system is affected during the process is not linear, and is better correlated to the burden of disease and functional status than to chronological age alone (9).

The immune response to influenza vaccine among the elderly has been shown to be lower than that of younger adults (10). As a result, clinical efficacy of influenza vaccine in the elderly has been questioned recently; however, there are other major arguments in favor of vaccination (11). Although it has been postulated that influenza vaccine-induced antibody titers decline more rapidly in the elderly than in young adults—falling below protective levels within 4 months of vaccination—this hypothesis has been rejected by a recent systematic review (12). Consequently, there is no need to vaccinate older adults on a different schedule than younger people.

In addition to direct immunization, indirect strategies for reducing the impact of influenza on the elderly is to focus vaccination programs on schoolchildren and on healthcare workers (13, 14). It has been shown that vaccination of health care workers decreases the morbidity and mortality associated with influenza, and that low vaccination rates have been associated with outbreaks in hospitals and long-term care institutions (15). Several major organizations have recommended that annual vaccination be mandatory for all health care workers and a condition for employment (16). The Panel strongly supports the mandatory vaccination of healthcare professionals as a means of protecting older adults from influenza and its complications. For older adults living in the community, the vaccination of their household contacts, particularly school-age children and direct caregivers, constitutes an important strategy that should be emphasized.

Pneumococcal vaccination of children and older adults is another indirect strategy shown to reduce influenza-associated complications, hospitalizations, and deaths among the older population through direct and indirect effects (17). Besides emphasizing influenza vaccination for children and older adults, the Panel stresses the current recommendations for pneumococcal vaccination in children and the elderly as a means of preventing influenza-related complications among older adults.

3. Is the clinical course of influenza in the elderly different than in other age groups?

In the elderly, the clinical presentation of influenza ranges from self-limiting upper respiratory tract infection to a severe illness with potentially fatal complications. The clinical course is dependent on the virulence of the virus, the burden of comorbidities, and the degree of frailty. In older adults, among the seasonal strains, the A(H3N2) strains are the most virulent, followed by the B strains (18).

The initial clinical characteristics in older patients commonly differ from those found in younger adults. A more subtle non-specific clinical presentation—loss of appetite, weakness, fatigue, and malaise—is frequent. Cognitive changes are also more prevalent, and increased lower respiratory tract symptoms, including productive cough, wheezing, and chest pain are more frequent. Low-grade fever and cough are the most common symptoms in more than 80% of cases. The atypical clinical presentation might be explained by the high prevalence of other chronic medical conditions or immunosenescence (18, 19).

Pneumonia is a serious complication in the elderly (5–38% of influenza cases) and can result in hospitalization and/or death. Signs and symptoms of the respiratory infection are worsened (18). The etiology of the pneumonia may be viral, bacterial, or mixed viral-bacterial (20). Primary viral pneumonias tend to have increased symptom severity, and patients can deteriorate rapidly with mortality rates close to 50%, about 5 days from the appearance of symptoms. Secondary bacterial pneumonias are more common and are a significant complication of influenza, accounting for 25% of all influenza deaths. The most common bacteria in the elderly are *Streptococcus pneumoniae* (50%) and *Staphylococcus aureus* (18, 21).

Influenza-related complications and death in the elderly are more likely to occur in patients with high-risk medical conditions (22). In the United States it has been reported that those 65–74 years with a high-risk medical condition had a higher hospitalization rate (4 235/100 000 persons) compared to those without serious medical conditions (605/100 000). The rate of hospitalization was even higher among those ≥ 75 years of age (8 797/100 000) (23).

Influenza is the most likely primary cause of the winter-season increase in mortality among patients with chronic pulmonary diseases, ischemic heart disease, stroke, diabetes, and pneumonia (18, 22, 24). Influenza is also associated with a greater decline in major physical functions and can be a trigger for major disability and greater susceptibility to functional impairment following infection (25, 26).

4. What steps should be taken for the diagnosis and treatment of influenza in the elderly?

Diagnosis

Because the clinical picture is not typical of influenza in general and the adverse consequences may be very high in the elderly, laboratory confirmation might be important. If the patient is frail, immunosuppressed, has severe comorbidities, is respiratory compromised, or needs to be admitted to the hospital, laboratory confirmation of influenza is recommended. Also, patients experiencing severe influenza-like symptoms out of an epidemic season should be tested. The impact of missing or delaying the diagnosis could not only have adverse consequences for these high-risk patients, but also for households or other patients in the hospital or long-term care facility.

Rapid tests are easy to perform, provide results in 10–15 minutes, and are useful for ruling out the disease. The main limitations of the rapid tests are a lack of sensitivity and a failure to differentiate subtypes of A viruses (19, 27). Physicians should be aware that a negative result with a clinical picture of influenza should be confirmed with a more accurate test, and specific infection control precautions should be taken until the diagnosis is definitively ruled out.

Immunofluorescense assays and PCR are the tests of choice to diagnose influenza. Fluorescent antibodies are more available than PCR and take 4–6 hours to obtain results (28). Their limitation is that they are relatively insensitive in detecting pH1N1 and adenovirus, but are sufficiently sensitive to detect other influenza viruses and other important respiratory viruses in the elderly, such as respiratory syncitial virus (RSV).

PCR assays have higher sensitivity than immunofluorescence for most viruses and allow the detection of other respiratory viruses, such as rhinoviruses and coronavirus. PCR is the preferred method for the diagnosis of the pH1N1 virus. It is also preferred to complement diagnosis if influenza A is identified by other methods (28). When a laboratory test is not indicated or performed, the clinical diagnosis of influenza can be made on the basis of signs and symptoms and the epidemiological presence of influenza in the community.

Treatment

In the elderly, several general measures should be considered in order to prevent complications and disability. Some of the measures are early mobilization, prevention and treatment of delirium, minimization of invasive procedures, and prevention of aspiration pneumonia (29).

Older adults with influenza are candidates for antiviral therapy if they are frail, immunocompromised, hospitalized or in a long-term care facility, have severe comorbidities, or experience severe influenza-like symptoms (30). Antiviral therapy should ideally commence within 48 hours of the beginning of symptoms. There are two classes of antiviral agents to treat influenza: the adamantanes and neuraminidase inhibitors. Although amantadine and rimantadine were approved decades ago, they are no longer recommended in most countries. The limitations of these drugs are their safety profile and their resistance by current influenza viruses.

There are two neuraminidase inhibitors: zanamivir, an inhalant, was approved in 1999 for the treatment of influenza A and B. It has few adverse side effects. Its primary limitation for use is in individuals with chronic obstructive pulmonary disease (COPD) and asthma due to the induction of bronchospasm, or when an inhalant is otherwise problematic.

Oseltamivir, an oral drug, was also approved in 1999 for treatment of influenza A and B. It, too, has few adverse side effects, but it does require dose adjustment in patients with renal dysfunction and is not recommended in individuals with a creatinine clearance under 10 ml/min. Both have been shown in some studies to decrease disease duration, mortality from influenza, and the need for hospitalization (31); however, there is still considerable debate about their overall effectiveness (30). A firm recommendation for or against their use cannot be made.

5. What measures should be taken to prevent influenza in the elderly?

Prevention of influenza in the elderly is of utmost importance for mitigating its impact on this high-risk population. The main components of prevention are measures that avoid transmission, prophylaxis with antiviral drugs, and vaccination. Among these strategies, vaccination is most important for reducing morbidity and mortality.

Measures to avoid transmission include non-pharmacological interventions, i.e., frequent hand washing, respiratory hygiene, and cough etiquette. Traditional infection control measures should obviously be instituted when there is any case of influenza (32, 34). In long-term care facilities, outbreaks of influenza should lead to the initiation of a comprehensive approach to contain virus transmission. Increased hand hygiene practices, as well as cleaning and disinfecting surfaces with an approved antiseptic product, use of droplet precautions (surgical masks), cohorting of residents, vaccination of those previously not immunized against influenza, and possibly prophylaxis with antiviral drugs. The utilization of these interventions should not replace vaccine administration (32).

Most of the available vaccines administered in this population are trivalent inactivated (split-virus or subunit) that contain two A strains (pH1N1 and H3N2) and one B strain, whichever one is most likely to cause disease in the following season (35).

There are several ways to assess the benefits of influenza vaccination. One is through the humoral response provided by the vaccine and its correlation with protection. Another is through efficacy trials or by effectiveness studies. Besides immunogenicity, efficacy, and effectiveness, safety is an important aspect with any vaccine and in every group in which it is given.

In terms of immunogenicity, a few days after vaccine administration, a rise in serum antibodies is observed and is correlated with protection at levels ≥ 1:40 hemaglutinin antibody inhibition (HAI) (12, 36). Levels reach a peak in 2– 4 months and fall to baseline usually before the next influenza season, emphasizing the need for annual vaccination (37, 38). Patients with chronic diseases, immunosuppressed individuals, and older adults may exhibit a lesser antibody response.

Efficacy can be assessed by immunogenicity trials that evaluate seroprotection levels and effectiveness through observational studies (32). According to one systematic review, influenza vaccination was found to have a modest effect in preventing influenza-like illness and laboratory confirmed influenza in the elderly (39). On the other hand, a more recent meta-analysis of vaccine efficacy and effectiveness concluded that there is no evidence of protection against laboratory-confirmed disease in the elderly when subjects received trivalent inactivated vaccine (11). However, well-matched vaccines (the circulating strains matching the strains of vaccine) prevented 45% hospitalization due to pneumonia and 42% of deaths from influenza or pneumonia; furthermore, there was a 60% reduction in all-cause mortality among the elderly living in long-term care facilities (39). Other studies performed among the elderly in Latin America showed that influenza vaccination decreased hospitalization and death due to myocardial infarction, and also decreased hospitalizations due to pneumonia (40, 41).

In order to improve influenza vaccine immunogenicity and efficacy among populations at-risk for complications, different strategies have been implemented, among them adjuvants. Adjuvants amplify the immune response by enhancing delivery and presentation of antigen and recruitment of inflammatory and immunocompetent cells (42, 43). Adjuvanted influenza vaccines, which include monovalent pH1N1 influenza strain and trivalent seasonal preparations, produced a more robust immune response (44, 45). In an elderly population, trivalent MF-59 adjuvanted influenza vaccine was shown to reduce the risk of hospitalization for influenza and pneumonia by 25% over the non-adjuvanted inactivated vaccine (46). Although some countries are recommending this strategy in the elderly, more

studies using adjuvanted influenza vaccines are necessary to prove their clinical value (8).

Another strategy to improve influenza vaccine immunogenicity is achieved by intradermal administration. The intradermal route for vaccine administration has been shown to result in a robust immune response (47). This response is achieved because the dermis contains a great number of resident and blood-derived antigen presenting cells (48).

A third strategy is to increase the dose of antigens in the vaccine (e.g., 60 µg hemaglutinin of each component instead of the standard 15 µg) resulting in increased immunogenicity against both of the vaccine's A strains when administered to adults ≥ 65 years of age living in the community (49). Once again, however, there are no data indicating improved clinical effectiveness with high-dose vaccines.

Safety issues for influenza vaccine in the elderly should not be a barrier against immunization in this population. Most of the data showed that the most common side effects in the elderly are local reactions, such as erythema, induration, pain, and increased local temperature. These side effects are more common with adjuvanted vaccines than non-adjuvanted, and also with intradermal administration, but the reactions are mild and of short duration (50). In terms of systemic side effects, influenza vaccines were safe and there is no evidence of increased serious side effects, such as Guillain-Barré syndrome.

In summary, all three strategies detailed above improve influenza vaccine immunogenicity and may possibly provide better protection against the consequences of influenza among the elderly. The indirect protection strategies discussed earlier are also an important way to prevent influenza and its complications in older adults. There are new vaccines and technologies on the horizon that promise improved protection against influenza (42). It is important to highlight, however, that the elderly should be vaccinated with the currently available vaccines (35).

MAJOR RECOMMENDATIONS

1. Better surveillance is greatly needed among all Latin American countries to better quantify the impact of influenza and to identify areas for improvement.
2. Patients with flu-like symptoms, who are frail, immunosuppressed, have severe chronic comorbidities, are respiratory compromised, or have been admitted to a hospital should have laboratory confirmation of influenza. Patients experiencing severe influenza-like symptoms out of an epidemic season should also be given a diagnostic test. Immunofluorescense assays or PCR are the tests of choice.
3. Evidence for use of antiviral agents to treat influenza in the elderly, to prevent its occurrence, or to mitigate its complications, is unclear. Until this issue is resolved, physicians should use antiviral agents on a case-by-case basis.
4. Even though older adults have a decreased immunological response to vaccination, influenza vaccination is still critical to preventing influenza-related complications.
5. Indirect strategies to reduce the burden of influenza in the elderly should include a focus on immunizing schoolchildren, mandatory vaccination of healthcare professionals, and pneumococcal vaccination of children and older adults.
6. Traditional infection control measures are essential when there is any case of influenza, especially when there is an outbreak in a long-term care facility.

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La gripe en los ancianos de la Región de las Américas: una declaración de consenso

RESUMEN

La gripe representa una fuerte carga para los ancianos, un segmento de la población que, según los cálculos, experimentará un rápido crecimiento en un futuro próximo. En el último decenio, la mayor parte de los países desarrollados y varios países en desarrollo han recomendado la vacunación antigripal de las personas mayores de 65 años de edad. La Organización Mundial de la Salud (OMS) estableció la meta de una cobertura de vacunación antigripal de 75% de los ancianos para el año 2010, pero no se alcanzó. En el 2011, el Grupo Consultivo Técnico de la Organización Panamericana de la Salud, Oficina Regional de la OMS para la Región de las Américas, reiteró la recomendación de la vacunación antigripal de los adultos mayores.

Se ha recabado relativamente poca información sobre los aspectos inmunológicos del envejecimiento o sobre cómo reducir su repercusión, información particularmente pertinente para médicos clínicos y gerontólogos que deben afrontar de primera mano sus efectos. Para salvar esta brecha en materia de datos, en el 2012, la *Americas Health Foundation* (Washington, D.C., Estados Unidos) y la *Fighting Infectious Diseases in Emerging Countries* (fundación sin ánimo de lucro para la lucha contra las enfermedades infecciosas en los países emergentes, con sede en Miami, Florida, Estados Unidos) convocaron un grupo de expertos, médicos clínicos y gerontólogos latinoamericanos con pericia en el tema de la gripe, con objeto de debatir aspectos clave y elaborar una declaración de consenso. Las principales recomendaciones fueron mejorar la vigilancia de la gripe en toda América Latina para que pudiera cuantificarse su repercusión; y llevar a cabo la confirmación de laboratorio en todos los pacientes con síntomas similares a los de la gripe debilitados, inmunodeprimidos, con comorbilidades, con compromiso respiratorio o que hubieran sido ingresados en un hospital. El grupo de expertos también señaló que, dado que no existen datos probatorios claros en relación con los antivíricos en los ancianos, su uso debe manejarse caso por caso; que, a pesar de la reducción de la respuesta inmunitaria, la vacunación antigripal en adultos mayores sigue siendo crucial; que se deben promover las estrategias de vacunación indirecta; y que, en los establecimientos de asistencia a largo plazo, las medidas tradicionales de control de las infecciones son esenciales.

Palabras clave Gripe humana; salud del anciano; anciano; anciano de 80 o más años; inmunización; vacunas contra la influenza; conferencias de consenso como asunto; América Latina.