Review

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Influenza disease burden and the need for highly immunogenic vaccines in older adults: a narrative review

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Influenza presents a considerable disease burden, particularly among adults over 65 years old. In this population, the disease is associated with high rates of infection, hospitalization, and mortality. The objective of this study was to assess the impact of influenza on older adults and to evaluate the effectiveness of influenza vaccines within this demographic. A literature search was conducted using PubMed to identify relevant English-language studies published from January 2000 to January 2024. The analysis indicated that influenza-related hospitalization rates (ranging from 10.1 to 308.3 per 100,000 persons) and all-cause excess mortality rates (1.1 to 228.2 per 100,000 persons) were notably high in older adults, although these rates varied over time and by location. Hospitalization rates due to influenza increased considerably after the age of 50 years, with the highest rates observed in individuals aged 85 years and older. Excess mortality attributable to influenza also rose with age, with rates between 17.9 and 223.5 per 100,000 persons in those over 75 years old. The effectiveness of influenza vaccines in preventing severe infections requiring hospitalization was found to be only 37% in individuals aged 65 years and older. The unadjuvanted, standard-dose influenza vaccine had an estimated effectiveness of just 25% against laboratory-confirmed influenza and between 37% and 43.7% in preventing hospitalizations. Therefore, considering the substantial burden of influenza and the limited efficacy of standard vaccines, the use of highly immunogenic influenza vaccines should be prioritized for older adults.

Introduction

Influenza accounts for the highest disease burden in terms of infection, hospitalizations, and mortality rates among acute infectious diseases, leading to high medical expenses and socioeconomic losses [1–3]. Each year, epidemics affect more than 5% to 10% of the global population, with the extent of impact varying based on the antigenic match of circulating strains and vaccination coverage during the season [4]. A community-based prospective cohort study from Korea reported an overall influenza incidence rate of approximately 7 per 100 persons over three seasons from 2012 to 2015 [5]. The number of hospitalizations and deaths from pneumonia and other complications surges following an influenza epidemic, particularly affecting children under 5 years of age and adults over 65 years. Most deaths occur in the latter population. Due to the consistently high impact of the disease on older adults, a thorough review of the influenza disease burden and the effectiveness of vaccines is crucial.

The objective of this narrative literature review was to evaluate the disease burden of influenza, with a focus on its impact on older adults in terms of infection, hospitalization, and mortality rates. Furthermore, this study aims to assess the effectiveness of influenza vaccines in older adults across different seasons, thereby providing insights that may improve vaccination strategies.

Ethics statement

It is a literature database-based review; therefore, neither approval by the institutional review board nor obtainment of informed consent was required.

Methods

In this narrative literature review, we first conducted a search on PubMed for relevant English-language articles, published between January 2000 and January 2024. We employed the snowballing search method throughout the review process. The key search terms included "influenza," "influenza-like illness," "older adults," "disease burden," "hospitalization," "excess mortality," efficacy," and "vaccine effectiveness," which were tailored to each topic. After reviewing titles, abstracts, and full manuscripts, we selected relevant studies for inclusion in this review. Furthermore, we manually searched the references cited in the chosen articles to identify additional sources pertinent to this review.

Results

Influenza-related hospitalizations in older adults

Influenza virus infections are more common among socially active young adults; however, hospitalizations due to pneumonia and severe infections predominantly affect older individuals, although rates vary across studies. Comparing influenza-related hospitalization rates between countries is challenging due to differences in the medical environment, including hospital accessibility and admission criteria. A population-based study in the United States estimated age-specific influenza-associated hospitalization rates for respiratory failure (Table 1) [6]. The overall rate was 2.7 per 100,000 person-years, with an increasing trend observed after the age of 50 years: 0.8 for ages 18–49; 4.0 for ages 50–64; 8.7 for ages 65–74; 16.5 for ages 75–84; and 27.9 for those aged 85 and older. In a 15-year study (1998–2012) in Hong Kong, an average of 32.7 per 10,000 persons were hospitalized annually for respiratory viral infections, most commonly due to influenza A (183 per 100,000 persons), respiratory syncytial virus (57 per 100,000 persons), and influenza B (35 per 100,000 persons). Hospitalizations were particularly common among adults aged 65 years and over, with rates two to three times higher than among those 50–64 years old [7]. In France, over eight epidemic seasons from 2010/2011 to 2017/2018, the estimated influenza-associated excess hospitalization rates ranged from 11.6 to 61.9 per 100,000 persons for influenza and pneumonia and from 20.4 to 75.3 per 100,000 persons for respiratory causes across all ages. For adults aged 65 years and over, the rates were 10.1 to 202.6 per 100,000 persons for influenza and pneumonia and 26.3 to 308.3 per 100,000 persons

Table 1. Estimated rates of influenza-related hospitalization

Study [reference]	Years	Country	Category of admission	Annual rates of influenza-related hospitalization (per 100,000 persons)
Ortiz et al. [6]	2003–2009	United States	Respiratory failure	Overall: 2.7
				18–49 years: 0.8
				50–64 years: 4.0
				65–74 years: 8.7
				75–84 years: 16.5
				≥85 years: 27.9
Chan et al. [7]	1998–2012	Hong Kong	Influenza A	≥65 years: 183
			Influenza B	≥65 years: 35
Lemaitre et al. [8]	2010–2018	France	Pneumonia and influenza	Overall: 11.6–61.9
				≥65 years: 10.1–202.6
			Respiratory	Overall: 20.4–75.3
				≥65 years: 26.3–308.3
Hong et al. [9]	2009–2019	Korea	Influenza	20.5–169.9

for respiratory causes [8]. A Korean study utilizing a nationwide healthcare database (associated with the Health Insurance Review and Assessment Service) over the decade from 2009 to 2019 found that the influenza-related hospitalization rate decreased following the 2009 H1N1 pandemic but increased during the 2013/2014 season, peaking at 169.9 per 100,000 people in 2017/2018 [9].

Influenza-attributable excess mortality among older adults

Using time series log-linear regression models based on vital death records and influenza surveillance data, global seasonal influenza-associated respiratory excess mortality rates were estimated for 33 countries. The results revealed an increase in this rate with age. Influenza-associated excess mortality rates ranged from 0.1 to 6.4 per 100,000 persons under 65 years, 2.9 to 44.0 per 100,000 persons between 65 and 74 years, and 17.9 to 223.5 per 100,000 persons over 75 years (Table 2) [10]. These rates varied over time and by location, influenced by factors such as age distribution, prevalence of chronic diseases, dominant influenza subtype, population density, and climate.

A study comparing the 2015/2016 and 2016/2017 influenza seasons across multiple countries indicated that the all-cause excess mortality rates were 4.7 and 14.3 per 100,000 persons in the United States, 20.3 and 24.0 per 100,000 persons in Denmark, and 22.9 and 52.9 per 100,000 persons in Spain, respectively [11]. The estimates for excess mortality due to respiratory and circulatory causes were two to three times lower than those for all causes. Another study in Denmark, spanning from 1994/1995 to 2009/2010, reported a median all-cause excess mortality rate of 35 (range, 6–100) per 100,000 persons; 88% of these deaths were among older adults aged 65 years and above, with higher mortality observed during seasons dominated by the A/H3N2 subtype [12]. In Portugal, from 1980 to 2004, the estimated all-cause excess mortality rate was 24.7 per 100,000 persons, with approximately 90% of these deaths occurring in seniors over 65 years old [13]. Excess mortality rates were three to six times higher during A/H3N2 subtype-dominant seasons compared to those dominated by A/H1N1 or B viruses. Due to more rapid

Table 2. Estimated excess mortality attributable to influenza

Study [reference]	Years	Countries	Category of death	Annual excess mortality rates (per 100,000 persons)
Iuliano et al. [10]	1999–2015	33 Countries	Respiratory	<65 years: 0.1–6.4
				65–74 years: 2.9–44.0
				≥75 years: 17.9–223.5
Schmidt et al. [11]	2015–2017	Denmark	All-cause	Overall: 20.3–24.0
		Spain		Overall: 22.9–52.9
		United States		Overall: 4.7–14.3
Nielsen et al. [12]	1994–2010	Denmark	All-cause	Overall: 35 (range, 6–100)
Nunes et al. [13]	1980–2004	Portugal	All-cause	Overall: 24.7
Giacchetta et al. [15]	1970–2001	Italy	All-cause	Overall: 11.6–18.6
				≥65 years: 91.1
			Pneumonia and influenza	Overall: 1.9–2.2
				≥65 years: 13.3
Lemaitre et al. [8]	2010–2015	France	All-cause	Overall: 0.3–26.6
				≥65 years: 1.1–151.3
			Pneumonia and influenza	Overall: 0.1–4.3
				≥65 years: 2.1–24.5
			Cardiovascular	Overall: 0.3–7.6
				≥65 years: 0.8–42.8
Li et al. [16]	1990–2018	China	All-cause	Overall: 49.6–228.2
			Pneumonia and influenza	Overall: 0.7–30.4
			Respiratory/circulatory	Overall: 30.8–170.2
Jang et al. [18]	2013–2017	Korea	All-cause	Overall: 49.5
Hong et al. [19]	2009–2016	Korea	All-cause	Overall: 10.6
				≥65 years: 74.1
Ohmi et al. [20]	1970–1980s	Japan	All-cause	≥65 years: 6.2
	1990s			≥65 years: 9.4
	2000s			≥65 years: 2.0

mutations and antigenic drifts, A/H3N2 viruses likely pose a greater disease burden—including higher hospitalization and mortality rates—than A/H1N1 and B viruses [14]. In Italy, three studies assessed nationwide excess deaths attributable to influenza between 1970 and 2001 [15]. The findings indicated influenza-related mortality rates of 1.9 to 2.2 per 100,000 persons for pneumonia and influenza, while the all-cause rates were 11.6 to 18.6 per 100,000 persons. Among older adults, the age-adjusted excess death rates were 13.3 per 100,000 persons for pneumonia and influenza and 91.1 per 100,000 persons for all causes. In France, between the 2010/2011 and 2014/2015 seasons, the all-cause influenza-associated excess mortality rates ranged from 0.3 to 26.6 per 100,000 persons for all ages and from 1.1 to 151.3 per 100,000 persons for older adults aged 65 years and above [8].

Several Asian countries have reported comparatively high excess mortality rates, with significant variations by country and season. A systematic review of 17 Chinese studies found

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that influenza-related excess mortality rates for all causes, respiratory and circulatory diseases, and pneumonia/influenza varied widely, with rates of 49.6–228.2, 30.8–170.2, and 0.7–30.4 per 100,000 persons, respectively [16]. Furthermore, Li et al. estimated the average annual influenza-associated excess mortality rates by age group, revealing rates of 0.9, 66.1, and 519.6 per 100,000 persons for the age groups of 0–59 years, 60–79 years, and ≥80 years, respectively, between 2015 and 2018 [17]. In Korea, a nationwide matched cohort study indicated an influenza-associated excess mortality rate of 49.5 per 100,000 persons, with the highest rate observed in older adults aged ≥65 years [18]. Another Korean study, which combined weekly mortality data from Statistics Korea with laboratory surveillance data from the Korea Disease Control and Prevention Agency from 2009 to 2016, estimated the all-cause excess mortality rate at 10.6 per 100,000 persons for all ages and 74.1 per 100,000 persons for older adults [19]. In Japan, age-adjusted average excess mortality rates were relatively low, averaging 6.2 per 100,000 persons during the 1970s and 1980s when vaccination of school-aged children was mandatory [20]. This rate increased to 9.4 per 100,000 persons in the 1990s upon discontinuation of the childhood vaccination program, then decreased to 2.0 when influenza vaccination was administered to older adults in the 2000s.

Low influenza vaccine effectiveness among older adults

Vaccination is recognized as 50% to 80% effective in preventing laboratory-confirmed influenza among young adults [21]. However, a recent meta-analysis revealed that the overall effectiveness of the influenza vaccine among older adults was only 25%, with no statistically significant protection against influenza A/H3N2 in the Northern Hemisphere [22]. Additionally, the analysis indicated that pooled vaccine effectiveness diminished with increasing age in both the Northern and Southern Hemispheres.

Most influenza-related hospitalizations and deaths occur among older adults. Thus, the primary objective of influenza vaccination in this population is to reduce the number of hospitalizations and deaths resulting from severe infections. However, one meta-analysis indicated that the effectiveness of the vaccine in preventing influenza-related hospitalization is only 43.7% (95% CI, 39.7%–47.4%) [23]. Another meta-analysis, which stratified participants by age, indicated that the influenza vaccine was 41% (95% CI, 34%–48%) effective in preventing severe infections that required hospitalization among individuals aged 18–64 years and 37% (95% CI, 30%–44%) effective among those aged 65 years and older [24].

Recent studies have assessed the effectiveness of influenza vaccines in preventing severe outcomes, such as organ failure and death. A study from the United States conducted during the 2022–2023 season found the effectiveness of vaccination against hospitalization due to type A influenza was 37% (95% CI, 27%–46%). This effectiveness varied by age group (18–64 years: 47% [95% CI, 30%–60%]; ≥65 years: 28% [95% CI, 10%–43%]) and by virus subtype (A/H3N2: 29% [95% CI, 6%–46%]; A/H1N1: 47% [95% CI, 23%–64%]) [25]. Additionally, the influenza vaccine was 65% (95% CI, 56%–72%) effective against influenza-related organ failure (involving the respiratory, cardiovascular, or renal systems) and 48% (95% CI, −70% to 84%) effective against death. In a separate study from Norway covering the same season, the effectiveness of vaccination against influenza-associated hospitalization was 34% (95% CI, 26%–42%) for adults aged 65–79 years and 40% (95% CI, 30%–48%) for individuals aged ≥80 years. The effectiveness against influenza-associated death was 6.6% (95% CI, −64% to 47%) for the 65–79 age group and 37% (95% CI, 0.5%–61%) for those aged ≥80 years [26]. While the influenza vaccine does reduce the risk of severe disease, its effectiveness is considerably lower than that of the vaccines for coronavirus disease 2019 (COVID-19). For preventing COVID-19–associated hospitalization, the effectiveness of vaccination was 65% (95% CI, 61%–69%) among adults aged 65–79 years and 55% (95% CI, 49%–60%) among those aged ≥80 years [26]. Regarding COVID-19–associated death, the effectiveness was 68% (95% CI, 48%–80%) for the 65–79 age group and 78% (95% CI, 65%–86%) for those aged ≥80 years.

Discussion

Given the high rates of hospitalization and death among older adults, reducing the disease burden of influenza through vaccination is essential. In Korea, the vaccination rate for seniors aged 65 years and older has been maintained at over 80% [27]. However, the antibody titer produced in older adult populations following influenza vaccination is approximately 40% to 80% of that in healthy adults, indicating relatively low vaccine effectiveness, ranging from 31% to 58% [28,29].

Influenza vaccines are currently approved based on a hemagglutination inhibition (HI) antibody titer of ≥40 for young adults under 60 years old and ≥30 for seniors over 60 years. However, an HI titer of 1:30 or 1:40 only represents the antibody level that can prevent 50% of influenza virus infections in healthy adults [30]. To achieve vaccine effectiveness greater than 90%, an HI titer exceeding 1:100 may be necessary; however, it is challenging to attain such high immunogenicity among older adults with available conventional vaccines [30]. Furthermore, since seasonal influenza epidemics can persist for more than 6 months, maintaining adequate protective immunity over this duration is crucial. However, HI titers typically start to wane after vaccination and decline sharply after 6 months [31]. The lower vaccine effectiveness observed in older adults aged 65 years and older may also stem from the short duration of vaccine-induced immunity and immune imprinting from repeated exposure, particularly to influenza A/H3N2. Consequently, a need exists for influenza vaccines that are highly immunogenic, induce long-lasting immunity, and minimize immune imprinting. To increase the efficacy of influenza vaccines in older adults, high-dose (Fluzone High-Dose, 60 μg hemagglutinin [HA]/strain), MF59-adjuvanted (Fluad, 15 μg HA/strain), and intradermal (Fluzone Intradermal, 15 μg HA/strain) vaccines have been developed [32-34]. Compared to the conventional standard-dose vaccine, these options have demonstrated higher immunogenicity in terms of their relative HI titer ratios [35]. Although intradermal vaccines are no longer produced, both MF59-adjuvanted and high-dose vaccines have been introduced and are currently available for use.

When evaluating the relative vaccine effectiveness of the MF59-adjuvanted influenza vaccine compared to the unadjuvanted standard-dose vaccine over three consecutive influenza seasons (2017–2018, 2018–2019, and 2019–2020) in the United States, the MF59-adjuvanted, trivalent vaccine displayed superior effectiveness over the quadrivalent alternative. The MF59-adjuvanted option displayed better prevention of influenza-related medical visits, with relative effectiveness estimates ranging from 20.8% (95% CI, 18.4%–23.2%) to 27.5% (95% CI, 24.4%–30.5%) [36]. Additionally, the MF59-adjuvanted trivalent influenza vaccine further reduced influenza-related hospitalizations, demonstrating a relative vaccine effectiveness of 6.5% (95% CI, 0.1%–12.4%). In a meta-analysis comparing the relative effectiveness of high-dose versus standard-dose, unadjuvanted influenza vaccines, the high-dose option displayed superior protection against influenza-like illness compared to the standard-dose vaccine, with a relative effectiveness of 15.9% (95% CI, 4.1%–26.3%) [37]. Moreover, the high-dose vaccine was more effective in preventing hospital admissions, with significant relative effectiveness against all causes (8.4%; 95% CI, 5.7%–11.0%), pneumonia/influenza (13.4%; 95% CI, 7.3%–19.2%), and cardiorespiratory events (17.9%; 95% CI, 15.0%–20.8%). When the relative effectiveness of the MF59-adjuvanted vaccine was compared to the high-dose vaccine in a meta-analysis that excluded studies sponsored by pharmaceutical companies, no significant difference was found in the prevention of influenza-related emergency room visits, hospitalizations, or pneumonia between the two vaccines [29].

Antigenic mismatches between newly developed vaccines and circulating strains can meaningfully reduce vaccine efficacy. In a randomized study, the MF59-adjuvanted influenza vaccine demonstrated greater cross-reactivity against antigenically drifted, heterovariant A/H3N2 strains compared to the unadjuvanted standard-dose influenza vaccine [14]. Further research is required to ascertain whether the MF59-adjuvanted or the high-dose influenza vaccine is more advantageous in terms of immunological outcomes, including cross-reactive immunity to variant viruses and the capacity to overcome immune imprinting.

In conclusion, influenza imposes a considerable disease burden on older adults, characterized by high rates of infection, hospitalization, and mortality. The effectiveness of influenza vaccines in this demographic fluctuates by season but is substantially lower than that observed in younger adults. Even with high vaccination rates among older adults, the suboptimal effectiveness underscores the need for improved vaccination strategies. These include the use of high-dose and adjuvanted vaccines to increase immunogenicity and afford more robust protection against influenza in this vulnerable age group.

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Authors' contributions

All work was done by Joon Young Song.

Conflict of interest

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