CURRENT OPINION

Burden of influenza in the elderly: a narrative review

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Purpose of review
This review provides an update on specificities of influenza in older adults (≥65-year-old), including epidemiology, burden in terms of hospitalization and mortality, extra-respiratory complications and specific challenges of prevention.

Recent findings
In the past 2 years, influenza activity was drastically reduced by barrier measures implemented during the COVID-19 pandemic. A recent French epidemiological study covering 2010–2018 epidemic seasons estimated that 75% of costs induced by influenza-associated hospitalizations and complications were attributable to older adults, a population bearing more than 90% of influenza-associated excess mortality. In addition to their age, comorbidities and reduced vaccine response, long-term facility residents are at risk for nosocomial outbreaks. Beyond respiratory complications, influenza triggers acute myocardial infarction and ischemic stroke. Influenza might drive significant functional loss in frail older adults, which can lead to ''catastrophic'' or severe disability in up to 10% of patients. Vaccination remains the cornerstone of prevention, with enhanced immunization strategies (i.e., high-dose or adjuvanted formulations) to be largely implemented in older adults. Efforts to increase influenza vaccination uptake during the COVID-19 pandemic should be consolidated.

Summary
Burden of influenza in the elderly is largely under-recognized, especially the cardiovascular complications and the impact on functional status, justifying more effective preventive strategies.

Keywords
elderly, influenza, vaccination

INTRODUCTION

Influenza is a major acute respiratory viral infection caused by influenza A or B viruses, occurring in seasonal outbreaks affecting 2–10% of the population in developed countries every year and causing annually up to 650 000 deaths worldwide, according to the WHO [1,2]. Consequently, influenza represents a major economic burden to the healthcare system and society [3▪▪,4,5]. Aside from community spread, transmission in healthcare facilities has been often reported, with healthcare practitioners frequently identified as index cases [6–8]. These nosocomial influenza outbreaks can have dramatic consequences, especially in vulnerable patients or residents of geriatric units and nursing homes [9,10]. Indeed, if influenza may occur at all ages, aging is a prominent risk factor for influenza infection and related complications [11]. Frailty and immuno-senescence lead to altered immune responses, predisposing the elderly to severe influenza infection, extra-respiratory complications, and mortality [12]. Higher viral loads and longer virus shedding have been described in this population [13]. Despite these assertions, data regarding the burden and consequences of influenza in the specific population of the elderly are sparse, especially in the recent years during which incidence of influenza was drastically diminished by the public health measures (including mask wearing, social distancing, lockdowns, and travel restrictions)

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KEY POINTS

- Influenza is associated with a major burden in the elderly, with an increased risk of hospitalization, complications, and mortality in the frailest individuals, including healthcare facility patients or residents.
- Extra-pulmonary complications, including cardiovascular events and functional decline, are largely under-recognized and responsible for excess loss of autonomy and mortality in older adults.
- Immuno-senescence is associated with decreased vaccine effectiveness, advocating for the implementation of enhanced vaccine strategies, which remain the cornerstone of prevention.
- Increasing influenza vaccine coverage should represent a public health priority to reduce life-threatening complications in older adults, and associated healthcare and societal economic burden.

implemented in the COVID-19 pandemic context [14].

Because the proportion of older adults is steadily increasing worldwide (e.g., the proportion of ≥65-year-old adults will exceed 25% of the entire population between 2035 and 2040 in France [15]), we chose to focus this review on the epidemiology and the consequences, including infectious complications, of influenza in the elderly (in general ≥65-year-old), and subsequent prevention measures.

MATERIALS AND METHODS

We searched for clinical studies including phase III-IV clinical trials, comparative or observational studies in French and English languages published between 2011 and 2023 on PubMed, using the keyword "Influenza" and the filter "Aged: 65+ years." Using this search strategy, 1380 titles and abstracts were screened and checked for consistency, including 197 in the past 2 years. References of the literature reviews published over the same period were also checked for completeness.

EPIDEMIOLOGY

Description of influenza epidemiology in the elderly is challenged by the highly diverse contexts of published studies. On the one hand, included individuals differ regarding demographics, vaccination coverage, outpatient or hospitalization settings and outcome definition (hospitalization, complications or mortality). In addition, the precision of the nosological setting toward influenza-like illness (ILI) episodes is heterogeneous regarding severity of infection (upper or lower respiratory tract infection [LRTI]) and the level of microbiological documentation. On the other hand, the epidemic season and/or the pandemic context affect the virulence of circulating viruses and their matching with vaccine strains.

Global epidemiology

According to the Global Burden of Disease Study 2017, the annual worldwide incidence of influenza LRTI has been estimated at 713 episodes/100 000, with a continuous increase after 65 years, exceeding 1000/100 000 after 85 years [16▪]. Observational data suggest that in an average season, 1.4% of seniors at least 75-year-old consult their general practitioner in the UK for an acute respiratory illness attributable to influenza [17]. In a Dutch prospective cohort study ran over two epidemic seasons, influenza accounted for 18.9% (2011–2012) and 34.2% (2012–2013) of ILI in individuals at least 60-year-old [18]. Studies specifically evaluating risk factors for influenza infection among elderly are sparse. Before the COVID-19 pandemic, influenza represented the first hospital-acquired viral respiratory infection among the elderly admitted to an Australian tertiary hospital, and was associated with important morbidity and mortality [19▪].

Hospitalization

The need for hospitalization due to influenza LRTI strongly correlates with age among adult individuals [16▪]. In recent studies, mostly enrolling individuals at least 65-year-old, comorbidities classically associated with LRTI, including chronic respiratory, cardiac or liver diseases, and immunosuppression seemed to have a greater impact on the risk of hospitalization during influenza infection compared with COVID-19 [20,21]. Of note, hospital admission rates due to respiratory diseases, the most common being influenza, have steadily increased in the past two decades in England and Wales [22▪]. This rise was at the expense of influenza and pneumonia in the elderly, mainly in the at least 75-year-old population. Interestingly, socioeconomic deprivation was associated with a lower vaccine coverage and a higher risk of hospitalization in the elderly [23▪]. In addition, influenza-related hospitalization rate among the elderly highly depends on the circulating influenza virus – higher during seasons with A(H3N2) being the dominant circulating virus – and/or mismatching with the vaccine strains [24,25]. Rate of complicated hospitalization, defined by ICU admission, mechanical ventilation requirement, and/or death significantly increases with age, especially after 50 years, reaching almost 20% in the 65 to 74-year-old age group according to a study of the Global Hospital Influenza Network [26]. In terms of economic burden, a recent French study based on 2010–2018 epidemic seasons estimated the average cost of influenza-related hospitalizations at €141 million per year, of which 77% were related to older adults [3▪▪].

Nosocomial outbreaks

A nosocomial origin can be suspected in 4–20% of patients hospitalized with influenza [27,28]. Regarding especially aged-care facilities, influenza represented the first cause of infectious outbreaks before the COVID-19 pandemic, with a median attack rate of 33% (range, 4–94%) and a fatality rate of 6.5% (0–55%) among residents [29]. Residents of nursing homes exposed to influenza have a well documented risk of hospitalization (relative risk [RR], 1.43; 95% confidence interval [95% CI], 0.99–2.08]) and death (RR, 2.77 [95% CI, 1.55–4.91]) of respiratory origin compared with unexposed residents, despite satisfactory vaccination rates (>90%) [30].

Mortality

Influenza-related mortality is strongly correlated with age, with an estimated influenza LRTI mortality rate (per 100 000) of 16.4 (95% uncertainty interval, 11.6–21.9) in at least 70-year-old individuals, compared with 1.9 (uncertainty interval, 1.3–2.6) in the general population, according to the Global Burden of Disease Study 2017 [16▪]. In another modeling study covering the 1999–2015 period, the rate (per 100 000) of seasonal influenza-associated respiratory deaths has been estimated at 4.0–8.8, rising at 51.3–99.4 after 75 years, with the highest burden of influenza-associated deaths in developing countries, especially sub-Saharan Africa and South-East Asia [31]. In the Northern hemisphere, the excess wintertime mortality was largely explained by influenza before the COVID-19 pandemic [32]. In the subset of patients hospitalized with or for influenza, a significant increase of mortality is also reported with age [33–35], 70–80% of in-hospital influenza-related deaths being reported among older adults in Western Europe [3▪▪,34]. Risk factors for influenza-related mortality in the elderly are age and comorbidities (including immunosuppression, chronic cardiovascular and liver diseases) [33,36]. Another major determinant might rely in the functional status, as a daily walking time of at least 1 h has been associated with a lower risk of pneumonia mortality [37▪,38]. Among circulating virus strains, the elderly are distinguished by influenza-attributable excess mortality due to A (H3N2) compared with A(H1N1) or B viruses [24,39,40]. Finally, the impact of viral coinfections (i.e., with the circulating SARS-CoV-2 Omicron variant) needs to be specified in the elderly during coming epidemic seasons, while coinfections are expected to occur more frequently in the future.

DISEASE BURDEN BEYOND RESPIRATORY ILLNESS

Beyond the classical ILI symptoms associating fever, chills, headache, soreness, and respiratory signs, clinical presentation of influenza is more frequently atypical among the elderly. At the initial phase, cardinal symptoms – and in particular fever – are often subtle or absent [41,42]. Confusion, fall, and decompensation of comorbidities may consequently be in the foreground [43]. Initial respiratory complications have not been specifically evaluated in older adults. Secondary bacterial pneumonia, mostly implicating *Streptococcus pneumonia* and *Staphylococcus aureus*, approximately affects a quarter of adults [44]. Risk of secondary fungal infection, especially aspergillosis, has recently been outlined among critically ill influenza patients [45].

Aside from respiratory complications, extra-respiratory consequences of influenza represent a major but under-recognized burden in the elderly in terms of morbidity and mortality (Fig. 1).

First, epidemiological studies show a seasonal relationship between influenza and mortality from cardiovascular events, including acute myocardial infarction and stroke, especially in older adults [32,46▪▪,47,48,49▪▪,50]. From a pathophysiological point of view, tachycardia and hypoxia at the time of infection, conjugated with the proinflammatory cytokine response, result in a prothrombotic state and a risk of atheroma plaque disruption [51]. The incidence peak occurs 7 days after infection for acute myocardial infection and up to 14 days for strokes, but the risk persists during the first year following infection [46▪▪,52]. The 90-day absolute risk of arterial thromboembolic events (acute myocardial infarction or ischemic stroke) following laboratory-confirmed influenza has been recently estimated at 14.4% in more than 8000 hospitalized patients [53]. Furthermore, indirect evidence for the association of influenza with cardiovascular events is provided by the favorable impact of influenza vaccination on the risk of myocardial infarction and stroke [54,55▪,56]. Even if most studies were not conclusive for older adults, a large meta-analysis of randomized clinical trials suggested that influenza vaccination reduced major adverse cardiovascular events, especially in high-risk

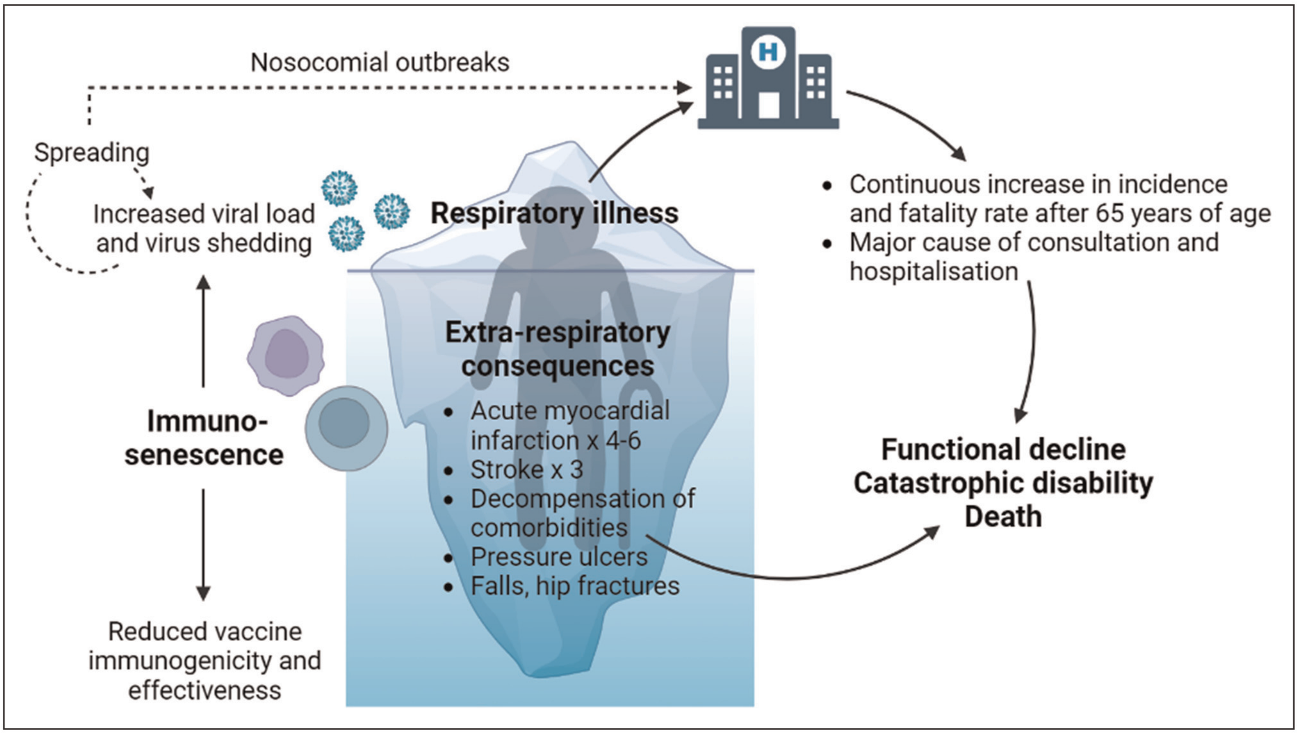

FIGURE 1. Schematic summary of direct and indirect consequences of influenza in older adults. Created with BioRender.com.

patients [57]. In addition, treatment with oseltamivir was associated with a 28% reduction in the risk of stroke in the 6 months following influenza infection [58].

Second, recovery from influenza can be prolonged, incomplete, and associated with worsening frailty. On the basis of a Canadian online survey including more than 1000 nonfrail seniors with ILI during the previous influenza season, 40% of patients indicated a recovery longer than 2 weeks, one-fifth had health and function declines during this time, and 3.1% never fully recovered [59]. Following influenza A infection, 67 and 25% of older patients became housebound or confined to bed, respectively, according to a prospective cohort of ILI in healthy elderly patients [60]. Complications secondary to bed rest and hospital stay are critical, but highly underappreciated consequences of influenza, including malnutrition and muscle loss, favoring bone loss, falling and fractures, and pressure ulcers. Influenza has shown to negatively impact these quality markers in American nursing homes, following a seasonal pattern as observed for cardiovascular events [61]. These observations led to unexpected seasonal correlations, such as the association of the ILI and hip fracture hospitalization rates in nursing home residents [62]. In addition, influenza infection triggers functional decline, especially in frail older adults, resulting in the reduction of activities of daily living [61,63▪▪]. Up to 12.5% of older frail individuals with laboratory-confirmed influenza experience "catastrophic" disability, defined by a Barthel index loss of at least 20 points [63▪▪].

More recently, a case–control study ($n = 61\,626$ individuals) from the Danish National Patient Registry suggested a link between influenza and the diagnosis of Parkinson disease (odds ratio, 1.73 [95% CI, 1.11–2.71]) more than 10 years later, mostly among at least 60-year-old adults [64].

IMPACT OF PREVENTION MEASURES

Barrier measures

Systematic implementation of mask wearing, social contact restrictions – including visit limitations in healthcare facilities during the COVID-19 pandemic – provided an unexpected confirmation of the major impact of these public health measures on preventing influenza spread [14,65–67]. Conversely, the relaxation of public health measures and social restrictions has been predicted to be associated with a resumption of influenza transmission in the upcoming years [68].

Antiviral prophylactic treatment

Data regarding the individual benefit of prophylactic treatment with oseltamivir among the elderly are conflicting, but at the institutional level, it might contribute to the control of influenza outbreaks in aged-care facilities [69,70].

Vaccination

In an at-risk-based approach, vaccination is the cornerstone of influenza prevention in the elderly. Vaccination of individuals at least 65-year-old is recommended by all international immunization guidelines and the WHO [71]. In the geriatric population, reduced vaccine responsiveness and immunogenicity due to immuno-senescence is however well documented, especially in frailer individuals [72–74]. Influenza vaccine effectiveness might consequently be impeded, but specific data are difficult to summarize due to annual vaccine composition change according to antigenic drift of seasonal influenza viruses; the heterogeneous adequacy between circulating and vaccine strains; the dominant circulating virus, with a higher burden in the elderly during A(H3N2) epidemics; and the differences in vaccination formulations or strategies (split or subunit, adjuvanted or not, standard *versus* high-dose, trivalent or quadrivalent formulations, and so on) evaluated and readouts (ILI, laboratory-confirmed cases, hospitalization, death, and so on) used. Despite these considerations, standard vaccination of the elderly has a globally proven benefit on ILI and laboratory-confirmed influenza episodes, claim for healthcare (medical visits and hospitalizations), and fatality rates by respiratory and cardiovascular diseases [25,55▪,75]. However, frailty is associated with a reduced vaccine effectiveness related to diminished immunogenicity [76▪▪]. Interdependency of frailty, influenza infection, and vaccine immunity advocate for an enhancement of influenza immunization approaches in the elderly. The better evaluated strategy relies on high-dose formulations, with compelling evidence for increased prevention of laboratory-confirmed influenza, influenza-related complications, including pneumonia and hospitalization, leading to a reduction in mortality compared with standard-dose formulations [77▪,78]. Other promising approaches include cell-cultured vaccines and adjuvanted vaccines [79,80].

Aside from these immunologic considerations, a key challenge remains to counter vaccine hesitancy to achieve better vaccine coverage rates in targeted populations, including older adults and healthcare workers, with imperious necessity of facilitating and promoting access to vaccination. Indeed, influenza vaccine uptake remains insufficient in most developing countries among the elderly, with important geographic disparities [81]. Finally, combined (i.e., mRNA-based) vaccines for influenza and COVID-19 are under development and might help to favor vaccine uptake for these two severe respiratory diseases in the elderly and other at-risk groups.

Other prophylactic approaches

Trained immunity, based on the activation of the innate immunity to improve responsiveness to subsequent infectious or vaccine triggers, is of growing interest. For instance, BCG vaccination has showed to protect against respiratory tract infections in older adults in a recent phase III clinical trial, and to improve immunogenicity of subsequent influenza vaccination [82,83].

Beyond vaccination, innovative preventives approaches are under study. For instance, mAbs targeting influenza surface antigens (hemagglutinin or neuraminidase) in clinical development for influenza treatment could be tools in postexposure prophylaxis in at-risk individuals [84].

CONCLUSION

Influenza represents a major burden in the elderly. Frailty and decreased immune response drive individual predisposition, a higher risk of severe clinical presentation and mortality. Extra-respiratory consequences are largely under-recognized, exposing this population to cardiovascular events, bed rest, and hospital stay related complications, with a significant proportion of elderly patients experiencing postinfluenza functional decline up to ''catastrophic'' disability. Vaccination remains the keystone of influenza prevention, the reduced vaccine immunogenicity due to immuno-senescence being counterbalanced by promising enhanced immunization strategies. Vaccination of the elderly reduces the risk of laboratory-confirmed influenza, influenza-related complications, and mortality, and should be promoted, as well as immunization of healthcare workers, to diminish the risk of nosocomial outbreaks.

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Conflicts of interest

There are no conflicts of interest.

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