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REVIEW ARTICLE

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The burden of influenza and the role of influenza vaccination in adults aged 50-64 years: A summary of available evidence

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ABSTRACT

Influenza is a vaccine-preventable disease and a global public health problem. Although most national influenza vaccination recommendations focus on subjects aged ≥65 years, an extensive burden of influenza has also been reported in those aged ≥50 years and is exacerbated by immune system aging. The main purpose of this review is to provide an overview of the burden of influenza and its potential prevention within the 50–64 age-group. These subjects account for a large proportion of the workforce, and play a central economic and social role. Individuals aged 50–64 years had a 3-times higher rate of hospitalization and a 9-fold higher mortality rate attributable to influenza than those aged 18–49-years, generating higher influenza-related hospitalization costs. Available data suggest that including healthy subjects aged 50–64 years in influenza vaccination recommendations would allow a broader population to be reached, reducing the economic and social burden of influenza.

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Introduction

Influenza, usually called "the flu," is a vaccine-preventable disease and a global public health problem. The World Health Organization (WHO) estimates that influenza alone causes 290,000 to 650,000 deaths due to respiratory diseases every year, without taking into account deaths from other potentially influenza-related diseases.[1] In Europe, seasonal influenza infects approximately 10–30% of the population each year and causes hundreds of thousands of hospitalizations.[2] Seasonal influenza is not only responsible for morbidity and mortality; it also has an economic impact in terms of absenteeism from work and the use of health services. The disease can affect all age-groups; however, the WHO identifies the following groups as being at greater risk of severe disease or complications: pregnant women, children under 5 years old, the elderly, individuals with chronic medical diseases or immunosuppressive conditions and healthcare workers.[3]

While most infected subjects recover within a week, influenza infection can sometimes result in severe disease, such as respiratory, cardiac, gastrointestinal and renal complications, co-infections and exacerbation of chronic conditions.[4] The body of evidence shows that influenza vaccination exerts a protective effect on influenza-related cardiac events.[5–8] Owing to the high incidence of hidden cardiopulmonary diseases in older persons, the Advisory Committee on Immunization Practices (ACIP) in 2006 recommended influenza vaccination for subjects aged ≥50 years.[9,10]

Influenza infections in humans are caused by influenza A (H1N1 and H3N2 subtypes) and B (Victoria and Yamagata lineages) viruses.[11,12] Vaccination is the most effective method of preventing and controlling seasonal influenza infections and of reducing the spread of possible pandemic events, as proved during the COVID-19 pandemic. The degree of protection elicited by influenza vaccines depends on a complex interplay among vaccine composition and circulating viruses, the characteristics of vaccinated subjects (i.e., age and health status), previous exposure to influenza and product-specific factors, such as formulation, manufacturing and the use of adjuvants.[13] Traditional vaccines were trivalent, containing A (H1N1) and A(H3N2) viruses and one lineage of B viruses. However, owing to frequent mismatches between circulating strains and vaccine strains and the co-circulation of both B lineages, the WHO has recommended the inclusion of both lineages (quadrivalent vaccine) since the 2013–2014 season.[14,15] Influenza vaccination programs for high-risk groups and the elderly have therefore been implemented in Europe since the 1980/1990s. In 1999, the American Academy of Family Physicians was the first national organization to recommend lowering the age for routine influenza vaccination.[16] Most European countries, including Italy, recommend vaccination for persons over 65 years of age and for high-risk groups. Since the 2020–2021 influenza season, the Italian Ministry of Health has further lowered the recommended age for vaccination to 60 years, owing to the co-circulation of influenza viruses and SARS-CoV-2. Other countries, such as Hungary, Germany, Greece and Portugal, have set the age threshold of 60 years for influenza vaccination, while several countries, including the United States (US), Canada and Belgium, recommend vaccination for adults aged over 50 years.[17–22] Since the 2010–2011

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influenza season, the US ACIP has issued a "universal recommendation" for influenza vaccination from 6 months of age.[23] Increasing the number of vaccinated adults in the 50–64 age-group will further reduce the annual impact of influenza. The burden of severe influenza in this age-group is significant, although it increases steadily with age.[24] The influenza fatality rate begins to rise at age 45 and is highest in subjects who have chronic medical conditions.[16] Vaccination of the 50–64 age-group has been found to be cost effective.[25–28] Evidence suggests that the expantion of the influenza vaccination program beyond the targeted population may constitute an alternative strategy to reduce the burden of influenza, resulting in an overall higher vaccination uptake and in an easier implementation than a risk-based recommendation.[21,24,29] However, in Italy, vaccination coverage in the 2019–2020 season was only 54.6% among subjects over 65 years of age, 16.8% in the general population and even lower (9.6%) among those aged 45–64 years.[30] Since vaccination has been reported to reduce hospitalization due to influenza by 63.9% in the 50–64 age-group,[31] it should be recommended for subjects over 60 or even younger (50 years old).

It has been predicted that, by 2030, 1 in 6 subjects in the world will be aged 60 years or over. In 2021, Europe was the continent with the oldest population, and in 2022, more than one fifth (21.1%) of the European population was aged ≥65 years, with Italy having the largest proportion of elderly people in Europe.[32–34]

Together with the increased life expectancy, an epidemiological transition is occurring, shifting the diseases from infectious diseases to a majority of chronic-degenerative diseases.[35] In Italy, about 24 million people suffer from at least one chronic disease, with a considerable number affected by two or more chronic conditions. Although chronic diseases can affect all age-groups, they are more frequent in the elderly. Indeed, more than 85% of subjects over 75 years old suffer from chronic diseases. However, the disease burden increases above the age of 55–60 years. One study has shown that cardiovascular disease is not only a disease of the elderly; but, virtually, half of all cardiovascular events in men and almost one-third in women occur before the age of 65 years. The risk of premature cardiovascular disease is low before the age of 40 years, increases gradually between 40 and 60 years and rises sharply thereafter.[36,37] The CDC reported that in 2018 30.4% of US adults aged 45 to 64 years have one of ten possible chronic conditions, while 33.0% two or more.[38] Aging is accompanied by a decline in immune efficacy and an increase in low-grade inflammation, which is associated with the emergence of chronic diseases, including neurodegenerative and cardiovascular diseases, diabetes mellitus type 2 and cancer.[39,40]

The main purpose of this review is to provide an overview of the burden of influenza and its potential prevention within the 50–64-year age-group, since these subjects account for a large proportion of the workforce and are also at increased risk of complications.

Materials and methods

The search strategy for this systematic review was performed through the PubMed database integrating data with a gray literature search, with language restricted to English and Italian. The search was restricted to PubMed as it is the most widely used database and search engine in the biomedical and healthcare fields.[41] The search strings were launched on 1st February 2023 and are detailed in Supplementary materials. The resulting articles were screened for inherence with the topics covered in the present review. The citation lists from relevant literature sources (e.g., previously published systematic reviews) was also manually screened.

Results

Burden of influenza in the 50–64-year age-group

The human potential lost as a result of inadequate health protection places a substantial burden on Public Health. Every year, influenza accounts for 81.8 Disability Adjusted Life Years per 100,000 population and is among the top infectious diseases in Europe in terms of morbidity and mortality in all age-groups, including adults.[42]

Apart from the hazard arising from flu infection, age is one of the main risk factors for the prevalent diseases in developed countries, where the WHO has reported a substantial increase in the prevalence of morbidities starting from the age of 50.[43,44] For this reason, and since the ≥65 age-group is already a recognized risk category, this review focused on studies assessing the burden of influenza in the 50–64-year age-group. The characteristics and main findings of these studies are summarized in Table 1.[24,29,45–58]

One of the first studies to investigate this field was conducted in the United Kingdom (UK) in 2000. During the 6 years of the study, 15.2% of influenza or influenza-like illness (ILI) reported occurred in subjects aged 50–64 years, 9% of whom developed clinical complications, as compared with 8.2% and 10.9% of 15–49 and ≥65-year-old individuals, respectively.[46] This slight difference among age-groups tended to fade, almost disappearing in the presence of a condition of frailty: 12.1%, 12.4% and 12.6% of those aged 15–49 years, 50–64 years and ≥65 years, respectively, with at least one chronic condition were found to present complications attributable to influenza.[46] This is in line with the increasingly affirmed observation that aging is not the only host factor that hinders the immune response to infection; rather, fragility in its broadest sense constitutes an obstacle to protection against flu.[59] These findings are fairly well aligned with those of a prospective cohort study conducted in US in the same age-groups.[48] That analysis revealed rates of 15.7% of ILI, 4.3% of ILI-related health visits and 3.5% of antibiotic prescriptions in vaccinated subjects. In unvaccinated participants, however, these percentages increased markedly, the rates of ILI, ILI-related medical encounters and drug prescriptions being 25.0%, 9.1% and 6.8%, respectively,[48] underlining the positive effect of vaccination on the burden of influenza in the 50–64-year age-group. Furthermore, this study highlighted another issue related to ILI and acute respiratory infection, namely antibiotic overuse, a widespread bad habit that could be partly countered with the support of adequate influenza vaccination coverage and timely viral diagnostic tests.[60,61]

With regard to clinically more severe outcomes, subjects with at least one underlying condition associated with a higher risk of influenza complications tend to consult the physician more

Table 1. Studies characteristics and main findings related to burden of influenza in the 50–64 age group ($N = 16$).

Age	Study population	Country/ Continent	Design of the study	Season/ Period	Outcome	Main Findings	First author, year [Reference]
50–64 years	436,423 individuals	United Kingdom	Case-control	1991–1996	Incidence of influenza-related physician visits, influenza cases, influenza-related complications (otitis media, gastrointestinal bleeding, respiratory tract, cardiovascular, central nervous system or renal complications; death), drug prescriptions.	15.2% of the base population had a diagnosis of influenza or ILI and the 9% had a clinical complication; influenza incidence rate of 0.049.	Meier et al.[46]
50–64 years	NA	United States	Case-control	1979–2001	Influenza-associated hospitalization rate.	Annual average rate of influenza-associated hospitalization for: -pneumonia and influenza: 37.9 (primary) or 53.3 (any) per 100,000 person years; -respiratory and circulatory causes: 83.8 (primary) and 11.3 (any) per 100,000 person years.	Thompson et al.[47]
50–64 years	497 working adults	United States (Minneapolis)	Prospective cohort	2006-2007	Burden of ILI (occurrences of ILI, ILI-associated visits, number of days of illness, disability, work absenteeism, presenteeism) and the benefits of vaccination.	17,1% of the population reported at least an ILI; of persons with ILI, 31% visited a GP ad 20% received an antibiotic prescription.	Nichol et al.[48]
50–64 years	959 individuals	United States	Prospective cohort	2005–2008	Laboratory-positive influenza -associated hospitalization rate	Rate of laboratory-confirmed influenza hospitalization: 7.78, 4.23 ad 14.78 per 100,000 persons, respectively, in 2005/6, 2006/7 and 2007/8.	Dao et al.[49]
50–64 years	214 individuals	Japan	Observational and test-negative case – control	2008-2009	Laboratory confirmed influenza in patients presenting with Acute Respiratory Infection.	61.4% of influenza cases in persons aged 50–64 years.	Ikematsu et al.[50]
45–64 years	NA	United Kingdom	ND	2000/1–2007/8	Influenza-associated health care outcomes (acute respiratory illness episodes leading to GP consultations, hospital admissions and deaths in hospital) in different age groups in those with and without high-risk conditions.	Rate of GP consultations of 1,829 per 100,000 persons; rate of hospital admissions of 27 per 100,000; 9.3 (not at-risk population) or 56 (at-risk population) deaths per 1,000 admissions.	Cromer et al.[52]
45–64 years	Medicaid database mean annual patients: 92445 (males) and 145,483 (females) aged 45–54 years; 67584 (males) and 95,274 (females) aged 55–64 years; Commercial database mean annual patients: 3,831,642 (males) and 4,281,293. (females) aged 45–54 years; 3,210,947 (males) and 3,574,713 (females) aged 55–64 years	United States	Cross-sectional	2006–2010	Vaccine-preventable diseases incidence proportions.	Mean incidence proportions of influenza infection (diagnosed by diagnostic codes): 270 to 397 per 100,000 in men and 493 to 521 per 100,000 in women in the 45–54 age group; 272 to 300 per 100,000 in men and 386 to 471 per 100,000 in women in the 55–64-years-olds, according to the database analyzed (Medicaid or commercial insurance database).	Krishnarajah et al.[53]
50–64 years	NA	Netherlands	ND	2010–2013	Average annual disease burden (DALYs) of influenza, pertussis, pneumococcal disease and herpes zoster.	Average annual influenza burden in DALYs: 53 per 100,000 persons and 27 per 1,000 cases.	Kristensen et al.[51]

(*Continued*)

Table 1. (Continued).

Age	Study population	Country/ Continent	Design of the study	Season/ Period	Outcome	Main Findings	First author, year [Reference]
50–64 years	NA	United Kingdom	Cross-sectional	1995–2009	Influenza-attributable hospitalization and deaths.	Mean seasonal hospitalization attributable to influenza of 39 and 0 per 100,000 persons respectively for influenza A and B; Mean seasonal mortality attributable to influenza of 4 and 0 per 100,000 persons respectively for influenza A and B.	Matias et al.[54]
50–64 years	NA	United Kingdom	Cross-sectional	1995–2009	Influenza-attributable GP consultations and antibiotic prescriptions.	1,076 (influenza A) and 179 (influenza B) per 100,000 persons GP consultations attributable to influenza in a mean season.	Fleming et al.[55]
50–64 years	4,076 persons	United States	ND	2013/14–2015/16	Number of outpatient influenza visits averted by vaccination.	Incidence of ambulatory visits of 28.9 cases per 1,000 (CI 95%:15.9–43.2).	Jackson et al.[56]
50–64 years	Total of 333,579 ≥ 50 years adults in the served area	Italy (Genoa)	Retrospective descriptive	2011–2017	Health and economic burden of influenza and its complications: annual incidence rates of ILIs and LRTIs requiring ED access, ILI followed by hospitalization, healthcare costs.	Median incidence of ILI/LRTI ED accesses per 1,000 persons: 2.08, 2.88 and 3.55, respectively, in the 50–54, 55–59 and 60–64 age group.	Trucchi et al.[45]
50–64 years	NA	Australia	Descriptive	2001–2017	Influenza-attributable hospitalization and death after diagnosis of influenza/pneumonia, respiratory, circulatory or myocardial infarction.	Hospitalization rate per 100,000 persons of 287.6, 1,301.2, 3,022.7 and 373.5, respectively, for influenza/pneumonia, respiratory, circulatory, myocardial infarction causes; Mortality rate per 100,000 persons of 3.6, 22.6, 93.9 and 32.4, respectively, for influenza/pneumonia, respiratory, circulatory, myocardial infarction causes.	Moa et al.[29]
50–64 years	NA	Global	ND	2010–2019	IHD mortality attributable to influenza.	63,871 IHD mean deaths; average rate of IHD deaths of 6.4 per 100,000 persons.	Chaves et al.[57]
50–64 years	16,350,052 (Brazil) and 2,106,794 (Mexico)	Brazil, Mexico	Cross-sectional	2010–2017 (Mexico); 2010–2018 (Brazil)	Hospital stay duration, admission to ICU, in-hospital mortality.	Brazil: Relative risk of ICU admission and in-hospital case-fatality rate of 5.4 (95% CI: 4.62–6.42) and 2.9 (95% CI: 2.4–3.6), respectively, in persons with any predefined comorbidity compared to patients without comorbidities. Mexico: Relative risk of ICU admission and in-hospital case-fatality rate of 2.0 (95% CI: 0.9–4.1) and 1.1 (95% CI: 0.9–1.4), respectively, in persons with any predefined comorbidity compared to patients without comorbidities.	El Guerche-Séblain et al.[58]
50–64 years	1,228 persons hospitalized with laboratory-confirmed influenza	Canada (Toronto and Peel region)	Prospective cohort	2010–2017	Epidemiology of laboratory-confirmed influenza resulting in hospitalization and death.	Annual average rate of influenza-associated hospitalization of 22.4 per 100,000 per year and average annual mortality rate of 0.9 per 100,000.	Kim et al.[24]

CI= Confidence Interval; DALYs= Disability Adjusted Life Years; ED= Emergency Department; GP=General Practitioner; ICU= Intensive Care Unit; IHD= Ischemic Heart Disease; ILI=Influenza-Like Illness; LRTIs=Lower Respiratory Tract Infections; NA=Not Available; ND=Not Defined.

often than individuals at low risk.[55] A similar trend in influenza-attributable mortality has been observed in individuals from 45 to 64 years of age, with a risk of in-hospital death 5.9 times higher in subjects with comorbidities than in those without.[51] In addition, Fleming et al.[55] observed that the average seasonal rates of influenza A-attributable general practitioner (GP) interventions in the unvaccinated high comorbid-risk group were 1.79-fold higher than in the low comorbid-risk group among older adults aged 50–64 years.[55] Conversely, this trend was not seen among adults aged 50–64 years infected by influenza B, in whom no statistically significant difference in terms a physician visits between high and low comorbid-risk persons was reported.[55] This difference may be explained by the fact that influenza A seems to affect persons aged 40–64 years more frequently than influenza B,[62] making it difficult to observe any differences between the two subgroups. Indeed, in that study,[55] a rising trend in influenza A cases was observed after the age of 50 years, while influenza B cases showed the opposite pattern, decreasing with age.

With regard to the different incidence of outpatient medical visits, the frequency of GP consultations has been reported as 28.9 cases per 1,000 (95% CI: 15.9 to 43.2) in persons aged 50–64 years.[56] Regarding access to the emergency department, an Italian study reported that the rate progressively increased with age: being 2.08, 2.88 and 3.55 per 1000 person-years in adults aged 50–54 years, 55–59 years and 60–64 years, respectively; the highest rate (18.92 per 1000 person years) was seen in the oldest elderly (≥85 years).[45] These findings were confirmed by several studies.[24,29,47,49,58] The median duration of hospitalization for primary pneumonia and influenza displayed the same age-related trend.[47] Kim et al.[24] estimated, across 7 influenza seasons, that individuals aged 50–64 years had a 3-times higher rate of hospitalization attributable to influenza than those aged 18–49 years (22.4 and 7.54 per 100,000 per year, respectively) and a 2-fold lower rate than those aged 65–74 years (45.9 per 100,000 per year). These results were also reflected in the mortality rate, with a 9-fold higher rate being recorded in persons aged 50–64 years than in those aged 18–49-years (0.9 and 0.1 per 100,000 per year, respectively) and 2-fold lower than in subjects 65–74 years old (2.0 per 100,000 per year).[24] These data, added to the UK estimate that about 75% of deaths in the 50–64 age-group occur in hospital,[54] reveal that influenza-related respiratory morbidity and mortality already begin to increase at the age of 50. Moreover, since the in-hospital management and treatment of influenza have a significant economic and health impact, the implementation of efficacious prevention strategies and early management can attenuate this overall burden and favor a smoother resolution of the illness.[63] In support of this, from 2001 to 2017 in Australia it was estimated that adults aged 50–64 years had an influenza-associated mean annual rate of hospitalization for respiratory causes of 78.9 (95% CI: 76.3, 81.4) per 100,000 persons and of 32.3 (95% CI: 31.2, 33.3) per 100,000 persons for influenza and pneumonia.[29] However, although respiratory complications are probably the most burdensome sequelae of influenza infection, influenza infection may have an impact on other, less specific outcomes. Worldwide, 18.4 annual deaths due to ischemic heart disease per 100,000 adults aged ≥50 years could be related to influenza. Of these, approximately 21.3% occur in the 50–64 age-group.[57]

Overall, the available studies suggest that the influenza-related burden already starts to increase before 65 years, rising with age and the presence of comorbidities.

Economic burden of influenza

Compared with other diseases, flu may give the impression of having a modest economic impact, owing to the moderate number of working days lost and the consequent limited impact on the individual's income. In reality, it has a substantial effect on social expenditure and total fiscal revenues, on account of the high number of persons infected. Indeed, one model has estimated that, assuming 2.1 million people infected by influenza in Italy annually, the total estimated economic burden (direct, indirect and fiscal) in the adult population aged 30–64 years is about €1 billion each year, approximately €160 million of which stems from the loss of tax revenues.[64] These results highlight the double damage caused by the inadequate control of the spread of influenza, namely the more evident loss resulting from direct and indirect costs, and the less obvious fiscal loss. Indeed, a decrease in tax revenues translates into a reduction in funds that could be re-invested in health and in improving healthcare services.

Focusing on persons aged 50–64 years, a 2015 US analysis estimated that influenza imposed the highest vaccine-preventable economic burden in this age-group, accounting for 67% of the total burden.[65] According to data collected in 2019, these findings were also applicable to Europe, where 15.8% of the 55–64-year-old workforce had left their previous job owing to illness or disability.[66]

Regarding this issue, a systematic review recently gathered and summarized the available literature on the economic burden of influenza in 18–64-year-olds from 2007 to 7th February 2020.[67] Individuals aged from 50 to 64 years generated higher influenza-related hospitalization costs, in general, than persons aged 18–49 years. The economic burden further rose in patients with comorbidities or factors that put them at increased risk of complications.[67] Similarly, an Italian analysis reported a 60% mean increase in individual costs among high-risk persons aged ≥50 years examined at the Emergency Department or admitted to hospital in comparison with no-risk subjects of the same age.[45,67] Moreover, when compared with those aged ≥65 years, 50–64-year-old subjects reported higher individual hospitalization charges. However, since the hospital admission rate increases with age, hospitalization expenses proved to be higher in elderly than in younger adults when costs were generalized at a population level.[67]

A possible solution to this heavy influenza burden was investigated by a previous Budget Impact Analysis, which considered the social savings yielded by an optimal influenza vaccination budget allocation.[68] More specifically, the optimal budget allocation is achieved when the investment in vaccination is equal to the cost of the antiviral treatments that are avoided as a result of improved protection and reduced influenza transmission. In Italy and France, an optimal budget allocation is achieved at vaccination coverage rates of 32.75%

and 32.4%, respectively, yielding savings of €125 million in Italy and €118 million in France. Savings continue to improve up to 100% as vaccination coverage increases. Similarly, in Germany and Spain, an optimal budget allocation is reached at 38.5% and 28.3% coverage, respectively (yielding savings of €148 million and €129 million), with social savings increasing up to 80% with further investments in influenza vaccination.[68]

Likewise, two systematic reviews have taken into consideration the cost-effectiveness of influenza vaccination in persons aged 50–64 years.[28,69] Both concluded that, in all the studies included and in all the perspectives analyzed (Healthcare System, Third Party Payer, Society), flu vaccination in 50–64-year-old healthy adults was a cost-effective or dominant strategy in comparison with a vaccination policy exclusively targeting adults at high risk.[28,69] The countries included were: Spain, France, Germany, Italy, the US, Australia and the UK. All the resulting Incremental Cost-Effectiveness Ratios (ICER) were lower than €30,000/quality-adjusted life-year (QALY), with only two exceptions; these two concerned a study conducted in Germany from a Third-Party Payer Perspective, in which the final ICER was €31,387/QALY, and an Australian study, which reported inconclusive results.[27,70–75] By contrast, influenza vaccination in overall healthy adults proved cost-saving from a societal perspective in Italy and Germany.[69,71] These findings are in line with data reported by De Courville et al.,[67] who observed that expenses in 50–64-year-old subjects are mainly due to indirect costs. The only analysis which compared vaccination of at-risk adults with a "no vaccination" strategy in the 50–64 age-class concluded that influenza vaccination was a cost-effective strategy.[69,76]

Thus, the evidence indicates that influenza causes a considerable economic burden in subjects aged ≥50 years, and that this can be alleviated by means of wider influenza vaccination coverage. Extending influenza vaccination to the general 50–64-year-old population may be feasible, requiring a relatively small investment in both at-risk and healthy subjects.

Absenteeism and "presenteeism" after influenza infection

Productivity losses are strictly related to absenteeism and so-called "presenteeism," i.e. in order, absence from work and presence at work but with reduced functionality owing to injury or illness (even when contagiously sick).

Nichol et al.[48] estimated that unvaccinated workers with ILI miss about 1.7 work days and spend a minimum of 5 days working despite their illness, even if they are symptomatic. In their study, ILI was responsible for a large portion of the total days of illness reported by the participants, accounting for 45% of cases, 39% of all working days missed and 49% of days of presenteeism.[48] Moreover, a study estimated that, in the 7–17 working days after disease onset, persons aged ≥18 years lost 67% of their productivity in terms of working hours because of absenteeism or presenteeism.[67,77]

Predictably, with regard to the adult working population, the greatest proportion and the longest duration of influenza-related absences from work involve the ≥ 40/45 age-class, and increase with age and/or the presence of risk factors.[78–82] An Italian study observed the highest absence-related costs in persons aged 40–59 years.[82] In that study, lower cumulative costs were ascribed to subjects aged >59 years; however, the data were strongly affected by the numbers of subjects in each age-group. Specifically, 72% of workers were 40–59 years old, while only 6% were ≥60 years old.[82] In the US, it was observed that from 2005–2006 to 2008–2009 influenza seasons the highest number of subjects with at least one day of influenza-related absence from work was in the 45–64 age-group, corresponding to a proportion of 30.82%–39.75%.[79] Comparable rates of absenteeism have been reported in individuals with comorbidities, independently of age.[79] A similar trend has been observed on shifting the focus to average working hours lost as a result of influenza infection or ILI presentation, in both American and Spanish studies.[78,79,82]

A further distinction was made in an Italian study, in which cases were divided into inpatient and outpatient.[80] Obviously, hospitalized cases accounted for a significantly higher number of lost workdays than outpatient cases, with 12 and 13 days of work lost in 18–49 and 50–64-year-olds, respectively, compared with 1 and 2 days of absence in non-hospitalized cases. Work loss was even greater in at-risk patients, reaching the maximum values in the 50–64 age-group, with 4 days of absence among outpatient cases and 24 days among inpatient cases.[80]

According to the available evidence, lost productivity due to influenza is particularly heavy in the 45–64 age-group. This burden is further worsened by the severity of the illness and the initial risk condition of the subject.

The caregiver's role

A large proportion of caregivers are adults aged 50 to 64 years. A representative study conducted in the US found that 35% of caregivers were aged 50–64 years, 12% 65–74 years and 7% ≥75 years; moreover, the longest care (mean 5.6 years) was provided by the 50–64 age-group.[83] Thus, concern for this population regards not only their personal care, but also the informal care that they often provide for fragile individuals. Indeed, in order to carry out their duties properly, caregivers must be physically and mentally fit. One European study reported that caregivers in the 50–70 age-group, especially women, had lower employment prospects.[84] A caregiver seems to have a 22% less probability of finding a job and 28% fewer paid working hours.[84] In addition, caregivers, even those aged 50–64 years, often suffer from underlying medical conditions, which means that they have two disadvantages, being both caregivers and vulnerable persons.[85]

For all these reasons, 50–64-year-old individuals need to be protected, in order to safeguard both their personal health and their role in society.

Immunosenescence

Age-related changes in the immune system, termed "immunosenescence," lead to a progressive reduction in the ability to trigger effective humoral and cellular responses to infections in older adults. As suggested by epidemiological data,[86,87] the first signs of declining immune competence occur by age 50 and accelerate after age 65–70.[88]

The quality and quantity of T and B cell responses change with advancing age, resulting in an inadequate immune response against newly encountered antigens and exacerbating the severity of infection in older adults.[40] Importantly, primary

vaccine responses in older individuals fail to generate complete protection and have reduced efficacy, as evidenced in several influenza vaccine studies.[86,89,90]

The reduced ability to respond to novel antigens is caused by the impoverishment of peripheral naïve T and B cells, owing to the involution of primary lymphoid organs. The regenerative capacity of hematopoietic stem cells decreases with age, impairing the production of mature B cells,[40,91] and the thymus begins to atrophy and is largely replaced by adipose tissue by the age of 50 years.[92–95] This results in a continuous decline in peripheral naïve T cells after 40 years of age, such that, by age 50, T cell production is less than 10% of previous peak levels.[96–98]

Lifelong exposure to pathogens leads to depletion of the reservoir of naïve T cells and their conversion to late differentiated memory cells, particularly in the case of chronic infections, which repeatedly stimulate the immune system throughout life.[99] Indeed, aged T cells display reduced proliferative capacity after antigen recognition, lower cytokine secretion, higher activation thresholds, a reduced T-cell receptor (TCR) repertoire, and poor effector functions following influenza vaccination.[100,101] Specifically, TCR repertoire diversity has been reported to decrease significantly by the age of 40.[102]

Age also affects the number and diversity of the B cell repertoire, as well as immunoglobulin isotypes and the receptor repertoire.[103] Along with a decrease in circulating B cells, several phenotypic differences among B cell subsets have been reported in subjects older than 60–65 years, including an accumulation of B cell memory and a decrease in plasma cell differentiation.[104,105] However, comparative analyses of B-cell receptor repertoires induced by yellow fever vaccination have revealed several differences between young and middle-aged subjects, indicating that changes in the humoral adaptive response are already detectable by the age of 50.[106]

Activated B cells isolated from older adults show a decrease in antibody avidity and antibody-mediated protection. A selective shift from immunoglobulins produced by naïve B cells (IgD, IgM) to immunoglobulins produced by memory B cells (IgG, IgA) is accompanied by a reduced ability to produce high-affinity protective antibodies in subjects aged >60 years.[103,104] Moreover, the duration of long-term protection is compromised in older individuals, as antibodies decline with advancing age.[91,104]

Lastly, "inflamm-aging," defined as a systemic state of chronic low-grade inflammation, is a common pathogenetic mechanism of age-related diseases and immunosenescence. Aging of the innate immune system has been shown to increase in levels of pro-inflammatory mediators,[107] and is in turn linked to impaired immune responses, as it interferes with B cell activation and contributes to a defective T cell response.[40] In monocytes, the pre-vaccination expression of genes related to inflammation and the innate immune response has been reported to be negatively correlated with the activation of antibody responses induced by influenza vaccination.[108]

Vaccine effectiveness in adults aged 50–64 years

Vaccine effectiveness (VE) is dependent on several variables, such as the age of vaccinees, their history of previous vaccination and their health status. The factor that may contribute most is the antigenic match between the circulating viruses and the vaccine strains. Indeed, influenza viruses are subject to frequent minor mutations, a phenomenon called "antigenic drift," that enable the virus to escape recognition by the host immune system. However, also the mutations that the virus may undergo during propagation in eggs may result in vaccine mismatch and reduced VE. Viruses propagated in mammalian cells, by contrast, are not subject to egg-adaptation, and have proved to be representative of the circulating strains, remaining unchanged in cell culture.[109–111]

In addition to the studies focused on VE in the elderly,[112–114] people aged 50–64 years are also of great interest, since this age-group comprises a large proportion of working individuals and subjects at increased risk of complications.[71] Two studies reported that influenza vaccination reduced the risk of influenza-associated hospitalizations[115,116] among subjects aged 50–64 years in two different influenza seasons (2003–2004 and 2010–2011). Despite the poor antigenic match between the influenza A(H3N2) strain contained in the vaccine and the circulating virus during the 2003–2004 season, VE was 60% and 48% among subjects without and with high-risk medical conditions, respectively.[115] In addition, another two studies documented shorter stays in the intensive care unit in vaccinated subjects aged 50–65 years than in unvaccinated subjects.[117,118] These findings reveal that, though mismatch may impair the ability of vaccination to prevent infection, it might be protective against severe influenza outcomes, providing evidence of the potential benefit of the strategy of vaccinating this age-group.[117]

Moreover, other studies reported that vaccination was not only associated with a significant reduction in the risk of ILI, even during a season characterized by drifted viruses (2019–2020), but was also associated with fewer days of illness and a significant reduction in the number of days in bed, working days lost and impaired job performance.[48,119] Interestingly, 45% of participants with ILI in this study conducted in the 2006–2007 influenza season[48] assumed that they had been infected at work, suggesting that the workplace plays an important role in the transmission of the virus. In addition, more than half of the participants had been vaccinated at their workplace, providing evidence that both traditional and non-traditional settings should be strongly promoted, in order to increase the proportion of vaccinated subjects. Overall, the vaccination of subjects aged 50 to 64 years has been seen to correlate with significant health and productivity benefits.[48] Indeed, it has been estimated that extending vaccination to people of this age-group is cost-effective, cost-saving and could potentially help to curb morbidity and mortality in other age-groups by reducing viral transmission.[71,120,121]

Discussion

Vaccination against influenza remains the most effective method of preventing infection, hospitalization and mortality. Nevertheless, the most appropriate age at which to vaccinate adults remains a matter of heated debate.[45] By the age of 40, the immune system starts to undergo changes capable of hindering the response to exogenous

Table 2. The table summarizes key points covered in this review.

- Seasonal influenza is not only responsible for morbidity and mortality; it also has an economic impact in terms of absenteeism from work and the use of health services.
- The first signs of decline in immune competence occur by age 50 and accelerate after age 65–70.
- Burden of influenza begins to increase at the age of 50, intensifying with age and in presence of underlying diseases.
- Influenza causes a considerable economic burden in subjects aged ≥50 years.
- Lost productivity due to influenza is particularly heavy in the 45–64 age-group.
- Vaccination against influenza remains the most effective method of preventing infection, hospitalization and mortality.
- Lowering the age recommendation for influenza vaccination to 50 years would allow a broader range of subjects to be reached.

stimuli, resulting in a progressive reduction of protection with advancing age.[96–98,102] Indeed, the WHO identifies the age of 50 years as the beginning of a significant increase in the prevalence of multi-morbidity in high-income countries.[43,44]

In Italy, influenza vaccination is mainly recommended for groups at high risk of complications, including subjects aged ≥65 years.[20] However, since 2012, the main scientific Italian associations of pediatricians, general practitioners and public health have supported the implementation of a national vaccination plan based on an age strategy instead of a risk strategy in adults aged 50–64.[21,122] Subjects of this age are also part of the workforce. The increase in clinical events, together with the prolongation of periods of absenteeism with age, suggests that this is the working-age group that bears the greatest economic burden.[45,67,80] Based on this body of evidence (Table 2), the proactive inclusion of healthy people aged 50 years and older in the influenza vaccination recommendation would promote healthy behaviors from an earlier age and favor better aging of the population. Lowering the age recommendation for influenza vaccination would allow a broader range of subjects to be reached, thereby reducing the economic and social burden of the disease in this pivotal age-group.

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Author contributions

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Disclosure statement

EM is founder and Chief Scientific Officer of VisMederi srl and VisMederi Research srl. CMT is an external consultant of VisMederi Research srl. E.F. and M.S. are full-time employees of Seqirus, a CSL company. The present study was, however, conceived and carried out during the PhD program at University of Siena by E.F. and M.S., and outside working hours at Seqirus. No product-specific information is presented in the present paper.

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