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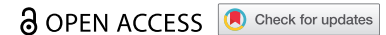
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REVIEW



# The influenza landscape and vaccination coverage in older adults during the SARS-Cov-2 pandemic: data from Several European Countries and Israel

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## ABSTRACT

**Introduction:** The Raise Awareness of Influenza Strategies in Europe (RAISE) group gathered information about the healthcare burden of influenza (hospitalizations, intensive care unit [ICU] admissions, and excess deaths), surveillance systems, and the vaccine coverage rate (VCR) in older adults in 18 European countries and Israel.

**Areas covered:** Published medical literature and official medical documentation on the influenza disease burden in the participating countries were reviewed from 2010/11 until the 2022/23 influenza seasons. Information on the framework for monitoring the disease burden and the provision for ensuring older adults had access to vaccination in their respective countries was provided. Data on influenza VCR in older adults were collected for the 2019/20 to 2022/23 influenza seasons. Data are reported descriptively.

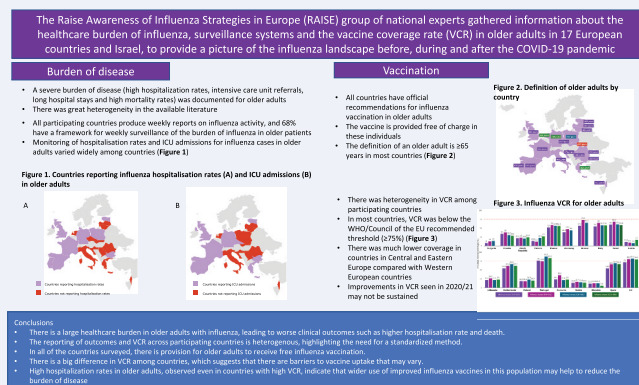
**Expert opinion:** Influenza presents a significant healthcare burden in older adults. Reporting outcomes across participating countries is heterogeneous, highlighting the need for standardized approaches. Although older adults receive free influenza vaccination, vaccine uptake is highly variable among countries. Moreover, hospitalization rates remain high even in countries reporting a high VCR. Increased awareness and education on the burden of disease and the broader use of improved influenza vaccines for older adults may help reduce the disease burden on this population.

## ARTICLE HISTORY


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## KEYWORDS

Influenza; burden of disease; older adults; vaccine coverage rate; influenza surveillance



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### Article highlights

- This survey highlights the heterogeneity in the available data and reporting methods for influenza disease burden among countries.
- Influenza is generally a vaccine-preventable disease, and all countries surveyed here have official recommendations for free vaccination for older adults.
- All countries surveyed have a defined framework for the monitoring and reporting of influenza activity and extreme outcomes.
- Despite this, in most of the countries the vaccine coverage rate (VCR) in older adults remains below the 75% threshold suggested by the World Health Organisation/Council of the European Union, with much lower rates reported in countries in Eastern and Central Europe than in those in Western Europe.
- Additionally, even countries with VCR above the WHO target (Portugal and UK) reported high hospitalization rates in older adults.

## 1. Introduction

While influenza and the common cold are both contagious viral respiratory tract illnesses [1], influenza can be a serious disease that could lead to severe complications and unfavorable outcomes due to broader consequences [2]. Some of these consequences include cardiovascular events, exacerbation of chronic underlying conditions, increased susceptibility to bacterial infections and functional decline, all of which may lead to an increased risk for hospitalization and death or profound disability in a substantial proportion of those affected [3]. Furthermore, influenza can trigger secondary bacterial infections [4], instigate a proinflammatory cytokine storm [5] and exacerbate preexisting chronic medical conditions [3], leading to severe complications, increased morbidity and mortality and increased use of antimicrobial agents, which is a key driver of antimicrobial resistance [6].

Before the COVID-19 pandemic, the World Health Organization (WHO) estimated that annual influenza epidemics resulted in about 3 to 5 million cases of severe illness and about 290,000 to 650,000 deaths globally; thus, influenza is a significant global public health burden [7]. Owing to the combination of COVID-associated lockdowns, national and international travel restrictions, and the use of other non-pharmacological mitigation measures [8], there was a drop in reported influenza cases during the COVID-19 pandemic. However, after one season without influenza activity, the 2021/22 season was defined in many countries by two waves of influenza of moderate influenza activity separated by more than 4 weeks, both of which were due to the H3 influenza subtype. This gave rise to one of the longest periods of influenza epidemic activity in the past 40 years – an unprecedented situation in the recent history of influenza. Following a decline in influenza activity during the subsequent warmer months, the number of influenza cases in Europe, according to the WHO, during the 2022/23 season reached epidemic levels by November 2022 [9], and the U.S.A. has seen the highest influenza hospitalization rates in a decade for the same season [10]. Furthermore, surveillance data for the 2022/23 season show that several countries in the Southern hemisphere are experiencing higher or earlier flu activity than before the COVID-19 pandemic. However, activity varies by country and

region [11]. In both Europe and the U.S.A., the 2022/23 influenza season has persisted for an unprecedented length of time, up to March 2023, thus being the second abnormal flu seasonal epidemic in the post-acute COVID-19 pandemic period [12,13]. As a whole, the COVID-19 pandemic has reset the landscape for many of the main respiratory viruses.

In the 28 European Union countries between 2002–2011 (excluding the 2009/10 H1N1 influenza pandemic) using a two-stage modeling approach, there were an estimated 27,600 (range 16,200–39,000) respiratory deaths associated with seasonal influenza each winter (88% in people aged  $\geq 65$  years). Furthermore, the rates of mortality in the  $\geq 65$  years group were approximately 65 times higher compared with younger patients [14].

Older patients are particularly at risk for infection, hospitalization and death due to influenza-related complications such as pneumonia [15] and they bear the highest burden of influenza-related mortality of any age group [16]. Recognition of these broader consequences of influenza virus infection is essential to determine the entire burden of influenza among different age groups, especially older adults, and to appreciate the value of preventive approaches such as vaccination.

High annual influenza vaccine coverage rates (VCRs) are considered crucial to reduce the disease burden, particularly in vulnerable populations such as the elderly. However, up to 2018 [17,18], great variation in VCRs across Europe were observed. Accordingly, the WHO/Council of the European Union set an influenza vaccination target of  $\geq 75\%$  in the elderly and other groups at high risk of serious illness, complications, and death [17].

The Raise Awareness of Influenza Strategies in Europe (RAISE) group of national experts in 18 European countries (Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Serbia, Slovakia, Spain and the United Kingdom) and Israel gathered data on influenza VCRs before, during and after the COVID-19 pandemic, to ascertain if the pandemic led to an increase in VCRs. The RAISE expert group also gathered data on the disease burden and mapped the influenza surveillance systems and vaccine implementation tools, recommendations and settings in the respective countries. To our knowledge, this is the first endeavor to collate locally available data on vaccine coverage, the infrastructure for influenza monitoring in the contributing countries and the burden of influenza, and make it available in the global domain.

## 2. Methods

The RAISE experts in each of the countries were asked to provide citable data on the framework for monitoring the burden of disease in each of the contributing countries. These data related to the influenza surveillance systems, official recommendations for influenza vaccinations in older adults, and the vaccination implementation framework, all of which were mapped for each country using official and publicly available sources. Data on influenza VCRs in older adults were collected from the respective official national sources for the 2019/20, 2020/21, 2021/22, and 2022/23 (where available) influenza seasons in the 19 countries.



**Figure 1.** Influenza vaccination coverage rates among older adults\* in Europe, by country and influenza season (where data are available).

\*Data are for  $\geq 65$ -year-olds as per national regulation in each country except Germany and Netherlands ( $\geq 60$  years), Slovakia ( $\geq 59$  years) and Poland ( $> 55$  years)

The dotted line indicates the WHO and Council of the European Union target of 75% coverage for older adults.

In addition, where available, the RAISE experts in each country were asked to provide evidence on severe influenza disease and its complications, including the incidence and severity in older adults, hospitalization and intensive care admissions and lengths of stays, hospitalizations due to respiratory and cardiovascular causes, and costs and economic burden. These data were collected from published medical literature and official medical documentation in the participating countries, starting from 2010/11 (after the H1N1 influenza pandemic in 2009/10), to provide a narrative overview of the influenza burden. The data were selected by the experts in each country.

All findings are reported descriptively.

### 3. Results

#### 3.1. Vaccine coverage rates (VCRs)

Updated influenza VCRs in older people in Europe were collected from the 2019/2020 season (before the COVID-19 pandemic) up to the 2022/23 season (where available). The VCR in older adults was heterogeneous, ranging from 5.6% (in Slovakia during the 2022/23 season) to 88.3% (in Portugal during the 2021/22 season) (Figure 1). Only two countries (Portugal and the UK) met the WHO/Council of the European Union target of  $\geq 75\%$  coverage for older adults [17], in the 2019/20, 2021/22 and 2022/23 seasons in Portugal and the 2020/21, 2021/22 and 2022/23 seasons in the UK [19].

Improvements in coverage were seen in fifteen (Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Italy, Israel, Lithuania, Netherlands, Romania, Serbia, Slovakia, Spain and UK)

of the nineteen countries in 2020/21 (the first year of the COVID-19 pandemic). However, a decrease in VCRs was observed in the 2021/22 season in eleven of these countries (Croatia, Czech Republic, France, Germany, Greece, Italy, Israel, Lithuania, Romania, Serbia, and Spain) (Figure 1). VCRs increased in the 2021/22 season in Bulgaria, Estonia, Netherlands, Poland, Portugal, Slovakia and the UK compared with the previous season. There was a clear trend for much lower VCRs in countries in Central and Eastern Europe (Bulgaria, Croatia, Czech Republic, Estonia, Latvia, Lithuania, Poland, Romania, Serbia, and Slovakia) compared with Western European countries (Figure 1). For those countries where the 2022/23 VCRs were available, all except Portugal and the UK were below the WHO target, and the trend persisted for countries in Eastern Europe to have lower VCRs compared with those in Western Europe (Figure 1 ; Table 1).

#### 3.2. The burden of disease in individual countries

Details of the source data on the disease burden for influenza-related complications (specifically GP visits, hospital and ICU admissions, and excess deaths) in each country are summarized in Table 2 and described in more detail in the Supplementary Material. Owing to the heterogeneity of the data collected across the countries surveyed, these data are presented as a narrative overview (Supplementary Material) to provide more context to the reader of the results presented in this manuscript. A brief overview of the findings is presented below and in Table 2.

While vaccination is protective, the burden of influenza in older adults is an unmet medical need, as evidenced by the results of the studies/reviews. The literature analyzing the

Table 1. Burden of disease monitoring framework.

	Framework for national surveillance for influenza cases in older adults				Official recommendations for influenza vaccination for older adults		Is the influenza vaccine free of charge to older adults in your country?		Fee paid to vaccinators for administering the vaccine to older adults		VCR in older adults*		
	Weekly reports on influenza activity		Hospitalisation rates		ICU admissions		Excess deaths (all causes)		Yes/No	Yes/No		Yes/No	Yes/No
	Yes [20]	Yes [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes [21]	Yes [21]		Yes	Yes
Bulgaria	Yes [22]	Yes [22]	No	No	No	Yes	Yes	Yes [21]	Yes [21]	Yes	Yes	€2	14.0% (2021/22) [20]
Croatia	Yes [27]	Yes [27]	No	No	No	Yes	Yes	Yes [23–26]	Yes [23–26]	No	No	Not applicable	28.6% [22]
Czech Republic	Yes [29]	Yes [29]	Yes	Yes	No	Yes	Yes	Yes [29]	Yes [29]	Yes [28]	Yes	€7	20.8% (2021/22)
Estonia	Yes [31]	Yes [31]	Yes	Yes	No	Yes	Yes	Yes [29]	Yes [29]	No	No	Not applicable	27.53% (65–79 years) [30]
France	Yes [42,43]	Yes [43]	Yes	Yes	Yes	Yes	Yes	Yes [33]	Yes [34]	Yes	Yes	€7.50–7.88 (nurses) [37–41]	56.2% (≥80 years) [30]
Germany	Yes [47]	Yes [47]	Yes	Yes	Yes	Yes	Yes	Yes [44]	Yes [45]	Yes [46]	Yes	€7.50–7.88 (pharmacists) [35,36]	44.0% (2022/23)
Greece	Yes [48]	Yes [48]	No	No	No	Yes	Yes	Yes	Yes	No	No	Not applicable	73.0% (2020/21)
Italy	Yes [51]	Yes [51]	Yes	Yes	Yes	Yes	Yes	Yes [49]	Yes [50]	Yes	Yes	Varies	58.1%
Israel	Yes [54]	Yes [54]	No	No	No	Yes	Yes	Yes [52]	Yes [53]	No	No	Not applicable	58.8%
Latvia	Yes [61]	Yes [61]	Yes	Yes	Yes	Yes	Yes	Yes [56]	Yes [56,57]	Yes [58]	Yes	€2.34	16.9%
Lithuania	Yes [65]	Yes [65]	Yes	Yes	Yes	Yes	Yes	Yes [63]	Yes [63]	Yes [63]	Yes	€11	23.0% [59,60]
Netherlands	Yes [69]	Yes [69]	Yes	Yes	Yes	Yes	Yes	Yes [65]	Yes [65]	Yes [67]	Yes	PLZ 21.83	74.1% (2020/21) [64]
Poland	Yes [70]	Yes [70]	Yes	Yes	Yes	Yes	Yes	Yes [71]	Yes [71]	No	No	Not applicable	15–23% [68]
Portugal	Yes [69]	Yes [69]	Yes	Yes	Yes	Yes	Yes	Yes [71]	Yes [71]	No	No	Not applicable	83.2% (2022/23) [72]

(Continued)



Table 1. (Continued).

	Framework for national surveillance for influenza cases in older adults			Official recommendations for influenza vaccination for older adults		Is the influenza vaccine free of charge to older adults in your country?		Fee paid to vaccinators for administering the vaccine to older adults		VCR in older adults* (2021/22)
	Weekly reports on influenza activity	Weekly	Hospitalisation rates	ICU admissions	Excess deaths (all causes)	Yes/No	Age definition	Yes/No	How much?	
Romania	Yes	No	No	No	Yes (integrated in annual influenza report)	Yes	>65 years	Yes	Not applicable	53.4% (2021/22)
Serbia	Yes	No (cases in older adults not reported publicly)	No	No	No	Yes [73]	≥65 years	No	Not applicable	14.21%
Slovakia	Yes [74]	No	No	No	No	Yes [74]	≥59 years	Yes	€5.60–6.32	5.6% [74]
Spain	Yes [75]	Yes	Yes	Yes	Yes	Yes [76]	≥65 years (national threshold, with region variation)	No	Not applicable	64.0% (2021/22)
United Kingdom	Yes [77,78]	Yes	Yes	Yes	Yes	Yes [79]	≥65 years	Yes [80]	£10.06	79.9% [82]

\*Data for 2022/23 season unless stated otherwise

burden of influenza in the elderly across wider regions of Europe generally reflect the clear trend observed in individual European country reports – a high burden (reflected by influenza-related complications [GP visits, hospital and ICU admissions and mortality]) coupled with high vaccination rates in countries in Western Europe compared with low rates in countries in Central and Eastern Europe [88,137,151], particularly in Poland [129–132,152–154].

This situation may have changed in the wake of the COVID-19 pandemic across Eastern Europe, as policies have been introduced to increase access to influenza vaccines in older adults in these regions as part of a cost-effective approach to reducing the burden of influenza [88,155]. However, based on the trends reported here, following the initial spike during the 2021/22 season coinciding with the COVID-19 pandemic, VCRs remain below the recommended level.

### 3.3. Burden of disease monitoring systems

To understand if significant differences in the countries would explain the high variability in VCRs, the influenza monitoring systems (influenza activity and case surveillance in older adults) and the vaccination implementation setting in each country were investigated (Table 1).

All countries have weekly reports on influenza activity (Table 1). Thirteen (68%) of the 19 countries have a weekly framework for national surveillance of influenza cases in older adults (Table 1). All countries produced an annual report at the end of each influenza season. The annual reports for nine countries included hospitalization rates in older adults, the annual reports for ten countries included ICU admissions for older adults, and the annual reports for 11 countries included all-cause excess deaths for older adults (Table 1).

Of interest, all countries have official recommendations in place for influenza vaccination in older adults. Thirteen of the countries surveyed defined older adults as being ≥65 years; in Estonia, Germany, Greece and Netherlands, the definition was ≥60 years; in Slovakia it was ≥59 years; and in Poland it was >55 years (Table 1). In all countries, the influenza vaccine was provided without charge to the vaccine for those designated as older adults at some point in the period investigated. In 12 of the 19 countries surveyed, there was a financial incentive for vaccinators to administer influenza vaccinations (Table 1).

## 4. Discussion

The results of the RAISE survey show that, although the overall influenza VCR slightly increased in most Western European countries after the first year of the COVID-19 pandemic, only two countries (Portugal and the UK) met the WHO/Council of the European Union target of ≥75% coverage in older adults. This is despite all countries having in place a defined framework for the monitoring and reporting of influenza activity and the delivery of universal vaccination for older adults. All the countries in the survey have weekly reports on influenza activity. However, these are not specific for influenza in older adults. Only thirteen of the 19 countries (Bulgaria, Croatia, Czech Republic, Estonia, Germany, Italy, Israel, Poland,



Table 2. Source data for burden of disease.

Country	SOURCE OF DATA	REPORTED BURDEN	REFERENCES
Bulgaria	No data available		
Croatia	Published literature available from open-access websites and databases, interviews with experts and individual hospital data	<ul style="list-style-type: none"> <li>Reported cases (including, deaths and deaths in ICU)</li> <li>GP visits/hospitalizations for circulatory diseases</li> <li>Hospitalizations for influenza in older adults</li> </ul>	[22,83–87]
Czech Republic	Published literature obtained from open-access websites and databases, and interviews with experts	<ul style="list-style-type: none"> <li>Reported cases in older adults (including deaths)</li> <li>Outpatient GP consultancy accounted for 35% of economic burden</li> <li>ICU admissions for severe influenza (including among older adults)</li> </ul>	[88,89]
Estonia	National databases only	<ul style="list-style-type: none"> <li>Reported cases, including older adults</li> <li>From 2012, the number of reported flu diagnoses among people <math>\geq 65</math> years increased owing to improved reporting, and 31.8% of all the diagnosed people in this age group needed hospitalization</li> <li>ICU admission and deaths decreased in older adults in 2019 (up to 2021)</li> <li>94.7% of all deaths due to influenza in 2018 were in people aged <math>\geq 65</math> years; however, the proportion dropped to 84.2% in 2019</li> </ul>	[90–94]
France	Published literature obtained from national databases (French Hospital Information Database [PMSIJ], the French Sentinels Network and the Assistance Publique-Hôpitaux de Paris [AP-HP]) and from individual hospital data.	<ul style="list-style-type: none"> <li>Between 2010/11 to 2017/18, the proportion of hospitalizations (influenza-associated respiratory), associated costs and excess mortality in older adults were 70%, 77% and <math>&gt;90\%</math> respectively</li> <li>Older adults had longer length of hospital stays, in-patient mortality and 3-month readmission rates (respiratory and cardiac) compared with younger patients</li> <li>Higher rates of excess hospitalization for pneumonia, influenza and respiratory causes in older adults from 2011/12 season</li> <li>However, lower cumulative incidence of influenza-like illness in older adults between 2014 and 2019, possibly due to previous exposure and greater vaccine coverage</li> <li>Older adults most affected in seasons where A(H2N2) was dominant</li> <li>In the 2016/17 season, patients aged <math>\geq 60</math> years accounted for 86% of the hospitalized days; in patients aged <math>\geq 80</math> years, the proportion of hospitalizations for severe influenza reached 48%, and the proportion of deaths was 10% (32% of deaths with ICU admission), with 54% of all deaths in this age group</li> <li>Age <math>&gt;65</math> years was an independent prognostic factor associated with 28-day mortality</li> </ul>	[95–99]
Germany	Published literature obtained from national databases/registries and insurance claims databases and directly from national databases.	<ul style="list-style-type: none"> <li>Older adults more likely to have at least one chronic condition over nine seasons (2010/11 to 2018/19)</li> <li>Incidence rate of influenza lowest in older adults, but this group had a higher probability of hospitalization and longer hospital stays due to influenza than younger age groups</li> </ul>	[100–106]
Greece	National Public Health Organisation and a sentinel network in primary healthcare.	<ul style="list-style-type: none"> <li>The majority of non-hospitalized, laboratory-confirmed deaths (2010/11 to 2017/18) were in unvaccinated patients aged <math>&gt;65</math> years</li> </ul>	[107]
Israel	Israeli Ministry of Health seasonal influenza summaries.	<ul style="list-style-type: none"> <li>Excess hospitalizations and hospitalization days were particularly high in very old patients (<math>\geq 85</math> years) as well as in the youngest patients</li> </ul>	[108–115]
Italy	Published literature and from the integrated findings of various surveillance systems of influenza-like illness.	<ul style="list-style-type: none"> <li>Seasonal influenza up to 2020 represented a significant burden in high-risk groups such as those aged <math>\geq 65</math> years</li> <li>This age group had significantly increased risk of influenza-related complications and six-times greater excess influenza-related deaths than the general population</li> <li>In the 2013/14 to 2016/17 seasons, death -rate peaks were especially prominent in older adults, and the majority of influenza related deaths were in older adults</li> <li>High incidence rates during 2016/17 to 2021/22 seasons in older adults and the majority of severe cases and deaths occurred in older adults (mean age 68 years)</li> </ul>	[116–123]
Latvia	Latvian Centre of Disease Prevention and Control	<ul style="list-style-type: none"> <li>Across the 2010/11 to 2019/20 seasons, the <math>\geq 65</math> year age group accounted for 23% of influenza or influenza plus pneumonia-related hospitalizations</li> </ul>	[124]

(Continued)



Table 2. (Continued).

Country	SOURCE OF DATA	REPORTED BURDEN	REFERENCES
Lithuania	Published literature and National Health Database	<ul style="list-style-type: none"> <li>• Age-specific seasonal influenza vaccine effectiveness over four influenza seasons (2014/15–2018/19) for in-patients aged <math>\geq 65</math> years suggested high vaccine effectiveness against influenza B in this elderly age group</li> <li>• The collection of aggregated data prevents age-specific reporting</li> </ul>	[125–127]
Netherlands	The State of Infectious Diseases in The Netherlands report	<ul style="list-style-type: none"> <li>• Influenza infection was negligible during COVID but a steep rise was observed following the end of the last lockdown period</li> <li>• Influenza led to a high burden of disability-adjusted life years – no age-specific data available</li> </ul>	[128]
Poland	Published reviews of the published literature, websites, databases, interviews with experts, and the Polish National Institute of Public Health	<ul style="list-style-type: none"> <li>• Between 2016/17 and 2019/20, more than half of deaths due to influenza occurred in those <math>\geq 65</math> years</li> <li>• Owing to the large older adult population, there was a high clinical (GP and hospital care) burden</li> <li>• Despite low influenza incidence rates (2011 and 2012) in the <math>\geq 65</math> year group, this group had the highest rate of influenza-related hospitalizations and a high fatality rate</li> <li>• Between 2016/17 and 2018/19, people aged <math>\geq 65</math> years comprised around 30% of confirmed cases</li> <li>• Between 2008/9 to 2017/19, 46% of influenza hospitalizations were in patients aged <math>\geq 65</math> years, increasing to 60% in 2017/18</li> <li>• 62% of those hospitalized with influenza and comorbidities were in this age group</li> <li>• Influenza-associated deaths were highest in the <math>\geq 65</math>-year and <math>\geq 75</math>-year groups</li> </ul>	[88,129–134]
Portugal	Data from the National Health Service	<ul style="list-style-type: none"> <li>• In the 2014/15 to 2018/19 seasons, the highest rates of incidence, hospitalization and presentation to the emergency department were in the age groups 0–4 years and <math>\geq 65</math> years, and the highest mortality rate was in the <math>\geq 65</math>-year age group</li> <li>• Estimated mean annual respiratory excess mortality rates were 6.6 per 100,000 in the 65–74-year age group and 17.9 in the <math>&gt;75</math>-year age group</li> </ul>	[135]
Romania	Published literature based on a health administrative database.	<ul style="list-style-type: none"> <li>• Influenza vaccine reported as protective in <math>\geq 65</math>-year-olds, with a significant difference in the all-cause mortality rates between vaccinated and unvaccinated participants in this age group (2017/18–2021/22 [with the exception of the 2020/21 season and during the 2018/19 season])</li> </ul>	[136]
Serbia	A published modelling study.	<ul style="list-style-type: none"> <li>• Rates of severe hospitalized confirmed influenza cases were highest in older adults (2009/10 to 2015/16), whereas the rates of mild confirmed influenza cases were lowest in this group – fatality rate was 18% in those <math>\geq 65</math> years</li> </ul>	[137]
Slovakia	A case–control study using the administrative data of one health insurance company.	<ul style="list-style-type: none"> <li>• During 2008/9 to 2017/18, nearly 70% of hospitalizations with a diagnosis of influenza were in patients aged <math>\geq 65</math> years and mean in-patient fatality increased with age</li> <li>• Patients <math>\geq 65</math> years accounted for 53% of the mean annual hospitalization costs and 76% of the mean annual cost of influenza-associated excess cardiac and respiratory hospitalizations</li> <li>• Influenza vaccination was effective in preventing hospitalizations in elderly individuals</li> </ul>	[138]
Spain	Published literature and based on the Spanish Influenza Sentinel Surveillance System and from a retrospective study and a case-control study	<ul style="list-style-type: none"> <li>• Rates of severe hospitalized confirmed influenza cases were highest in older adults (2009/10 to 2015/16), whereas the rates of mild confirmed influenza cases were lowest in this group – fatality rate was 18% in those <math>\geq 65</math> years</li> </ul>	[139–141]
United Kingdom	Annual surveillance of influenza and other respiratory viruses and from the published literature.	<ul style="list-style-type: none"> <li>• During 2008/9 to 2017/18, nearly 70% of hospitalizations with a diagnosis of influenza were in patients aged <math>\geq 65</math> years and mean in-patient fatality increased with age</li> <li>• Patients <math>\geq 65</math> years accounted for 53% of the mean annual hospitalization costs and 76% of the mean annual cost of influenza-associated excess cardiac and respiratory hospitalizations</li> <li>• Influenza vaccination was effective in preventing hospitalizations in elderly individuals</li> <li>• Between 2012/13 and 2020/21, high levels of excess mortality were reported, with increased outbreaks in care homes across most seasons but particularly in the 2014/15, 2016/17 and 2018/19 seasons, during which influenza A(H3N2) was the predominant circulating strain</li> <li>• The cumulative number of deaths in England associated with influenza was highest in those aged <math>\geq 65</math> years compared with the total for all age groups (2015/16 to 2019/20 seasons)</li> <li>• Over ten seasons (2010/11 to 2019/20), the burden of influenza (hospitalizations and GP consultations) was prominent in populations with underlying clinical conditions and in relation to age</li> </ul>	[19,142–150]

Portugal, Serbia, Slovakia, Spain, and the UK) have a weekly framework for national surveillance of influenza cases in older adults. Fourteen countries have a framework for the reporting of extreme outcomes (either hospitalizations, ICU admissions, all-cause mortality, or combinations thereof) during an influenza season.

Older adults are particularly vulnerable following influenza infection [156–160] and are at greater risk of serious complications from influenza than younger, healthy adults because their immune defenses are reduced with increasing age and comorbidities are common. Influenza can lead to primary viral or secondary bacterial pneumonia, serious cardiovascular events, such as myocardial infarction or stroke, and neurological complications in otherwise healthy older adults [2]. In addition, influenza can also aggravate underlying chronic illnesses, such as congestive heart failure, chronic obstructive pulmonary disease, asthma, and diabetes [161], many of which have interconnected pathologies and are recognized as conditions that can lead to profound disability. Overall, age-related factors, such as underlying conditions and frailty, in conjunction with influenza in the vulnerable older population contribute to increased hospitalizations, reduced autonomy [160] and increased mortality. Aging also leads to a decline in immune function (immunosenescence), which is associated with increased vulnerability to common infections and a decreased and more evanescent response to vaccination. Pertinently, as the proportion of elderly persons is growing, and because age and its associated immunosenescence, chronic diseases, and frailty are risk factors for severe influenza, the toll from influenza can only be expected to increase unless control measures are applied more vigorously [162–164].

As shown here, the significant burden of influenza infection in older adults is an unmet medical need, with high hospitalization and mortality rates, even in countries with high VCRs. In light of this, it may be postulated that a VCR target of  $\geq 75\%$  may be insufficient with currently available influenza vaccines, and a target of 90% VCR in older adults, as is the case in the U.S.A. [165], could be more appropriate. However, given the documented difficulties in increasing VCR, even in a favorable setting (i.e. the necessary recommendations and funding are in place), a focus on raising awareness and education on the burden of disease and broader usage of improved influenza vaccines for older adults could be considered as a complementary approach.

While the typical view of the burden of influenza considers the visible cases and outcomes (laboratory-confirmed cases seen by general practitioners, ICU or non-ICU hospitalizations, and deaths attributed to influenza), the true burden of influenza may be much larger and incorporate many ‘hidden’ elements (e.g. patients not seen by healthcare professionals or those seen by other healthcare services, hospitalizations and deaths triggered by influenza, complications triggered by influenza in at-risk patients, the disruption to the healthcare system and the increased use of antibiotics). In actuality, influenza represents a major disease burden: it had the highest burden among 31 infectious diseases from 2009–2013 and represented 30% of the disability-adjusted life year (DALY) burden of infectious disease in Europe when measured during this period [166]. Moreover, the effects of complicated

influenza are not confined to the respiratory system; it can involve other major organ systems with devastating complications, including heart attack and stroke [167–170]. Another important social factor to consider in this regard is the global expansion of the elderly population, particularly in high-income countries such as those in the European Union. These factors add greater urgency to the current landscape reported and discussed in this article.

Overall, influenza is a vaccine-preventable disease, and annual influenza vaccination is the most effective method for prevention [171–173]. Any protection conferred following vaccination should protect against influenza infection and the severe secondary complications of influenza that often require hospitalization and can result in death in older adults. All countries surveyed have in place official recommendations for the provision of free influenza vaccination to older adults or those with chronic conditions that place them at high risk of complications from influenza infection. However, for the most part, VCRs remain below the recommended threshold, with much lower rates reported in countries in Eastern Europe compared with those in Western Europe. Indeed, only two of the countries surveyed (Portugal and the UK) consistently exceeded the threshold VCR of  $\geq 75\%$  over the survey period, with both countries reporting VCRs in the region of 80% in the 2021/22 and 2022/23 seasons. The results for Portugal were in accord with the Vacinómetro® initiative (monitoring influenza vaccination rates amongst high-risk groups in Portugal), which showed an increased vaccination coverage rate in people aged  $\geq 65$  years, rising from 58.6% in 2008/09 to 76.0% in 2019/20, and meeting the WHO target for the elderly of  $\geq 75\%$  [174]. In fact, real-time monitoring of influenza activity during a season has been crucial for monitoring a dynamic picture of the number of cases of influenza. For example, the Gripómetro telematic survey validated in Spain [175], could anticipate deviations in flu vaccine coverage during the course of an influenza vaccination campaign, which could lead to the timely implementation of mitigating measures. Furthermore, the Research & Surveillance Centre of the Royal College of General Practitioners in England provides weekly information, and the UK National IT system in the participating general practitioners’ offices (1956 practices, representing one third of the population of England) enable regular VCR reports.

The COVID pandemic did not seem to have a detrimental effect on influenza vaccine uptake, as reported here, which is an unexpected finding in light of the problems with vaccine acceptance surrounding the COVID vaccination programs. Indeed, different concerns have been identified among adults with respect to the COVID-19 and influenza vaccines. For COVID-19, the major reasons cited were wanting more research done, worries about vaccine safety and effectiveness, and believing they are already well-protected through prior vaccination or infection [176]. Indeed, it is well documented that vaccine acceptance is a complex phenomenon [177], with more than 70 influencing factors identified, many of which are time-specific and context-specific [178]. These include, but are not limited to, mistrust of government and health authorities, concerns about vaccine safety and efficacy and, in some countries, age and minority race or ethnicity [179–181].

While analysis of this complex behavioral phenomena is beyond the scope of this manuscript, our findings do suggest that there are differences in vaccine uptake across the countries who provided data that was particularly evident between countries in Western and Eastern Europe: for Western European countries, these include fear of adverse events, a lack of trust among the general public and healthcare professionals regarding the effectiveness of the influenza vaccine, and denial of the risk of catching influenza; for Eastern European countries these include a lack of appreciation of the true burden of influenza, particularly with regard to risk and severity, and a lack of trust in the health authorities [178,182]. We hope that the results presented herein will act as a call for future investigation that focusses on the disparities across Europe as a means to address the differences and harmonize vaccine uptake across the region.

Another noteworthy finding from this survey was that some of the countries with the lowest VCRs in older adults had the broadest recommendations for influenza vaccination in at-risk populations (e.g. children, adolescents, pregnant women). Based on the low VCR results presented here, we call for further studies to investigate the reasons that drive low vaccine uptake, on a country-by-country basis, with the intention to identify the commonalities and differences in the reasons as an initial step to address them. Furthermore, acceptance of a common list of recommendations for influenza vaccination in Europe could enable better comparison of VCRs among these countries.

We acknowledge several limitations of this survey. Firstly, when reporting the country-specific burden, no account was made for differences in population sizes among the different countries included in the survey. As some of the countries were small and we could not determine the demographic distribution or whether influenza care was universally distributed across the whole country or was focused on large cities/regions, we have not accounted for such differences and have chosen to report a snapshot of the overall data as reported in the publications. Secondly, we fully acknowledge the criticisms that have been raised about studies reporting vaccine effectiveness data for all-cause mortality and the efforts made to implement study designs that differentiate vaccine effects from selection bias in elderly populations [183–191]. However, we again feel that further discussion of this topic is outside the scope of this manuscript. Finally, in a similar vein, we acknowledge that, even when VCR is high, there are many factors that could contribute to low vaccine effectiveness reported in older population, such as immunosenescence and during antigenic drift and egg adaption, which may be ameliorated through enhanced and non-egg-based vaccines. However, suggesting recommendations to improve vaccine effectiveness would be beyond the remit of this manuscript, the aim of which is to provide a snapshot of the current situation across the countries surveyed. Our results do, however, raise the question whether high VCRs alone are sufficient to fully tackle the burden of influenza or whether additional parallel measures should be adopted. For example, despite having consistently high vaccination coverage, NHS England mandated early vaccination for 2–3-year-olds and school-age children (reception to year 11, a super-spreader

population) and children in clinical risk groups, commencing from 1 September 2023 or as early as possible after the vaccine becomes available, with the vaccination program completed by 15 December. The aim of prioritizing this group early in the season was to reduce transmission and ensure minimal impact on routine immunizations in the new year [192]. We eagerly await the full report on the effect this intervention had on the influenza data for the 2023/24 season.

## 5. Conclusions

To our knowledge, this is the first endeavor to publish local data on vaccine coverage, the infrastructure for influenza monitoring in the contributing countries and the burden of influenza. The results of this analysis show there is an urgent need for a standardized, aligned, and consistent methodology for reporting influenza burden of disease and VCRs across Europe. As seen from the country-specific literature reported here, the VCRs remain below the WHO-recommended target in most of the countries surveyed, with a lower trend for uptake in countries in Eastern Europe compared with Western Europe. Data on increased hospitalization rates in the older population were available for Portugal and the UK, despite these being the only two countries consistently meeting the recommended VCR of  $\geq 75\%$ . These data show that the disease burden in older adults remains high. Factors contributing to this may include the loss of or reduced immunity during the COVID-19 lockdown periods, when the overall population were not exposed to influenza virus, and the use of non-pharmacological measures to limit disease transmission. This may indicate the need for complementary measures, such as increased awareness and education on the burden of disease, and broader usage of improved influenza vaccines for older adults. Unexpectedly, the COVID pandemic did not seem to have a detrimental effect on influenza vaccine uptake, and this finding could provide a unique insight for future studies on the behavioral basis of vaccine acceptance. Furthermore, owing to the great heterogeneity in the data and reporting methods among regions, recommendations for a standardized reporting framework may provide greater transparency and visibility on influenza severity and disease burden. These may also enable the impact of interventions, such as increased VCRs, improvements in the perception of the vaccines, and the introduction of improved vaccines for older adults, to be measured accurately.

## 6. Expert opinion

Periodic surveys, such as this one conducted by the RAISE expert group, provide an invaluable snapshot on the burden of influenza and the measures in place to tackle influenza across Europe. Pertinently, the results of this survey show that the burden of disease in older adults (influenza-associated GP visits, hospitalizations, ICU admissions and deaths), remains high, while VCR is below the WHO/Council of the European Union recommended threshold of  $\geq 75\%$  in all but two of the countries. There is a wide disparity in VCR between countries in Western Europe and in those in Central and Eastern Europe. Annual vaccination leading to an appropriate VCR in high-risk populations is considered a necessary

approach to reduce the disease burden. Such a strategy may also improve protection beyond influenza itself and address the 'hidden' burden of influenza in high-risk groups such as older adults. Recognition of the broader consequences of influenza virus infection is essential to determine the entire burden of influenza among different subpopulations, especially in older adults, and appreciate the true value of preventive approaches such as vaccination.

Notably, following the COVID-19 pandemic there seems to have been a modest increase in influenza VCR in the 2020/21 season; however, the situation in the subsequent seasons would suggest that levels are once again returning to pre-pandemic levels. This highlights the pressing need to capitalize on the 'COVID-19 effect' and to implement ways in which this can be maintained and improved upon, leading to a sustained change in attitudes to vaccination across the continent. Whether this requires the application of complementary measures, such as increased awareness and education on the burden of disease, wider use of improved influenza vaccines in older adults, targeting other populations that are affected by seasonal influenza and act as super-transmitters (e.g. children) or the application of a more stringent VCR threshold – as is the case in the U.S.A., where a 90% VCR threshold has been recommended – needs to be thoroughly investigated.

Although beyond the scope of this manuscript, there are several recognized barriers to flu vaccine uptake in older adults. Furthermore, the barriers to vaccine acceptance may vary between Western European countries (fear of side effects, a lack of trust among the general public and healthcare professionals regarding the effectiveness of the influenza vaccine, and denial of the risk of contracting influenza) and Eastern European countries (a lack of appreciation of the true burden of influenza, particularly with regard to risk and severity, and a lack of trust in the health authorities). Furthermore, additional educational interventions should be aimed toward healthcare workers because members of some countries pointed out the problem of vaccine acceptance among this group is inevitably reflected in the vaccine acceptance among the general population. This clearly demonstrates that a one-size-fits-all approach will not be sufficient to address the barriers to vaccine acceptance across Europe. Only by identifying and addressing the root causes of these and acknowledging that the causes may vary among regions, can country-by-country contingency plans be developed and instigated with the aim to identify the commonalities and differences in the reasons. Acknowledging this may be an initial step to bring all countries up to the recommended threshold for vaccine coverage.

Finally, owing to the great heterogeneity in the data and reporting methods among regions, developing a standardized reporting framework and standardized recommendations for influenza vaccination among the European countries may provide greater transparency and visibility on influenza severity and the burden of disease. These may also enable the impact of interventions, such as increased VCR, improvements in the perception of the vaccines and the introduction of improved vaccines for older adults, to be measured accurately.

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