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Public health impact of influenza vaccination in Italy: barriers, benefits and interventions in the field of prevention

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ABSTRACT

Influenza represents one of the infectious diseases with the major clinical and economic burden on health systems and society. Seasonal influenza vaccination (IV) is the most effective defense we have against this infection, despite IV coverage rate is still suboptimal. The main objective of this PhD thesis is to investigate the different benefits and determinant factors of IV, to support public health stakeholders and decision makers in the continuous development of best practices, behaviors and policies in the field of prevention. In order to investigate any potential for improvement in the flu prevention field, two ecological studies were conducted in the seasons 2010/11-2016/17 and 2017/18-2021/22, respectively, to analyze the pneumonia- and influenza (P&I)-related mortality in Italian individuals ≥65 years and to explore if a different IV distribution and administration velocity can affect the incidence of all-cause and respiratory-related hospitalization. Moreover, an economic and fiscal impact model of an influenza immunization programme among Italian healthcare workers (HCWs) has been implemented. In the first ecological study, we investigated spatiotemporal patterns of pneumonia- and influenza-related deaths in Italian adults ≥65 years over the course of 7 years. Fixed- and random-effects panel regression models have than explored possible associations between different factors that play a role in the flu immunization season and local pneumonia- and influenza-related mortality. The spatiotemporal analysis highlighted a North-South gradient whereas regression models correlated a reduction of 1.6–1.9% in P&I-related mortality to each 1% increase in IV coverage rate ($P < 0.001$). An additional decrease of 0.4% was observed for each 1% increase in the proportion of adjuvanted trivalent IV used. The second ecological study analyzed distributing and administering velocities of adjuvanted trivalent and quadrivalent IVs (aTIV and aQIV, respectively) in a primary care setting and its potential impact on Italian older adults hospitalization risk over 5 epidemic seasons. This study associated a minimization of the time lag between vaccine distribution and administration to a further mitigation of the flu burden. From an economical and fiscal point of view, an incremental 10% increase in IV coverage in Italian HCWs over a five-year period could reduce productivity losses by €4,475,497.16 and increase tax revenues by €327,158.84, promoting a value-based allocation of available healthcare resources. Furthermore, to investigate possible drivers of IV, changes in perception have been monitored through cross-sectional computer assisted web interviews (CAWIs) carried out 2-3 times per year. Each questionnaire involved from 1979 to 2513 adults,

representative of the Italian population. The longitudinal survey monitored a general increase in willingness to receive IV from May 2020 to May 2021, partly influenced by the COVID-19 pandemic situation, but even a hesitancy toward COVID-19 and influenza vaccine co-administration. Text/instant messages or email reminders, in particular if sent by the general practitioner, seem to be the most effective resources for increasing IV uptake through active invitation, with greater odds to be vaccinated in the last season in the population group that received a reminder compared to those who did not receive it (adjusted odds ratio (aOR) 6.47, 95% CI: 5.35-7.83). These studies support a higher annual IV coverage in Italy, based on appropriateness criteria and on the adoption of proactive measures and strategies to overcome the observed determinants of hesitancy.

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List of Abbreviations

ACIP= Advisory Committee on Immunization Practices

AIC= Akaike information criterion

AIOM= Italian association of medical oncology

aOR= adjusted odds ratio

aQIV= adjuvanted quadrivalent influenza vaccine

ARI= Acute Respiratory Infection

ATAGI= Australian Technical Advisory Group on Immunization

ATC= anatomical therapeutic chemical

aTIV= adjuvanted trivalent influenza vaccine

BCoDE = Burden of Communicable Diseases in Europe

CAWI = computer-assisted web interviewing

CD= cross-sectional dependence

CDC= Centers for Disease Control and Prevention

CI= confidence interval

DALY = disability-adjusted life year

DDD= defined daily dose

EC= European Commission

ECDC= European Centre for Disease Prevention and Control

EEA= European Economic Area

EHR= electronic healthcare record

ENCePP= European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EU= European Union

EXPH= Expert Panel on Effective Ways of Investing in Health

FCP= Free Choice Pediatrician

FE= fixed-effects

FFU= fluorescent focus units

GISRS= Global Influenza Surveillance and Response System

GP= general practitioner

HA (or H)= hemagglutinin

HAC= heteroscedasticity-autocorrelation

HCW= healthcare worker

HD= Health Department

HSD= health search database

ICD= International Classification of Diseases

ICD-9-CM= International Classification of Diseases, 9th revision, clinical modification

ILI= influenza-like illness

IQR= interquartile range

ISCED= International Standard Classification of Education

ISPRA= Italian National Institute for the Environmental Protection and Research

ISS= Superior Institute of Health

ISTAT= Italian National Institute of Statistics

IV= influenza vaccination (or influenza vaccine)

IVC= influenza vaccination coverage

JCVI= Joint Committee on Vaccination and Immunisation

KAP= knowledge, attitudes and practices

LHA= Local Health Authority

LHU= local health unit

LISA= local indicators of spatial association

MAH= marketing authorization holder

MDCK= Madin Darby Canine Kidney

MMR= measles, mumps and rubella

NA (or N)= neuraminidase

NHS= National Health Service

OECD= Organization for Economic Co-Operation and Development

OR= odds ratio

P&I= pneumonia- and influenza

PNPV= National Vaccination Plan

QALYs= quality-adjusted life-years

RCT= randomized controlled trial

RE= random-effects

ROI= return of investment

RWE= real-world evidence

SARI= severe acute respiratory infection

SD= standard deviation

SE= standard error

SES= socio-economic status

SIV= seasonal influenza vaccination

UK= United Kingdom

US= United States

VBHC= Value-Based Healthcare

VE= vaccine effectiveness

VIF= variance inflation factor

VPD= vaccine-preventable disease

WHO= World Health Organization

Chapter 1. Introduction

1.1 Influenza Virus

The first isolation of influenza viruses in humans dates back to 1933 in England (National Institute of Health, 2018a). Nonetheless, the first pandemic that obviously reported the features of influenza infection was in 1580 (Centers for Disease Control and Prevention (CDC), 2021a). Three other worldwide epidemics have been documented in the 20th century: in 1918, the "Spanish flu", attributed to A/H1N1 virus, which caused at least 50 million deaths globally; in 1957 the "Asian Flu", due to the newly emerged A/H2N2 virus, with approximately 1.1 million deaths worldwide; in 1968, with the emergence of the new A/H3N2 virus, which killed a total of 1 million people. Of note, in late 1930s and 1940s the first inactivated influenza vaccine has been developed and, then, administered to the population. More recently, in 2009, the A/H1N1pdm09 provoked a pandemic, related to about 100.000-400.000 deceased only in the first year of time, and, after that, remained the A/H1N1 predominant circulating virus, causing, occasionally, epidemics (Centers for Disease Control and Prevention (CDC), 2019a, 2019b, 2022a; National Institute of Health, 2015).

Influenza is a single-stranded, segmented, negative-sense RNA virus belonging to the Orthomyxoviridae family. Four species or genera, distinct by their core proteins, are known to infect mammals: A, B, C, D. Of these, only A, B and C types have been detected in humans, even if influenza virus C is sporadically reported, probably because of the mild symptoms it can generate or the subclinical course it can assume (Centers for Disease Control and Prevention (CDC), 2021a; Hutchinson, 2018). Whereas influenza B can be further divided into two lineages, namely B/Victoria and B/Yamagata, type A influenza can be classified in various subtypes according to the different combination of the surface antigens hemagglutinin (HA or H) and neuraminidase (NA or N). Actually, 18 different HA and 11 NA have been identified (Centers for Disease Control and Prevention (CDC), 2021a, 2021b; European Centre for Disease Prevention and Control (ECDC), 2022).

Influenza main way of transmission is the air transmission, spreading through droplets ($\geq$5 μm) or aerosols (droplet nuclei) (<5 μm) released by respiratory secretions of infected persons (Uyeki et al., 2022; World Health Organization (WHO), s.d.-a). The contagion may occur by person-to-person direct interaction or contact with contaminated surfaces or objects (i.e. fomites) (Killingley & Nguyen-Van-Tam, 2013). Seasonal influenza basic reproduction number is estimated to be of approximately 1.3, with a median incubation period of 1.4 and 0.6 respectively for type A or B (Uyeki et al., 2022). The duration of influenza infection may vary according to the characteristics, age and health status of the host and basing on severity of the illness. Anyway, the more the illness is severe, the more the shedding period will last (Uyeki et al., 2022). Typically, the contagiousness starts from one day before the onset of the flu symptoms and continues up to five to seven days, with a usual peak of infectivity 3-4 days after the onset of the disease. A particular attention should be posed to children and people with a weakened immune system, that may represent an exception and carry the infection for over than seven days (Centers for Disease Control and Prevention (CDC), 2021c; National Institute of Health, 2018b). Deeply immunocompromised individuals can even present a particularly prolonged infectious condition of months (Uyeki et al., 2022).

From a clinical presentation point of view of the illness, influenza virus infection may not always present with acute or severe symptoms. A systematic review and meta-analysis of 55 studies reported an overall pooled prevalence of asymptomatic cases of any type of influenza virus of 19.1%, ranging from a value of 5.2% to 35.5%, whereas 25.4% to 61.8% may be subclinical (Furuya-Kanamori et al., 2016). In case of asymptomatic illness, people may still be able to spread the infection (Centers for Disease Control and Prevention (CDC), 2021c; National Institute of Health, 2018b).

In case of symptomatic influenza, on the contrary, it may result as uncomplicated or severe (European Centre for Disease Prevention and Control (ECDC), 2022). Uncomplicated flu illness presents as quick onset of one or more:

-systemic symptoms: fever or feverishness, headache, muscle pain, general malaise/asthenia;

-respiratory symptoms: runny nose, pharyngodynia, non-productive cough.

The World Health Organization (WHO) provides a more stringent definition of influenza-like illness (ILI), defined as an acute respiratory disease with fever ≥38 °C and cough and an onset within the previous 10 days (Fitzner et al., 2018). If a hospital admission is required, the condition turns to the so-called severe acute respiratory infection (SARI).

In contrast, we talk about severe influenza if the flu disease progresses to pneumonia (more commonly) or, less often, to encephalitis, myocarditis or even to death (sporadically). The condition can be triggered by the influenza virus itself, but even by a bacteria secondary infection, favored by the influenza primary disease. Moreover, this situation may lead to the exacerbation of underlying diseases, deteriorating significantly the clinical picture of the patient (European Centre for Disease Prevention and Control (ECDC), 2022). Secondary bacterial pneumonia, indeed, is a frequent complication of influenza infection, particularly in elderly people and individuals with certain chronic diseases, resulting in a significant level of morbidity and mortality (World Health Organization (WHO), s.d.-d).

1.2 Burden of Influenza

Influenza is a widespread disease all over the world, ranging from an annual global attack rate of 5 - 10% in adults and 20 - 30% in children. Each year, it has been estimated that influenza infection may account for 290,000 - 650,000 deaths worldwide, imputable exclusively to respiratory illness (World Health Organization (WHO), s.d.-a, s.d.-d). However, the burden of flu can fluctuate substantially from year to year, basing on the features of circulating viruses, characteristics and timing of the flu season, influenza vaccination coverage and protection among the population (Centers for Disease Control and Prevention (CDC), 2022c). On this basis, the Centers for Disease Control and Prevention estimates that influenza causes 9 million - 41 million symptomatic diseases, 140,000 – 710,000 hospital admissions and 12,000 – 52,000 deaths every year in United Sates (US), representing a significative burden for public health (Centers for Disease Control and Prevention (CDC), 2022c).

Furthermore, in pre-COVID-19 pandemic phase, the Burden of Communicable Diseases in Europe (BCoDE) consortium estimated the impact of 31 selected infectious diseases in terms of disability-adjusted life years (DALYs). Influenza resulted the infectious disease with the heaviest burden on the European population, representing the 30% of its whole weight and positioning at the first place in the elderly and always in the top-3-

podium in the other age groups (Cassini et al., 2018). Indeed, about 4–50 million symptomatic cases, 15,000–70,000 deaths and 150,000 influenza-related hospitalizations are attributed to flu in Europe each year (Villani et al., 2022). In Italy, an average of 8,000 deaths is attributed to influenza and its complications every year and up to 8,7 million subjects per year can require a visit for influenza-like illness to the general practitioner or the pediatrician during the influenza season (EpiCentro, s.d.-b; National Institute of Health, s.d.; Rosano et al., 2019).

Thus, the considerable impact of influenza in everyday life is evident and affects the society and health system both in terms of illness, complications and costs.

The remarkable economic burden of flu derives from healthcare expenses and absenteeism at work and school, impairing the population even in the social dimension (Ruggeri et al., 2020; World Health Organization (WHO), s.d.-d).

Given the importance of correctly and productively allocate available healthcare system funds, reliable analysis able to allow and drive this decision are required to support policy-makers in a completely conscious evaluation and prioritization of their strategies.

Cost-effectiveness analysis are essential from a point of view of access and reimbursement, testing the value of different vaccination options, whereas a fiscal impact model can support in understanding how and where allocate efficiently government tax revenues to get an adequate return (Mauskopf et al., 2022).

The fiscal health model assumes that a higher productivity of the worker translates into an increased individual income, resulting in additional government tax revenues available to re-invest in healthcare services and workforce. If an illness decreases the individual productivity, all the system is negatively affected (Ruggeri et al., 2020).

Ruggeri et al. (Ruggeri et al., 2020) calculated the financial charge related to influenza in the Italian country, estimating that, considering a total of 2.1 million of infected individuals with an age between 30 and 65 years, influenza is able to cost about €1 billion yearly, of which €160 million in relations to the fiscal impact. This compared to pneumococcus and herpes zoster infections, that instead, considering a total of 90,000 and 6,400 people infected, accounted for an overall impact of €148,055,040 and €4,777,200 and a fiscal impact of €23,639,040 and €630,000, respectively. Thus, to face with the huge economic burden of influenza, the analysis underlines the value of the implementation of a robust flu vaccination program, since preventing about 200,000 influenza cases, it could be saved approximately €111 million in terms of productivity and approximately €18 million in terms of fiscal revenue (Ruggeri et al., 2020).

1.3 Influenza Vaccination

Vaccination is the most effective protection against flu. The flu vaccination campaign begins in early October, since at least 10-14 days are required to achieve an adequate development of post-vaccination immunity (European Centre for Disease Prevention and Control (ECDC), 2017; Italian Ministry of Health, 2023). The goal of the seasonal influenza vaccination campaign is to achieve a minimum influenza vaccination coverage (IVC) rate of 75% or an optimal IVC of 95%, with the purpose of: (i) decreasing the individual risk of disease, hospitalization and death; (ii) waning the risk of transmission to subjects at high risk of influenza-related complications or hospitalizations; (iii) abating social costs associated with morbidity and mortality (Italian Ministry of Health, 2023). This objective is particularly relevant in the categories at high-risk of influenza complications, specifically, according to the WHO, subjects ≤5 years or ≥65 years, pregnant women, individuals with chronic underlying conditions and healthcare personnel (World Health Organization (WHO), 2018).

After achieving a sufficient protective immunity before the influenza epidemic begins, the protection conferred by seasonal influenza immunization can be influenced by a number of determinants, shaping the final result. These factors can be broadly summarized as follow (*ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022; Centers for Disease Control and Prevention (CDC), 2022f; Fiore et al., 2009; Rajaram et al., 2020; Wu et al., 2019):

1) *Virus-related factors*: diverse circulating influenza virus types and subtypes and the different level of match between circulating strains and viruses included in the vaccine may result in different level of protection conferred by the vaccine (*ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022). During its normal circulation over time, the influenza virus can accumulate minor genetic mutations that can result in small changes in the surface antigens, namely hemagglutinin and neuraminidase, causing the so-called "antigenic drift". The

more the virus differs from the one contained in the flu vaccines, the harder will be for the vaccine-stimulated immune system to recognize and defend the subject against that pathogen (Centers for Disease Control and Prevention (CDC), 2022f);

2) *Manufacturing process*: most licensed flu vaccines are produced through egg-based manufacturing processes. However, the avian and human sialic acid on the host cell surface (i.e. the influenza viruses binding receptor) differ in their structure. This can lead to a form of drift and potential antigenic mismatch caused by the selective pressure that emerges during strain propagation in eggs, related to the final selection of variants containing mutations that favor a better growth on eggs (Rajaram et al., 2020; Wu et al., 2019);

3) *Host-related factors*: immune aging (the physiological decline of the immune system which takes place with the age) and age of the subject, previous immunization against influenza, comorbidities and polytherapies may affect the response to vaccination (Abedin et al., 2005; *ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022; Haq & McElhaney, 2014);

4) *Specificity of the outcome*: the greater is the specificity of the outcome, the larger is the expected effect size observed (Fiore et al., 2009).

On the basis of the yearly variation of these factors and of the analyzed vaccine type, vaccine effectiveness (VE) can vary from suboptimal values to protection above 90%, although it typically ranges from approximately 30% to 70% (Belongia et al., 2016). Moreover, the progressive and continuous antigenic variation in influenza viruses dictates the way of production of influenza vaccines, driving to the yearly update of candidate vaccine strains. To allow a better correspondence between circulating strains and virus included in the vaccine, the global circulation of influenza viruses is monitored through the Global Influenza Surveillance and Response System (GISRS), while WHO Collaborating Centres carry out the genetic and antigenic profiling. This procedure guides the WHO biannual recommendations on the flu vaccines composition for the Northern and Southern hemisphere, which take place, respectively, on February and September (World Health Organization (WHO), 2023).

Therefore, the strong seasonality of the influenza viruses, the chosen outcome, the used productive process and the factors related to the host imply the need of a continuous surveillance of the virus circulation and vaccine benefit over multiple seasons and in different populations to get an adequate assessment of the impact of all the diverse types of immunization against flu. The currently available seasonal flu vaccines can be differentiated according to the presence of certain features (Grohskopf et al., 2023; Italian Ministry of Health, 2023; National Institute of Health, 2021; Nuwarda et al., 2021; World Health Organization (WHO), 2018):

- Formulation: trivalent (containing A/H1N1, A/H3N2 and B/Victoria or B/Yamagata strains) or quadrivalent (containing A/H1N1, A/H3N2, B/Victoria and B/Yamagata strains);
- Method of preparation: live attenuated, inactivated or recombinant;
- Level of purification: whole virus, split or subunit vaccines. In split vaccines, the virus is inactivated and chemically disrupted through treatment with a detergent. In subunit vaccines, the hemagglutinin and neuraminidase antigens are further purified removing all the other viral components;
- Platform of production: egg-based or cell-based;
- Presence of adjuvants: adjuvanted or non-adjuvanted;
- Quantity of antigen: standard dosage or higher dosage;
- Way of administration: intranasal or intramuscular.

According to available data and diverse properties, different influenza vaccines may also be approved in distinct age groups. On this basis, six different seasonal influenza vaccines typologies are available in the Italian recommendations for the prevention and control of influenza in Italy in the 2023/2024 season (Italian Ministry of Health, 2023), as listed extensively in **Table 1.1**.

Table 1.1. Available seasonal influenza vaccines in Italy for the 2023/2024 season (Centers for Disease Control and Prevention (CDC), 2023b; European Medicines Agency (EMA), 2018a, 2018b; Italian Ministry of Health, 2023).

Vaccine	Indication	Administration	Contained Surface Antigen	Antigen Quantity (Per Strain)	Adjuvant	Platform
Subunit or split quadrivalent inactivated influenza vaccines	≥ 6 months	Intramuscular	HA, NA	15 micrograms	-	Egg
Cell-culture quadrivalent inactivated influenza vaccine	≥ 2 years	Intramuscular	HA, NA	15 micrograms	-	MDCK cell-culture
Live attenuated quadrivalent influenza vaccine	2-18 years	Intranasal (spray)	HA, NA	$10^{7,0\pm0,5}$ FFU	-	Egg
Recombinant quadrivalent influenza vaccine	≥ 18 years	Intramuscular	HA	45 micrograms	-	DNA recombinant, prepared in insect cell culture
MF59-adjuvanted quadrivalent influenza vaccine	≥ 65 years	Intramuscular	HA, NA	15 micrograms	MF59	Egg
High-dose quadrivalent influenza vaccine	≥ 60 years	Intramuscular	HA, NA	60 micrograms	-	Egg

FFU= fluorescent focus units; HA=hemagglutinin; MDCK= Madin Darby Canine Kidney; NA= neuraminidase.

Among them, the high-dose seasonal quadrivalent influenza vaccine and the MF59-adjuvanted seasonal quadrivalent influenza vaccine are specifically recommended in the Italian population ≥65 years for the 2023/24 influenza season (Italian Ministry of Health, 2023), since overall currently available evidence favors the benefit of each enhanced vaccine (higher dose or adjuvanted influenza vaccines) over standard-dose, unadjuvanted vaccines in the elderly population, with no one prevailing above the others (*ACIP*

February 23-24, 2022 Presentation Slides | Immunization Practices | CDC, 2022; Grohskopf, 2022; Grohskopf et al., 2023).

Despite the clear indications and objectives of the Italian Ministry of Health for the flu control and prevention, influenza immunization rates are still systematically below the minimum required threshold in Italy (Italian Ministry of Health, 2022a). For this reason, it would be advisable to routinely offer influenza vaccination during all healthcare encounters and hospital admissions, at any time during the flu season, avoiding missed vaccination opportunities and proactively caring for patient's health (Nypaver et al., 2021).

1.4 Vaccine Hesitancy

Roots of vaccine hesitancy are as old as Jenner's smallpox vaccine, although it was able to eradicate an atrocious disease (Plotkin & Mortimer, 2018). Vaccine hesitancy is defined as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" (MacDonald & SAGE Working Group on Vaccine Hesitancy, 2015). The delay is consequently a factor associated by definition to hesitancy and an increased risk of loss of candidates for vaccination. In an ideal situation, in the flu field, all the population should be vaccinated within the end of October, before influenza viruses begin to spread in the community (Centers for Disease Control and Prevention (CDC), 2022g). To achieve this purpose, an active offer of influenza vaccination is warmly advised from the beginning of the influenza season campaign, to avoid missed opportunities of vaccination, particularly in at risk subjects (Advisory Committee on Immunization Practices et al., 2006).

Immunization is, indeed, regarded as one of the greatest public health achievements of the 20th century, playing a central role in the fight against infectious diseases and their elimination (European Commission, 2020). Having safe and effective vaccines is not enough, without a successful vaccination program: high vaccine coverage levels are required to minimize the spread of the infection. Vaccine availability and delivery are essential to achieve high rates of immunization, as well as a population's willingness to receive a vaccine (European Commission, 2020). Consequently, the monitoring of the change in citizens' perception becomes a priority to better understand the psychological, environmental and social dimensions of vaccine acceptance, build good measures that can identify and track vaccine hesitation patterns in populations over time and test interventions in a systematic way, using robust and reliable outcome measures (European Centre for Disease Prevention and Control (ECDC), 2016; European Commission, 2020; Leask et al., 2014).

1.5 Rationale and Objective of the PhD program

Partnerships among stakeholders are essential to gain awareness of unmet needs, favor cooperations, support economically entities and countries, offer common points of contact or platforms where stakeholders can collaborate (World Health Organization (WHO), s.d.-f). The different involved stakeholders include both the public field and private businesses, nongovernmental or governmental organizations, academic institutions and foundations (World Health Organization (WHO), s.d.-f). The positive combination of the relative strengths of these diverse parties allows the development of objectives, the achievement of benefits and represents an added value for public health.

For this reason, the main purpose of this project is to investigate the different benefits and determinant factors of influenza vaccination, to support public health stakeholders and decision makers in the continuous improvement of best practices, behaviors and policies in the field of prevention.

Chapter 2. Changes in Attitudes and Beliefs Concerning Vaccination and Influenza Vaccines between the First and Second COVID-19 Pandemic Waves: A Longitudinal Study

Declarations

This chapter is a slightly modified version of the manuscript entitled "Changes in Attitudes and Beliefs Concerning Vaccination and Influenza Vaccines between the First and Second COVID-19 Pandemic Waves: A Longitudinal Study" by Alexander Domnich, Riccardo Grassi, Elettra Fallani, Alida Spurio, Bianca Bruzzone, Donatella Panatto, Barbara Marozzi, Maura Cambiaggi, Alessandro Vasco, Andrea Orsi and Giancarlo Icardi (© 2021 by the authors) published in Vaccines (Domnich et al., 2021). The article is published in open access modality and distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), which permits any use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

2.1. Introduction

Annual vaccination is a key public health intervention to reduce the socioeconomic burden of seasonal influenza. The World Health Organization (WHO) recommends (World Health Organization (WHO), 2012) influenza vaccination (IV) for pregnant women, the elderly, children aged 6 months to 5 years, subjects with specific chronic conditions, and healthcare workers (HCWs). Despite these recommendations (World Health Organization (WHO), 2012) and the well-known public health benefits (D'Angiolella et al., 2018; de Waure et al., 2012), IV coverage rates are suboptimal in most at-risk groups and jurisdictions (European Centre for Disease Prevention and Control (ECDC), 2018; Organization for Economic Co-Operation and Development (OECD), s.d.). Italy was the first European country where SARS-CoV-2 spread significantly, with the so-called "first pandemic wave" starting in March 2020 (Bosa et al., 2022). Owing to fears of the possible co-circulation of SARS-CoV-2 and influenza viruses, which share several clinical signs and symptoms, some changes were made to

Italian IV policy. Specifically, it was recommended that the start of the 2020/21 IV campaign should be brought forward to early October, and the free-of-charge vaccination offer was broadened to children aged 6 months to 6 years and older adults aged 60–64 years (Italian Ministry of Health, 2020). Some regions introduced compulsory IV for healthcare workers and/or the elderly (especially if institutionalized) (Region of Calabria, 2020; Region of Lazio, 2020; Region of Sicily, 2020). The first available estimates of 2020/21 IV coverage rates suggest a significant increase in IV uptake among Italian HCWs (Di Pumpo et al., 2021), the general population, and the elderly (Italian Ministry of Health, s.d.-b). In May 2020, we conducted a representative cross-sectional survey on attitudes and beliefs concerning seasonal IV (Domnich, Cambiaggi, et al., 2020). Briefly, we found that most Italian adults judged IV positively, and that the main determinants of reluctance to receive the 2020/21 seasonal IV were younger age, lower perceived income, and no IV in the previous season. Moreover, about 20% of interviewees declared that, if no COVID-19 pandemic occurred, they would not receive the 2020/21 seasonal IV (Domnich, Cambiaggi, et al., 2020). Since that time, several changes have occurred in the epidemiology of both influenza and SARS-CoV-2 infections and associated public health policies. First, the 2020/21 season in Europe saw a 99.8% reduction in influenza virus detections, with only 33 (of 25,606 specimens tested) positive samples reported by sentinel surveillance systems (Adlhoch et al., 2021). In Italy, no influenza virus detections were officially reported (National Institute of Health, s.d.). Second, since December 2020, alpha, beta, gamma, and delta variants of SARS-CoV-2 have been described (World Health Organization (WHO), s.d.-e); these spread rapidly, owing to their greater transmissibility, becoming dominant in several countries (Abdool Karim & de Oliveira, 2021; Campbell et al., 2021). Third, in December 2020, the first COVID-19 vaccines were granted conditional approval and a massive immunization campaign began (Cavaleri et al., 2021). These changes prompted us to transform an initial cross-sectional sample into a longitudinal panel in order to monitor public opinion towards (influenza) vaccination at different stages of the ongoing COVID-19 pandemic. In this paper, we describe changes in knowledge, attitudes, and beliefs regarding (influenza) vaccines between the first and second COVID-19 pandemic waves.

2.2. Materials and Methods

2.2.1. Study Design

The study population was composed of 2543 adults aged ≥18 years who participated in a cross-sectional online survey on 18–24 May 2020 with the aim of evaluating their beliefs, attitudes, and practices concerning (influenza) vaccination (Domnich, Cambiaggi, et al., 2020). On 19–27 May 2021 (i.e., exactly one year after the first survey), participants were invited to take part in the second round of a computer-assisted web interview (CAWI). The sample was representative of the Italian adult population from the point of view of principal socioeconomic characteristics, and was drawn from a pool of over 60,000 well-characterized individuals sampled by means of a two-stage probabilistic quota method. The sampling procedure is described elsewhere (Domnich, Cambiaggi, et al., 2020).

2.2.2. Questionnaire

In the present study, we slightly modified the original 2020 survey (Domnich, Cambiaggi, et al., 2020) by adding some novel items/response options that were judged essential in order to capture the above-described epidemiological and policy changes. However, most items were identical. Briefly, the first part recorded the participants' principal socioeconomic characteristics: sex, age, macro-area of residence (North-East, North-West, Center, South and Islands), educational level, perceived income, and self-reported health status (excellent, very good, good, fair, and poor). The highest educational attainment reported was then converted to international standard classification of education (ISCED) levels, where level 1 corresponds to primary education (Italian National Institute of Statistics (ISTAT), 2003). The main variable of interest was willingness to receive the 2021/22 IV. Previous (seasons 2019/20 and 2020/21) IV uptake was also recorded in both surveys. Knowledge, attitudes, and beliefs concerning (influenza) vaccination were assessed through nine items rated on an anchored 4-point Likert-type response scale. Trust in different sources of information on IV (friends, traditional media, social networks, physicians, pharmacists, and public health institutions) was measured on a 1–10 scale, where 1 indicated the lowest level of trust. Those interviewees who were unlikely to receive the next seasonal IV were asked to indicate the main reasons for their decision. Finally, participants were asked whether they had received/arranged/planned to receive any available COVID-19 vaccine and whether they would be willing to receive both influenza and COVID-19 vaccines at the same time or a combined influenza/COVID-19 vaccine. The survey items are reported in **Table 2.1**.

Table 2.1. Survey Instrument.

Item	**2020 survey**	**2021 survey**
Did you have a flu shot in the last season? - I have never had a flu shot; - I had a flu shot in the past, but not in the last season; - I had a flu shot in the last season for the first time; - I had a flu shot both in the last season and sometimes in the past.	Yes	Yes
To what extent do you agree or disagree with the following statement? Vaccines are a fraud designed to profit the pharmaceutical companies. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? Vaccines are crucial to guaranteeing public health and should be mandatory. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? All vaccines are safe. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	No	Yes
To what extent do you agree or disagree with the following statement? I need more information on vaccines. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? Influenza vaccination is a human right and must be guaranteed for people that would like to have it. - Strongly agree; - More agree than disagree;	Yes	Yes

- More disagree than agree; - Strongly disagree.		
To what extent do you agree or disagree with the following statement? It is unacceptable that there are no influenza vaccines in the future season for people that would like to be vaccinated. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? If there were no a free-of-charge influenza vaccine, I would pay for it out of my own pocket. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? There are different influenza vaccine types. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
To what extent do you agree or disagree with the following statement? I would be more willing to get a flu shot if it were personalized. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.	Yes	Yes
Regarding influenza vaccination, on a scale from 1 (not at all) to 10 (completely) how much do you trust information from each of the following sources? - Friends and acquaintances; - My physician; - My pharmacist; - Public health institutions; - TV/newspapers; - Social networks.	Yes	Yes
Do you intend to have a flu shot in the upcoming season? - Yes definitely; - Probably yes; - I don't know; - Probably not; - Definitely not.	Yes	Yes

What are the main reasons why you would not get a flu shot? Select up to 2 of the following: - Influenza vaccines do not work; - I had a flu shot but got a fever/cold anyway; - I'm afraid of needles; - Influenza vaccines are designed only to profit the pharmaceutical companies; - My doctor advised against it; - Flu has diminished drastically since the COVID-19 pandemic began, so I don't think it is necessary any more;[a] - Other.	Yes	Yes
If there were an influenza vaccine shortage during the next season, whose fault it would be? Select up to 2 of the following: - Ministry of Health; - Pharmaceutical companies; - Regional authorities; - Local health units; - Pharmacies; - Wholesalers;[a] - Other.	Yes	Yes
Have you been vaccinated against COVID-19? - Yes; - Not yet, but I have already booked my shot; - Not yet, but I will get a shot as soon as possible; - No, and I don't intend to get a shot in the future.	No	Yes
If it were possible, would you have both the COVID-19 and flu shots at the same time? - Totally agree; - Agree; - Disagree; - Totally disagree.	No	Yes
What do you think of the idea of having a combined COVID–Flu vaccine? - Strongly agree; - More agree than disagree; - Neither agree nor disagree; - More disagree than agree; - Strongly disagree.	No	Yes

2.2.3. Statistical Analysis

Continuous and categorical variables were expressed as means with standard deviations (SDs) and percentages with 95% confidence intervals (CIs), respectively. Paired t and

McNemar's tests were used to compare repeated-measures continuous and dichotomous variables, respectively. The corresponding effect sizes were expressed as Cohen's d and odds ratios (ORs), respectively. Multivariable logistic regression analysis was performed in order to discern statistically significant associations between participants' willingness to receive the 2021/22 seasonal IV and the above-described socioeconomic, vaccine-related, and attitudinal variables. The final model was selected by minimizing the Akaike information criterion (AIC). The independent variable "age" was treated as a continuous variable, since the different age categorization rules applied were associated in a substantially collinear manner with the variable "Employment pattern". Possible multicollinearity issues in the final model were formally checked by quantifying the variance inflation factor (VIF) (Vatcheva et al., 2016). The explained variance was quantified by means of Nagelkerke's pseudo-R2. Statistical associations with a two-tailed $\alpha < 0.05$ were deemed significant. Data analysis was performed by means of R stats packages, version 4.0.3 (R Core Team, s.d.).

2.3. Results

2.3.1. Characteristics of the Study Panel

All 2543 individuals who participated in the first survey (2020) were invited to take part in this study. A total of 1981 agreed to do so (retention rate of 77.9%). At the time of the second survey (2021), two subjects (0.1%) no longer resided in Italy and were excluded from the analysis. Therefore, a total of 1979 paired 2020–2021 responses were analyzed. The mean age of participants was 48.3 (SD 15.1) years and males slightly prevailed (54.9%). **Table 2.2** reports the principal socioeconomic and health-related characteristics of the study participants.

Table 2.2. Socioeconomic characteristics of the study population (N = 1979).

Variable	**Level**	**% (N)**	**95% CI**
Sex	Male	54.9 (1086)	52.6–57.1
	Female	45.1 (893)	42.9–47.3
Age-group, years	18–24	5.7 (113)	4.7–6.8
	24–34	16.2 (321)	14.6–17.9
	35–44	18.9 (374)	17.2–20.7
	45–54	23.7 (469)	21.8–25.6
	55–64	18.9 (375)	17.2–20.7
	65–74	12.6 (249)	11.2–14.1
	≥75	3.9 (78)	3.1–4.9
Geographic area	North-East	19.0 (376)	17.3–20.8
	North-West	28.0 (555)	26.1–30.1
	Center	21.2 (419)	19.4–23.0
	South	21.9 (434)	20.1–23.8
	Islands	9.9 (195)	8.6–11.3
ISCED educational level	1	0.7 (14)	0.4–1.2
	2	7.8 (154)	6.6–9.1
	3–4	48.0 (949)	45.7–50.2
	5	41.5 (821)	39.3–43.7
	6	2.1 (41)	1.5–2.8
Employment pattern	Employed	63.7 (1261)	61.6–65.8
	Student	6.2 (122)	5.1–7.3
	Housekeeper	6.1 (121)	5.1–7.3
	Unemployed	5.8 (114)	4.8–6.9
	Retired	16.1 (319)	14.5–17.8
	Other/prefer not to reply	2.1 (42)	1.5–2.9
Perceived income	Low	2.0 (39)	1.4–2.7
	Lower than average	7.6 (150)	6.5–8.8
	Average	32.3 (639)	30.2-34.4
	Higher than average	42.7 (846)	40.6–45.0
	High	2.0 (40)	1.5–2.7
	No personal income	13.4 (265)	11.9–15.0
Self-reported health status	Excellent	9.1 (181)	7.9–10.5
	Very good	45.5 (901)	43.3–47.8
	Good	42.0 (832)	39.9–44.3
	Fair	3.0 (59)	2.3–3.8
	Poor	0.3 (6)	0.1–0.7
Influenza vaccination in 2019/20 season	Yes	26.5 (524)	24.5–28.5
	No	73.5 (1455)	71.5–75.5

ISCED: international standard classification of education.

A total of 805 subjects (40.7%, 95% CI: 38.5–42.9%) had received at least one dose of a COVID-19 vaccine, while 357 (18.0%, 95% CI: 16.4–19.8%) stated that they had already booked their vaccination, and 584 (29.5%, 95% CI: 27.5–31.6%) claimed that they would do so as soon as possible. The remaining 233 subjects (11.8%, 95% CI: 10.4–13.3%) declared that they did not intend to be vaccinated against COVID-19.

2.3.2. One-Year Change in Knowledge, Attitudes and Beliefs concerning Vaccination and Influenza Vaccines

As in the 2020 survey, most participants judged (influenza) vaccination positively. However, there was a significant increase in trust in vaccinations in general. For instance, more people (77.3% vs 75.0%) agreed that vaccines were crucial to public health and should be mandatory. Similarly, significantly fewer participants (18.3% vs 25.6%) believed that vaccines were a "*fraud created only to enrich pharmaceutical companies*". In 2021, more participants than in 2020 (82.6% vs 78.9%) stated that they would like to have more information on vaccination. Regarding IVs, more people were aware of the different types available (59.7% vs 51.8%) and their willingness to receive a more personalized IV increased (from 68.8% to 72.3%). Other attitudes towards IV did not change significantly (**Table 2.3**).

Table 2.3. Responses on knowledge, beliefs and practices regarding (influenza) vaccination, by survey (N=1,979).

Item	% (95% CI)				P
	Agreed[a] in both 2020 and 2021	Agreed[a] in 2021, but disagreed[b] in 2020	Agreed[a] in 2020, but disagreed[b] in 2021	Disagreed[b] in both 2020 and 2021	
Vaccines are crucial to guaranteeing public health and should be mandatory	64.9 (62.8–67.0)	12.3 (10.9–13.9)	10.1 (8.8–11.5)	12.7 (11.2–14.2)	0.037
I need more information on vaccines	69.1 (67.0–71.1)	13.5 (12.1–15.1)	9.8 (8.5–11.2)	7.6 (6.5–8.8)	0.001
Vaccines are a fraud designed to profit the pharmaceutical companies	12.0 (10.6–13.5)	6.3 (5.3–7.5)	13.5 (12.1–15.1)	68.1 (66.0–70.2)	<0.001
Influenza vaccination is a human right and must be guaranteed for people that would like to be vaccinated	82.5 (80.8–84.2)	7.5 (6.4–8.7)	7.1 (6.0–8.3)	2.9 (2.2–3.7)	0.72
It is unacceptable that there are no influenza vaccines in the coming season for people that would like to be vaccinated	77.7 (75.8–79.5)	9.5 (8.2–10.9)	8.4 (7.3–9.8)	4.4 (3.5–5.4)	0.29
If there were no free-of-charge influenza vaccine, I would pay for it out of my own pocket	38.2 (36.0–40.3)	15.4 (13.8–17.1)	14.4 (12.8–16.0)	32.1 (30.0–34.2)	0.41
There are different types of influenza vaccine	37.0 (34.9–39.2)	22.7 (20.9–24.7)	14.8 (13.3–16.4)	25.5 (23.6–27.4)	<0.001
I would be more willing to get a flu shot if it were personalized	56.5 (54.3–58.7)	15.8 (14.2–17.4)	12.2 (10.8–13.8)	15.5 (13.9–17.1)	0.003

[a] Comprise response options “Strongly agree” and “More agree than disagree”; [b]Comprise response options “Strongly disagree” and “More disagree than agree”.

The newly introduced item "*All vaccines are safe*" produced the following output: 21.8% (95% CI: 20.0–23.7%), 46.6% (95% CI: 44.4–48.8%), 21.7% (95% CI: 19.9–23.6%) and 9.9% (95% CI: 8.6–11.3%) strongly agreed, more agreed than disagreed, more disagreed than agreed and strongly disagreed, respectively.

In line with the previous survey, physicians, public health institutions and pharmacists were believed to be the most trustworthy sources of information on IV. Generally, all information sources (except for friends) had higher average rankings in 2021. However, the effect size was small (d < 0.4). The largest increase in trust was seen with regard to traditional media and pharmacists (**Table 2.4**).

Table 2.4. One-year change in perceived credibility of different sources of information on influenza vaccination, by survey (N=1,979).

Information source	**Mean (SD)**		**P**	**Effect size, d**
	2020 survey	**2021 survey**		
My physician	7.4 (2.2)	7.9 (2.0)	<0.001	0.23
Public health institutions	6.8 (2.4)	7.3 (2.2)	<0.001	0.22
My pharmacist	6.3 (2.3)	7.0 (2.1)	<0.001	0.32
Newspapers/TV	4.6 (2.2)	5.5 (2.2)	<0.001	0.37
Friends	4.4 (2.3)	4.5 (2.3)	0.054	0.04
Social media	3.2 (2.3)	3.7 (2.4)	<0.001	0.22

2.3.3. Influenza Vaccination in the Past Season, Willingness to Receive the 2021/22 Influenza Vaccination and Its Correlates

We first analyzed the actual 2020/21 IV uptake and compared it with the willingness to be immunized, as recorded in the 2020 survey. It emerged that most (84.9%) people who stated in 2020 that they would definitely have a flu shot actually did have a shot. Analogously, a total of 88.9% of respondents who had declared no intention to have a flu shot, did not receive one. On the other hand, only 47.3% of interviewees who replied "Probably yes" were actually vaccinated (**Table 2.5**). Compared with subjects (N=588) who had declared some willingness to receive IV and were actually vaccinated, those

(N=285) who were not vaccinated were significantly younger (44.6 vs 56.7 years; P<0.001); the effect size was large (d=0.82).

Table 2.5. Between-survey comparison of the declared willingness to receive the 2020/21 influenza vaccine (2020 survey) and actual 2020/21 vaccine receipt.

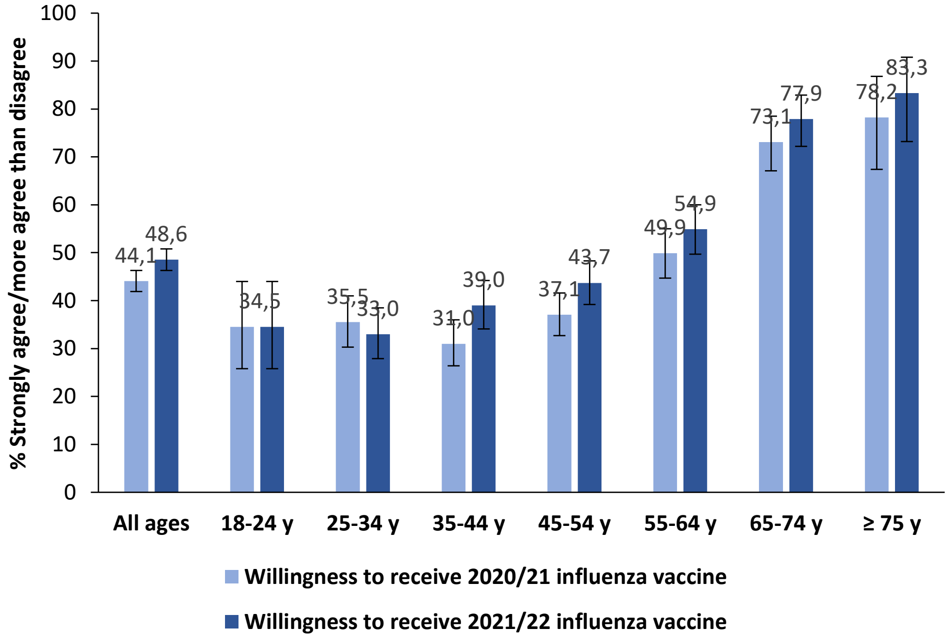
Willingness to receive 2020/21 influenza vaccine (2020 survey)	**2020/21 season reported vaccination (2021 survey), % (95% CI)**	
	Yes	**No**
Yes definitely (N=465)	84.9 (81.4–88.1)	15.1 (11.9–18.6)
Probably yes (N=408)	47.3 (42.4–52.3)	52.7 (47.7–57.6)
I don't know (N=282)	18.1 (13.8–23.1)	81.9 (76.9–86.2)
Probably not (N=444)	17.8 (14.3–21.7)	82.2 (78.3–85.7)
Definitely not (N=380)	11.1 (8.1–14.6)	88.9 (85.4–91.9)
Total (N=1979)	38.4 (36.3–40.6)	61.6 (59.4–63.7)

Declared willingness to receive the seasonal IV significantly increased from 2020 to 2021 (from 44.1% to 48.6%, P<0.001). This increase was seen in almost all age-groups (except for young adults aged 18–34 years) (**Figure 2.1**). IV refusal was reported by 12.6% (95% CI: 11.2–14.2%) of respondents.

Notably, of those subjects who had already received, arranged for or planned COVID-19 vaccination, a total of 42.2% (95% CI: 39.8–44.5%) declared that they had been vaccinated against influenza in the 2020/21 season. By contrast, only 10.3% (95% CI: 6.7–14.9%) of interviewees who declared no intention to be immunized against COVID-

19 had received IV. This 4-fold difference was statistically significant (P<0.001) and the effect size was large (OR 6.35; 95% CI: 4.12–9.78).

Figure 2.1. Between-survey comparison of the declared willingness to receive 2020/21 and 2021/22 influenza vaccines, by age-group (N=1979).



[a]Comprise response options "Strongly agree" and "More agree than disagree".

The main reasons for not having IV in the next season are reported in **Table 2.6**. Although the 2020 and 2021 surveys cannot be compared directly (since another response option was added to the 2021 survey), there was some decrease in participants' selection of options regarding the effectiveness of IV. Indeed, in the 2021 survey, the most frequently selected (13.9%) option was "*Flu has diminished drastically since the COVID-19 pandemic began, so I don't think a flu shot is necessary any more*".

Table 2.6. Reasons for not having influenza vaccination, by survey.

Reason	2020 (N=997)	2021 (N=887)
Influenza vaccines are designed only to profit the pharmaceutical companies	21.0 (18.5–23.6)	12.9 (10.7–15.2)
Influenza vaccines do not work	17.9 (15.5–20.4)	12.0 (9.9–14.3)
I'm afraid of needles	8.5 (6.9–10.4)	8.2 (6.5–10.2)
I had a flu shot but got a fever/cold anyway	8.5 (6.9–10.4)	5.5 (4.1–7.2)
My doctor advised against it	7.9 (6.3–9.8)	7.0 (5.4–8.9)
Flu has diminished drastically since the COVID-19 pandemic began, so I don't think a flu shot is necessary any more	NA[a]	13.9 (11.7–16.3)
Other	36.2 (33.2–39.3)	40.6 (37.3–43.9)

[a]This item was not assessed in the 2020 survey.

Finally, we investigated potential predictors of the likelihood of having the 2021/22 IV. As expected, the largest effect sizes were seen for previous IV vaccination in both the 2019/20 (aOR 4.11) and 2020/21 (aOR 13.62) seasons. Subjects already vaccinated against COVID-19 or those who planned to be so were also more prone to be vaccinated against influenza (aORs 5.52–9.46). Males and older people were more likely to have the intention to be vaccinated. Each 1-point increase in confidence that the respondent's own physician is a reliable source of information on IV was associated with an 18% increase in the likelihood of having the 2021/22 IV. Moreover, several attitudes towards IV were significant predictors (**Table 2.7**). The model explained 65.5% of variance and no multi-collinearity issues emerged (VIFs < 1.4).

Table 2.7. Multivariable logistic regression analysis to predict willingness to receive the 2021/22 influenza vaccine.

Variable	Level	aOR (95% CI)	P
Sex	Female	Ref	–
	Male	1.34 (1.03–1.75)	0.032
Age	1-year increase	1.01 (1.00–1.02)	0.014
Influenza vaccination in the 2019/20 season	No	Ref	–
	Yes	4.11 (2.73–6.19)	<0.001
Influenza vaccination in the 2020/21 season	No	Ref	–
	Yes	13.62 (9.64–19.25)	<0.001
COVID-19 vaccination status	No, and I don't intend to get a shot in the future	Ref	–
	Not yet, but I will get a shot as soon as possible	5.52 (2.60–11.69)	<0.001
	Not yet, but I have already booked my shot	6.13 (2.85–13.21)	<0.001
	Yes	9.46 (4.48–19.97)	<0.001
Vaccines are crucial to guaranteeing public health and should be mandatory	Disagree[a]	Ref	–
	Agree[b]	1.87 (1.25–2.80)	0.002
All vaccines are safe	Disagree[a]	Ref	–
	Agree[b]	1.53 (1.10–2.14)	0.011
Influenza vaccination is a human right and must be guaranteed	Disagree[a]	Ref	–
	Agree[b]	2.08 (1.16–3.73)	0.014
It is unacceptable that there are no influenza vaccines in the future season	Disagree[a]	Ref	–
	Agree[b]	2.83 (1.63–4.89)	<0.001
If there were no free-of-charge influenza vaccine, I would pay for it out of my own pocket	Disagree[a]	Ref	–
	Agree[b]	1.64 (1.25–2.16)	<0.001
I would be more inclined to get a flu shot if it were personalized	Disagree[a]	Ref	–
	Agree[b]	2.37 (1.69–3.34)	<0.001
Confidence in one's own physician	1-point increase	1.18 (1.09–1.28)	<0.001

[a]Comprise response options "Strongly disagree" and "More disagree than agree"; [b]Comprise response options "Strongly agree" and "More agree than disagree".

2.3.4. Public Opinion on the Co-Administration of COVID-19 and Influenza Vaccines and Willingness to Have a Combined Influenza/COVID-19 Vaccine

A total of 34.1% (95% CI: 32.0–36.2%) of respondents expressed firm willingness to receive both COVID-19 and IV at the same time, while 33.4% (95% CI: 31.3–35.5%) expressed some willingness to do so. Analogously, about three-quarters (73.7%, 95% CI: 71.7–75.6%) of interviewees favored having a combined influenza/COVID-19 vaccine. If such a combined vaccine were available, 34.8% (95% CI: 32.7–37.0%) stated that they "would definitely have it", and 35.9% (95% CI: 33.8–38.1%) replied "I think I would have it".

2.4. Discussion

This longitudinal study revealed a significant 1-year increase in respondents' overall confidence in vaccines and willingness to receive the next seasonal IV. Some socioeconomic and attitudinal factors were independently associated with the propensity to being immunized in the upcoming 2021/22 season. We will now discuss the principal findings in the context of the available Italian and international research and provide suggestions for future IV campaigns. Both influenza-associated risk perception and preventive behaviors may change over time. This dynamic pattern was, for example, reported during the last A(H1N1)pdm09 pandemic (Ibuka et al., 2010) and the ongoing COVID-19 pandemic (Caserotti et al., 2021). Indeed, we ascertained a 10% relative increase (from 44.1% in 2020 to 48.6% in 2021 surveys) in people's intention to be immunized against influenza. It is, however, unclear whether this growth in willingness will translate into increased coverage. On the other hand, in our surveys, we observed a 45.0% relative increase (from 2019/20 to 2020/21) in self-declared IV uptake, which is very close to the officially reported (Italian Ministry of Health, s.d.-b) increase of 41.1% (from 16.8% to 23.7%) in IV coverage in the general population. Only a few studies on changes in attitudes and beliefs concerning IV in the COVID-19 era are currently available. The Vaccine Confidence Project (European Commission, 2020) reported an increase (from 2018 to 2020) in public trust in vaccines, and in IVs in particular, across most European countries. In Italy, overall vaccine confidence grew from 53% to 60%, while public awareness that IV is important rose from 67.6% to 78.4%. A similar significant increase was seen in other European countries, with the exceptions of Estonia, Romania, Hungary, and the United Kingdom (UK), where no significant changes were recorded. Among other possible reasons, the authors linked this increase to the perceived severity of the COVID-19 pandemic (European Commission, 2020). An Italian study by Caserotti et al. (Caserotti et al., 2021) reported an increase in willingness to receive IV from the pre-lockdown period (from the end of February to March 8, 2020) to the post-lockdown period (from May 19 to the end of June 2020) (aOR 1.82; 95% CI: 1.16–2.87). By contrast, a six-wave longitudinal study conducted in California between March and August 2020 showed a decreasing trend in intentions to receive IV (Fridman et al., 2021). These apparent discrepancies may be explained by several factors, including different survey time periods, and therefore SARS-CoV-2 epidemiology and restrictive public health measures adopted by single jurisdictions. In Italy, the observed increase in intentions to receive IV may also be explained by the "more effective" influenza prevention campaign promoted by the Ministry of Health in 2020 (Odone et al., 2020). According to the effect size observed, the main drivers of the uptake of the next seasonal IV were both previous IV vaccination and COVID-19 vaccination status (or at least intention to be vaccinated against COVID-19). Indeed, IV in the previous season has been systematically shown to determine current IV status in all principal risk groups, including HCWs, the elderly, pregnant women, young children, and subjects with underlying health conditions (Dini et al., 2018; Nagata et al., 2013; Okoli et al., 2021; Schmid et al., 2017; Yeung et al., 2016). However, we noted that, although IV status in both previous seasons (2019/20 and 2020/21) was a positive predictor of the next IV, the effect size of the latter was about three times higher than that of the former. In an Italian study by Fabiani et al. (Fabiani et al., 2019), elderly subjects vaccinated in the two previous seasons were 8.36 (95% CI: 8.17–8.55) times more likely to receive the 2016/17 IV than those who had not been vaccinated. Indeed, if people have a positive initial experience, most of them will probably seek IV the following year (Nagata et al., 2013). It is therefore essential to ensure the continuity of effective IV counseling strategies. In this regard, the role of general practitioners, who are the most trusted source of information on IV, is central. Unwillingness to receive IV and COVID-19 vaccines may be interrelated. In a UK survey, willingness to undergo COVID-19 vaccination was significantly associated with willingness to receive a 2020/21 IV (Bachtiger et al., 2021). Analogously, among Italian undergraduates, previous IV was associated with greater acceptance of COVID-19 vaccination (aOR 3.81; 95% CI: 1.18–12.27) (Gallè et al., 2021). Finally, a meta-analysis of four studies showed that previous IV was a strong predictor (OR 3.17; 95% CI: 1.84–5.46) of COVID-19 vaccine acceptance (Q. Wang et al., 2021). It is therefore likely that effective vaccination counseling on one infection may have indirect positive effects on the other. Of the structural social determinants analyzed, only increasing age and male sex were associated with a greater intention to receive the 2021/22 IV. That older age is a correlate of IV acceptance has been amply demonstrated by a number of systematic reviews and/or meta-analyses (Nagata et al., 2013; Okoli et al., 2021; Schmid et al., 2017; Yeung et al., 2016). By contrast, the role of sex remains to be clarified. Although men tend to report a higher uptake rate than women, the difference becomes non-significant on adjusted analysis (Nagata et al., 2013). It is also possible that there is a significant interaction between age and sex; it has been shown that IV uptake in females decreases with increasing age, but increases in males (Sarría-Santamera & Timoner, 2003). In our model, the interaction term was not statistically significant. In our study, positive attitudes towards IV were associated with greater willingness to receive the next seasonal IV. This finding is in line with those of a systematic review by Schmid et al. (Schmid et al., 2017), which reported that a negative attitude towards IV was a major barrier to IV uptake in all principal risk groups. Among the various negative attitudes analyzed, lack of confidence in the efficacy of IVs held a prominent place (Schmid et al., 2017). A recent US survey (Kaplan & Milstein, 2021) has shown a significantly reduced probability of taking the COVID-19 vaccine if the vaccine effectiveness was 50% (comparison to 70% or 90%), while the difference between a 70% and a 90% protection rate was not statistically significant. Laypeople's statistical literacy is generally low (Gal, 2002). Indeed, Tentori et al. (Tentori et al., 2021) reported that most people are unaware of the meaning of vaccine effectiveness and confuse this term with the non-incidence rate among vaccinated people. This misinterpretation leads the overall undervaluation of the individual benefits of the vaccine. Moreover, according to the authors, this misunderstanding was aligned with expectations based on misreports in the media (Tentori et al., 2021). It has been reported (Bodemer et al., 2012) that the media often report unbalanced messages from the point of view of completeness, transparency, and correctness. We therefore believe that the media should convey their messages through a more balanced reporting and, ideally, adopt shared standards and norms. In our study, the traditional media (e.g., TV or newspapers) showed the largest 1-year increase as a trusted information source. In this regard, interventions such as media training for medical experts and regular meetings that may facilitate communication between experts and journalists may be beneficial (Larsson et al., 2019). More generally, it is still unclear whether the expected vaccine effectiveness should be provided to laypeople. Zhao et al. (Zhao et al., 2019) have stated that "vaccine effectiveness studies are designed to inform public health decisions rather than for individual decision-making" and "an individual's decision to get vaccinated should be primarily informed by their risk of influenza illness and their risk of transmitting influenza to vulnerable people". We, however, believe that anticipated suboptimal (which varies substantially by season, location, age group, and average 40–60% (Centers for Disease Control and Prevention (CDC), 2022b)) IV effectiveness should be openly disclosed by healthcare providers. In fact, even if the efficacy is only 20% (and the coverage rate is 43%), IV is still able to avert 20.99 million infections, 129,701 hospitalizations, 61,812 deaths, and 2.22 million disability-adjusted life years (Sah et al., 2018). Effective public health communication strategies should therefore provide balanced and laypeople-friendly risk–benefit information on immunization. In turn, effective vaccine promotion campaigns should stress the importance of talking to a healthcare professional about all vaccination aspects, including safety and effectiveness (Head et al., 2020). For what concerns the main reasons for not having a flu shot, our 2021 survey revealed a substantial 1-year decrease in respondents' selection of options regarding the presumed low effectiveness of IV. On the other hand, the leading reason for not having a flu shot in the upcoming 2021/22 season was the apparent disappearance of influenza viruses in the previous 2020/21 season (National Institute of Health, s.d.). The epidemiology of influenza and influenza-like illness in the upcoming 2021/22 season is unclear and will probably depend on non-specific COVID-19 pandemic prevention measures, such as social distancing, lockdowns, the wearing of masks, etc. Several scenarios of the evolution of influenza in the COVID-19 pandemic era (e.g., influenza viruses will return, and the same clades will circulate; influenza viruses will return, but some subtypes/lineages/clades will disappear; influenza viruses will return, causing occasional outbreaks) have been proposed (Laurie & Rockman, 2021). Moreover, by exerting the so-called "trained immunity" effect (i.e., by boosting the innate immune system), IV may reduce the incidence of some COVID-19-related outcomes. A systematic review and meta-analysis by Wang et al. (R. Wang et al., 2021) recently demonstrated a 14% (aOR 0.86, 95% CI: 0.81–0.91) reduction in the odds of being positive to SARS-CoV-2 in subjects vaccinated against influenza, as compared with non-vaccinated subjects. This argument could also be used to increase IV acceptance. It is clear that influenza (at least type A), being a zoonosis, cannot be eliminated; IV uptake goals (World Health Organization (WHO), 2012) must therefore be pursued. Over one year, people's awareness of the existence of different IVs increased. In our opinion, two main factors may have contributed to this increase. First, ongoing controversies over the effectiveness and safety of different COVID-19 vaccines (Boytchev, 2021) may have increased people's willingness to receive one vaccine type rather than another. Second, in 2020, four novel influenza vaccines were authorized and/or commercialized in Italy: quadrivalent egg-based standard-dose adjuvanted, quadrivalent egg-based high-dose, quadrivalent recombinant, and quadrivalent live-attenuated vaccines (Italian Ministry of Health, 2021a). Finally, most interviewees looked favorably on the idea of receiving both IV and COVID-19 shots at the same time and/or a combined influenza/COVID-19 vaccine. From the public health perspective, vaccine co-administration or combined vaccines have several benefits, including fewer missed opportunities to vaccinate, simplified immunization schedules, logistical advantages, and reduced costs (Dodd, 2003; Gilchrist et al., 2012). The first available clinical data (Toback et al., 2022) suggest that influenza and COVID-19 vaccines can be co-administered with little interference in terms of immunogenicity and efficacy and only a slight increase in solicited adverse events. By contrast, the rate of unsolicited adverse events was similar among the study arms. The most recent interim clinical considerations for the use of COVID-19 vaccines issued by the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention (CDC), 2022e) suggest that SARS-CoV-2 and other vaccines may be co-administered without regard to timing, but each shot should be inoculated in a different injection site. Further large-scale phase III and pharmacovigilance studies on vaccine co-administration (in terms of both immunological inference and safety) are warranted. Analogously, the first preclinical studies suggest that combined vaccines are promising. A combination of a Matrix-M-adjuvanted quadrivalent nanoparticle IV and NVX-CoV2373 COVID-19 vaccine was immunogenic and efficacious in ferret and hamster models (Massare et al., 2021). Another approach consists of a recombinant influenza type A virus genetic platform that encodes the receptor-binding domain of SARS-CoV-2. This vaccine candidate also proved immunogenic and efficacious against lethal challenge by both viruses (Chaparian et al., 2021). Our study has some limitations, which should be considered when interpreting the results. First, like all web-based surveys, our study may have been subject to the digital divide bias. However, both probabilistic quota sampling and the longitudinal nature of the survey should mitigate the effects of this bias. Second, self-reported IV uptake was substantially higher than that officially registered. For instance, in this study, self-reported 2019/20 IV uptake (results not shown) was 18.1% (95% CI: 15.5–20.9%), 23.7% (95% CI: 20.9–26.7%), and 45.6% (95% CI: 40.1–51.1%) among subjects aged 18–44, 45–64, and ≥65 years, respectively. The corresponding officially reported (Italian National Institute of Statistics (ISTAT), 2022) statistics were 3.1%, 9.6%, and 54.6%, respectively. This discordant result is unlikely to have been due to the characteristics of the sample (representative of the adult Italian population) or participation bias (interviewees were not aware of the survey topic beforehand). Possible reasons include the social desirability (Boggavarapu et al., 2014) and recall (especially in subjects with irregular IV uptake patterns) (King et al., 2018) biases.

2.5. Conclusions

In conclusion, although a significant proportion of Italian adults are reluctant/hesitant toward both influenza and COVID-19 vaccines, public confidence in (influenza) vaccines increased significantly. This positive trend was at least partially determined by the ongoing COVID-19 pandemic. Our future work will focus on the continuous (at least two surveys per year) follow-up of the same panel, in order to capture even small changes in laypeople's knowledge, attitudes, and beliefs concerning influenza vaccination. Moreover, future research should scrutinize laypeople's attitudes towards safety aspects.

Chapter 3. Acceptance of COVID-19 and Influenza Vaccine Co-Administration: Insights from a Representative Italian Survey

Declarations

This chapter is a slightly modified version of the manuscript entitled "Acceptance of COVID-19 and Influenza Vaccine Co-Administration: Insights from a Representative Italian Survey" by Alexander Domnich, Riccardo Grassi, Elettra Fallani, Roberto Ciccone, Bianca Bruzzone, Donatella Panatto, Allegra Ferrari, Marco Salvatore, Maura Cambiaggi, Alessandro Vasco, Andrea Orsi and Giancarlo Icardi (© 2022 by the authors) published in Journal of Personalized Medicine (Domnich et al., 2022). The article is published in open access modality and distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), which permits any use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

3.1. Introduction

The ongoing 2021/22 Northern Hemisphere season is characterized by the co-circulation of SARS-CoV-2 and influenza viruses, although as of December 2021 detections of the latter remain relatively low (World Health Organization (WHO), s.d.-b). At the population level, the "disappearance" of influenza viruses in the previous season determined a progressive waning of acquired immunity; the susceptible fraction of the population is therefore likely to have increased considerably. Moreover, in the current 2021/22 season, many young children have never been exposed to influenza viruses (Academy of Medical Sciences, 2021). Similarities in the clinical presentation of influenza and COVID-19 disease, the risk of overburdening healthcare systems and the fact that seasonal influenza vaccination (SIV) is among the most effective preventive tools available have prompted a call to increase SIV coverage rates (Bhatt, 2021; McCauley et al., 2022; Peacock et al., 2021).

It has recently been suggested (Conlon et al., 2021; Marín-Hernández et al., 2021; R. Wang et al., 2021) that SIV may exert non-specific effects on SARS-CoV-2-related clinical endpoints. In particular, a systematic review and meta-analysis by Wang et al. (R. Wang et al., 2021) showed a 14% (95% CI: 9–19%) reduction in the odds of testing positive for SARS-CoV-2 in subjects vaccinated against influenza. These non-specific effects may be ascribable to both innate (induction of trained immunity) and adaptive (e.g., cross-immunity and bystander activation) immune-related mechanisms (Marín-Hernández et al., 2021). Indeed, Debisuran et al. (Debisarun et al., 2021) reported that, compared with non-vaccinated adults, those who received SIV displayed improved responsiveness of immune cells to heterologous stimuli: SIV modified the anti-SARS-CoV-2 response by reducing IL-1β and IL-6 production and increasing IL-1Ra release.

The co-administration of COVID-19 vaccine and 2021/22 SIV may yield some potential benefits, including logistical advantages, cost reduction and the possibility to increase the uptake of both vaccines (Domnich et al., 2021; Gilchrist et al., 2012). Preliminary data suggest that the concomitant administration of COVID-19 and SIV vaccines is a feasible option. Specifically, a recent phase IV randomized placebo-controlled trial (Lazarus et al., 2021) established that both ChAdOx1 and BNT162b2 COVID-19 vaccines could be safely co-administered with either MF59-adjuvanted or cell culture-derived SIVs, with no clinically significant increase in adverse events or immunologic inference. Although the available data are limited, the interim guidelines issued by the World Health Organization (WHO) (World Health Organization (WHO), 2021) suggest that such co-administration is acceptable. The United States Centers for Disease Control and Prevention (CDC) advocates that COVID-19 vaccines be simultaneously administered with other vaccines, including SIV (Centers for Disease Control and Prevention (CDC), 2022e). Analogously, in October 2021 (i.e., just before the start of the 2021/22 SIV campaign) the Italian Ministry of Health gave the green light to the vaccine co-administration (Italian Ministry of Health, s.d.-a).

Most available research on people's knowledge, attitudes and practices (KAP) concerning COVID-19 vaccines and/or SIV has focused on socio-structural, contextual and attitudinal determinants of vaccination acceptance, hesitancy or reluctance. As shown by recent systematic reviews (Cascini et al., 2021; Luo et al., 2021), previous SIV has usually proved to be a strong facilitator of COVID-19 vaccine uptake. On the other hand, very little is as yet known about laypeople's KAP regarding vaccine co-administration. The objectives of this study were to assess public opinion concerning the simultaneous administration of COVID-19 and SIV vaccines, to quantify the proportion of citizens who are hesitant/reluctant to undergo co-administration, and to identify correlates of the willingness to receive both vaccines at the same time. These latter are essential to planning and establishing effective and targeted health promotion interventions to increase immunization coverage rates.

3.2. Materials and Methods

3.2.1. Study Design and Setting

This cross-sectional survey is part of a longitudinal panel study that aims to monitor public opinion towards SIV during the ongoing COVID-19 pandemic. Briefly, data collection is performed 2–3 times a year via computer-assisted web interview (CAWI). During each survey round, we aim to obtain at least 2,000 valid responses; this sample size was judged sufficiently powered during the first survey round (Domnich, Cambiaggi, et al., 2020). The panel is drawn from a well-characterized database of about 60,000 adults (≥18 years) and is representative of the adult Italian population. Subjects were sampled by applying a two-stage probabilistic quota method. Specifically, the whole dataset was first grouped into mutually exclusive strata according to sex, age (18–24, 25–34, 35–44, 45–54, 55–64, 65-74 and ≥75 years), geographical macro-area (North-East, North-West, Center, South and Islands) and size of their municipality of residence. Subsequently, subjects in each stratum were selected randomly. The survey instrument is regularly updated in order to keep pace with the changing epidemiology and public health measures against both COVID-19 and influenza.

The present survey was conducted between 27th October and 12th November 2021. This period was characterized by: (i) the ongoing administration of booster COVID-19 vaccine doses to healthcare professionals, subjects aged ≥60 years and at-risk individuals aged 18–59 years; (ii) the start of the 2021/22 SIV campaign. Of note, just before the survey, the Italian Ministry of Health authorized the co-administration of COVID-19 and SIV vaccines (Italian Ministry of Health, s.d.-a).

Participation in the survey is voluntary and anonymity is guaranteed. As the replies to all survey items are mandatory, no missing data are expected. The quality of the responses registered was formally checked by analyzing the pattern of responses to signal questions. Specifically, responses to the negatively-worded item "*Vaccines are a fraud designed to profit the pharmaceutical companies*" were compared with those to a positively-worded and semantically similar item "*Vaccines are crucial to guaranteeing public health and should be mandatory*". Discordant responses to these two items may indicate untruthful or careless responses. These responses were therefore excluded from the dataset in a sensitivity analysis.

3.2.2. Study Outcome

The study outcome was the attitude towards simultaneous COVID-19 and SIV vaccine administration and was measured on a 4-point Likert scale ("Strongly agree", "More agree than disagree", "More disagree than agree" and "Disagree").

3.2.3. Study Variables

The following socio-economic variables were collected: sex, age, highest educational attainment (categorized into six levels according to the International Standard Classification of Education (ISCED) levels adopted in Italy (Italian National Institute of Statistics (ISTAT), 2003), where level 1 corresponds to primary education, while level 6 corresponds to advanced research qualifications), employment pattern (employed, student, housekeeper, retired, unemployed, other/prefer not to reply), perceived income (low, lower than average, average, higher than average, high and no personal income) and self-rated health (excellent, very good, good, fair and poor). Participants were also asked whether they had recently searched for information on SIV.

COVID-19 and SIV vaccination status were assessed by means of two items. With regard to SIV, participants were able to select among the following response options: (i) *I have never received SIV*; (ii) *I received SIV in the past, but not in the last 2020/21 season*; (iii) I received SIV in the 2020/21 season for the first time and (iv) *I received SIV in 2020/21 and sometimes in the past*. Regarding COVID-19, participants were categorized as follows: (i) fully vaccinated (i.e., those immunized with either two doses of mRNA or ChAdOx1 vaccines or a single dose of Ad26.COV2-S); (ii) partially vaccinated (i.e., those immunized with the first dose of mRNA or ChAdOx1 vaccines); (iii) not vaccinated but having planned/arranged to receive any available COVID-19 vaccine as soon as possible, and (iv) individuals who affirmed that they would not receive any available COVID-19 vaccine.

KAP on influenza and/or vaccination were measured on 19 anchored Likert-based items; these are reported in **Table 3.1**. The comprehensibility of these items was judged sufficient and a post-hoc psychometric evaluation showed acceptable reliability (standardized Cronbach's α 0.83).

Table 3.1. Survey items on knowledge, attitudes, and practices (KAP) regarding influenza and/or vaccination.

Item
To what extent do you agree or disagree with the following statement? Vaccines are a fraud designed to profit the pharmaceutical companies. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.
To what extent do you agree or disagree with the following statement? Vaccines are crucial to guaranteeing public health and should be mandatory. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.
To what extent do you agree or disagree with the following statement? All vaccines are safe. - Strongly agree; - More agree than disagree; - More disagree than agree; - Strongly disagree.

To what extent do you agree or disagree with the following statement? I need more information on vaccines.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

Influenza vaccination is a human right and must be guaranteed for people that would like to have it.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

It is unacceptable that there are no influenza vaccines in the future season for people that would like to be vaccinated.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

If there were no free-of-charge influenza vaccine, I would pay for it out of my own pocket.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

On the basis of people's age and health conditions, there are different influenza vaccine types.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement? I would be more willing to get a flu shot if it were personalized.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

Influenza is a banal disease: social distancing and wearing masks are sufficient to defeat it.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

Influenza should not be underestimated, influenza virus did not circulate in the last season because more people were vaccinated, while the restrictions adopted further slowed down transmission.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

COVID-19 pandemic is not finished and viral variants continue to circulate; if you get seasonal influenza, you double the risk of having serious complications.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

To what extent do you agree or disagree with the following statement?

Only the elderly are at high risk, neither influenza nor COVID-19 is a problem for other age-groups.

- Strongly agree;
- More agree than disagree;
- More disagree than agree;
- Strongly disagree.

Regarding influenza vaccination, on a scale from 1 (not at all) to 10 (completely) how much do you trust information from each of the following sources?

- Friends and acquaintances;
- My physician;
- My pharmacist;
- Public health institutions;
- Traditional media (radio/TV/newspapers);
- Social networks.

3.2.4. Data Analysis

For descriptive analysis, categorical variables were expressed as proportions with 95% confidence intervals (CIs), while continuous variables were expressed as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). Independent proportions were compared by applying Fisher's exact test, and the corresponding effect size was expressed as an odds ratio (OR). Ordinal multivariable logistic regression was computed in order to obtain adjusted proportional ORs (aORs) on the association between the willingness to receive COVID-19 and SIV vaccines simultaneously and the independent variables considered. On preliminary analysis, identification of the classes "More agree than disagree" and "More disagree than agree" was suboptimal; these two response options were therefore combined into a single category "Unsure". In summary, the intention to undergo co-administration of COVID-19 and SIV vaccines had three ordered levels ("Strongly disagree", "Unsure" and "Strongly agree"). On the principle of parsimony, and owing to possible multicollinearity issues, the final model was selected by minimizing the Akaike information criterion (AIC). The goodness-of-fit, explained variance and discrimination of the model were computed by applying Lipsitz's test, Nagelkerke's pseudo-R^2 and C index, respectively. Multicollinearity of the final model was checked by quantifying variance inflation factors (VIFs). The independent variable "Age" was treated as continuous, since different categorization rules or the introduction of non-linear terms did not improve the model fit.

Data analysis was performed in R stat packages, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team, s.d.).

3.3. Results

3.3.1. Characteristics of the Study Participants

Of 3,630 invitations sent out, a total of 2,463 responses (response rate of 67.9%) were received and analyzed. The principal socio-economic characteristics of respondents are reported in **Table 3.2**. Briefly, the sample was judged to be geographically representative, men and women were approximately equally distributed, and their mean age was 50.9 (SD 16.8) years, with a range of 18–91 years. Most participants had completed at least secondary education (ISCED level ≥4), were employed, and claimed to be in good health (**Table 3.2**).

Table 3.2. Socio-economic characteristics of the study participants (n = 2,463).

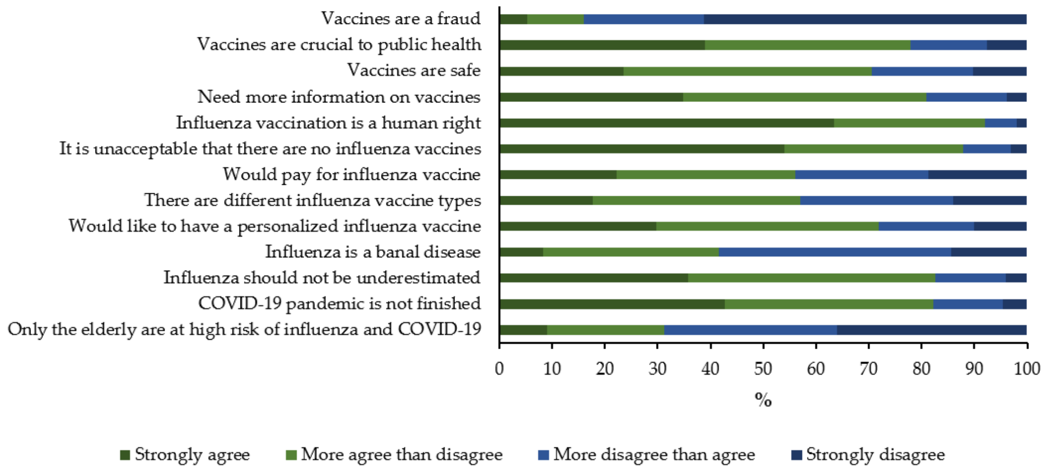
Variable	**Level**	**% (*n*)**	**95% CI**
Sex	Male	47.8 (1,177)	45.8–49.8
	Female	52.2 (1,286)	50.2–54.2
Age, years	18–24	7.9 (194)	6.8–9.0
	25–34	12.5 (309)	11.3–13.9
	35–44	15.4 (380)	14.0–16.9
	45–54	19.8 (488)	18.3–21.4
	55–64	16.7 (412)	15.3–18.3
	65–74	21.0 (516)	19.4–22.6
	≥ 75	6.7 (164)	5.7–7.7
Geographic macro-area	North-West	27.0 (664)	25.2–28.8
	North-East	18.9 (465)	17.4–20.5
	Center	20.1 (496)	18.6–21.8
	South	22.9 (563)	21.2–24.6
	Islands	11.2 (275)	9.9–12.5
Educational level	1	1.5 (38)	1.1–2.1
	2	8.0 (197)	7.0–9.1
	3-4	48.2 (1,188)	46.2–50.2
	5	40.5 (997)	38.5–42.4
	6	1.7 (43)	1.3–2.3
Employment pattern	Employed	55.4 (1,364)	53.4–57.4
	Student	6.7 (165)	5.7–7.8

	Housekeeper	8.3 (204)	7.2–9.4
	Unemployed	5.2 (129)	4.4–6.2
	Retired	23.5 (580)	21.9–25.3
	Other/Prefer not to reply	0.9 (21)	0.5–1.3
Perceived income	Low	1.8 (44)	1.3–2.4
	Lower than average	41.2 (1,014)	39.2–43.1
	Average	30.8 (759)	29.0–32.7
	Higher than average	7.6 (187)	6.6–8.7
	High	2.4 (59)	1.8–3.1
	No personal income	16.2 (400)	14.8–17.8
Self-rated health	Excellent	11.5 (284)	10.3–12.9
	Very good	48.3 (1,190)	46.3–50.3
	Good	36.2 (891)	34.3–38.1
	Fair	3.5 (86)	2.8–4.3
	Poor	0.5 (12)	0.3–0.8

3.3.2. Knowledge, Attitudes and Practices concerning Influenza and Vaccination

As shown in **Figure 3.1**, most participants valued (influenza) vaccination positively, would like to have more information on vaccines and prefer to have to a more personalized SIV. On the other hand, 41.5% of subjects believed that influenza was a banal disease, and only 56.1% would pay for SIV. Analogously, only 57.0% of respondents agreed to some extent that there were different types of SIV (**Figure 3.1**).

Figure 3.1. Knowledge, attitudes, and practices on influenza and/or vaccination. [1]

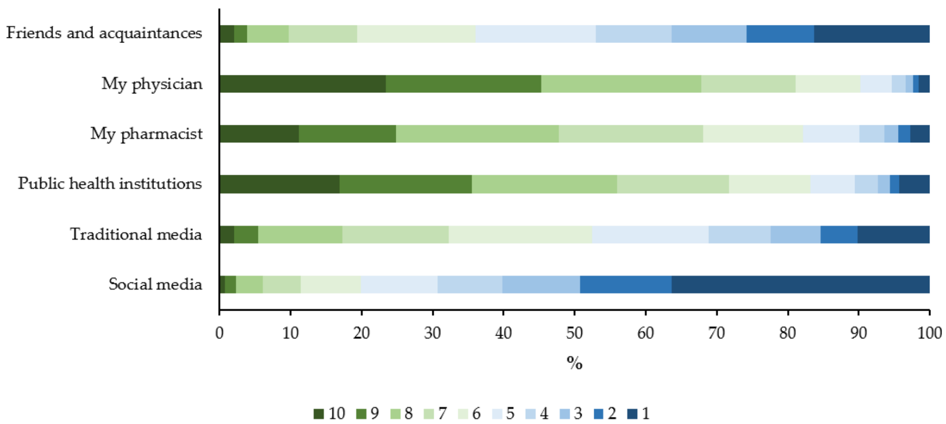


[1] Complete wording of the items is reported in **Table 3.1**.

With regard to sources of information on SIV, on a scale of 1-to-10 the most rated source was one's own physician [median 8 (IQR: 7–8)], followed by public health institutions [median 8 (IQR: 6–8)] and one's own pharmacist [median 7 (IQR: 6–7)]. Social media websites were deemed the least reputable information source [median 3 (IQR: 1–3)]. (**Figure 3.2**).

Approximately a quarter [27.7% (95% CI: 26.0–29.5%)] of participants had recently searched for SIV-related information.

Figure 3.2. Participants' trust in different information sources on influenza vaccination (10 indicates the highest trust).



3.3.3. Influenza and COVID-19 Vaccination Uptake

As expected, most [85.1% (95% CI: 83.6–86.4%)] participants had completed the primary schedule of COVID-19 vaccination, while 7.8% (95% CI: 6.8–8.9%) declared that they had no intention of being vaccinated. A total of 42.6% (95% CI: 40.6–44.6%) of subjects claimed that they had received the 2020/21 SIV, while 44.2% (95% CI: 42.2–46.2%) had never been vaccinated against influenza. There was a clear relationship between COVID-19 vaccine and SIV uptake. For instance, the self-declared 2020/21 SIV uptake was 45.2% (95% CI: 43.1–47.4%) among subjects fully immunized against COVID-19, but only 9.9% (95% CI: 6.1–15.0%) among those who had no intention of being immunized against COVID-19, with an OR of 7.51 (95% CI: 4.62–12.87; $p < 0.001$) (**Table 3.3**).

Table 3.3. Cross-tabulation of the declared uptake of COVID-19 and seasonal influenza vaccines (n = 2,463).

Influenza vaccination	**COVID-19 vaccination, % (*n*)**				
	Complete	Partial	Planned	No intention	Total
Never	35.9 (885)	1.0 (25)	1.5 (36)	5.8 (142)	44.2 (1,088)
In the past but not in 2020/21	10.7 (263)	0.6 (14)	0.7 (18)	1.3 (31)	13.2 (326)
In 2020/21 but not in the past	10.6 (262)	0.4 (11)	0.7 (17)	0.2 (5)	12.0 (295)
Both in 2020/21 and in the past	27.8 (685)	1.3 (33)	0.9 (22)	0.6 (14)	30.6 (754)
Total	85.1 (2,095)	3.4 (83)	3.8 (93)	7.8 (192)	100 (2,463)

3.3.4. Attitude Towards Influenza and COVID-19 Vaccine Co-Administration and Its Correlates

When participants were asked about the co-administration of COVID-19 and influenza vaccines, 22.9% (95% CI: 21.3–24.6%) and 36.1% (95% CI: 34.2–38.0%) of subjects strongly agreed or more agreed than disagreed, respectively. The remaining 16.6% (95% CI: 15.1–18.1%) and 24.4% (95% CI: 22.8–26.2%) replied "Strongly disagree" and "More disagree than agree", respectively.

From the point of view of the observed effect size, the main determinant (aOR = 7.78) of a positive attitude towards COVID-19/SIV co-administration was completion of the primary COVID-19 vaccination schedule (**Table 3.4**). Both partial completion and intention to receive a COVID-19 vaccine as soon as possible were also positive predictors. Analogously, receipt of the previous 2020/21 SIV and recent information seeking on SIV were associated with significantly higher odds of the willingness to undergo co-administration of COVID-19 and SIV vaccines. Among the structural determinants analyzed, only age and sex were significant predictors: women and younger individuals showed lower odds of having a positive attitude towards simultaneous vaccine administration. Beliefs that vaccines are safe and crucial to guaranteeing public health, that influenza is not a banal disease, and that the COVID-19 pandemic is not finished and that viral variants continue to circulate were associated with 37–111% higher odds of having a positive attitude towards vaccine co-administration. Interestingly, respondents who would pay for SIV out-of-pocket (aOR = 1.79) and would prefer to have a more personalized SIV (aOR = 1.55) showed significantly greater odds of the study outcome. By contrast, subjects with a greater propensity to undergo vaccine co-administration agreed less frequently (aOR = 0.60) that they needed more information on vaccines. Among the different sources of information on SIV, only trust in public health institutions showed a statistically significant association with the study outcome (**Table 3.4**). According to Lipsitz's test, the model fitted the data well (p = 0.10), explained 41.8% of variance and displayed acceptable discrimination (C = 0.80). No multicollinearity issues emerged (VIFs < 3) nor were significant interaction terms established.

Finally, following a quality check, a total of 38 responses were judged to be at high risk of untruthfulness or carelessness and were excluded from the dataset in the sensitivity analysis. The results (**Table 3.5**) showed no substantial changes, although the model fit slightly improved with a reduction of 68 in AIC.

Table 3.4. Multivariable ordinal logistic regression model to predict positive attitude towards COVID-19 and seasonal influenza vaccine co-administration (n = 2,463).

Variable	**Level**	**aOR (95% CI)**	***p***
Sex	Male	Ref	–
	Female	0.56 (0.47–0.67)	<0.001
Age	1-year increase	0.99 (0.98–0.99)	<0.001
Previous influenza vaccination	Never	Ref	–
	In the past but not in 2020/21	1.09 (0.83–1.44)	0.53
	In 2020/21 but not in the past	1.52 (1.14–2.04)	0.005
	Both in 2020/21 and in the past	1.89 (1.49–2.41)	<0.001
COVID-19 vaccination	No intention	Ref	–
	Planned	4.97 (2.70–9.12)	<0.001
	Partial	3.44 (1.81–6.55)	<0.001
	Complete	7.78 (4.91–12.33)	<0.001
Recently searched for influenza vaccination information	No	Ref	–
	Yes	1.38 (1.13–1.69)	0.001
Vaccines are crucial to public health [1]	Disagree [2]	Ref	–
	Agree [3]	1.37 (1.05–1.80)	0.021
Vaccines are safe [1]	Disagree [2]	Ref	–
	Agree [3]	2.11 (1.64–2.70)	<0.001
Need more information on vaccines [1]	Disagree [2]	Ref	–
	Agree [3]	0.60 (0.48–0.75)	<0.001

Would pay for influenza vaccine [1]	Disagree [2]	Ref	–
	Agree [3]	1.79 (1.46–2.19)	<0.001
Would like to have a personalized influenza vaccine [1]	Disagree [2]	Ref	–
	Agree [3]	1.55 (1.25–1.94)	<0.001
Influenza is a banal disease [1]	Agree [3]	Ref	–
	Disagree [2]	1.36 (1.12–1.64)	0.002
COVID-19 pandemic is not finished [1]	Disagree [2]	Ref	–
	Agree [3]	1.32 (1.01–1.73)	0.043
Only the elderly are at high risk of influenza and COVID-19 [1]	Agree [3]	Ref	–
	Disagree [2]	1.20 (0.98–1.47)	0.078
Trust in public health institutions	1-point increase	1.22 (1.16–1.28)	<0.001

[1] Complete wording of the items is reported in Table 3.1; [2] Comprise response options "Strongly disagree" and "More disagree than agree"; [3] Comprise response options "Strongly agree" and "More agree than disagree"; aOR, adjusted proportional odds ratio.

Table 3.5. Multivariable ordinal logistic regression model to predict positive attitude towards COVID-19 and seasonal influenza vaccine co-administration: Sensitivity analysis (n = 2,425).

Variable	**Level**	**aOR (95% CI)**	***p***
Sex	Male	Ref	–
	Female	0.55 (0.46–0.66)	<0.001
Age	1-year increase	0.99 (0.98–0.99)	<0.001
Previous influenza vaccination	Never	Ref	–
	In the past, but not in 2020/21	1.04 (0.79–1.37)	0.77
	In 2020/21, but not in the past	1.53 (1.14–2.05)	0.005
	Both in 2020/21 and in the past	1.97 (1.54–2.52)	<0.001
COVID-19	No intention	Ref	–
	Planned	5.65 (3.03–10.53)	<0.001

vaccination	Partial	3.90 (2.02–7.51)	<0.001
	Complete	8.47 (5.30–13.54)	<0.001
Recently searched for influenza vaccination information	No	Ref	–
	Yes	1.40 (1.15–1.71)	0.001
Vaccines are crucial to public health	Disagree[2]	Ref	–
	Agree[3]	1.38 (1.05–1.81)	0.020
Vaccines are safe[1]	Disagree[2]	Ref	–
	Agree[3]	2.17 (1.68–2.79)	<0.001
Need more information on vaccines[1]	Disagree[2]	Ref	–
	Agree[3]	0.60 (0.48–0.75)	<0.001
Would pay for influenza vaccine[1]	Disagree[2]	Ref	–
	Agree[3]	1.78 (1.45–2.18)	<0.001
Would like to have a personalized influenza vaccine[1]	Disagree[2]	Ref	–
	Agree[3]	1.58 (1.27–1.97)	<0.001
Influenza is a banal disease[1]	Agree[3]	Ref	–
	Disagree[2]	1.35 (1.11–1.64)	0.002
COVID-19 pandemic is not finished[1]	Disagree[2]	Ref	–
	Agree[3]	1.33 (1.01–1.75)	0.039
Only the elderly are at high risk of influenza and COVID-19[1]	Agree[3]	Ref	–
	Disagree[2]	1.16 (0.94–1.42)	0.17
Trust in public health institutions	1-point increase	1.21 (1.15–1.27)	<0.001

[1]Complete wording of the items is reported in Table 3.1; [2]Comprise response options “Strongly disagree” and “More disagree than agree”; [3] Comprise response options “Strongly agree” and “More agree than disagree”; aOR, adjusted proportional odds ratio

3.4. Discussion

To our knowledge, this is among the first representative surveys aimed at quantifying laypeople's willingness to undergo concomitant COVID-19/influenza vaccination and identifying its correlates. For what concerns the latter, we found that several determinants of vaccine co-administration were shared with those of either COVID-19 or SIV administered separately, although some specific associations also emerged. Together with subsequent official reports on 2021/22 SIV coverage (expected to be released in summer/fall 2022 and hopefully accompanied by data on the co-administration of the booster COVID-19 dose and SIV), our findings may be useful for planning vaccination campaigns in the next seasons. The future of both the COVID-19 pandemic and its associated immunization policies is largely unknown, and the possibility that SARS-CoV-2 may settle into a seasonal pattern cannot be ruled out; indeed, it seems increasingly likely (Phillips, 2021).

The main finding of this study is that the public's acceptance of COVID-19/SIV co-administration is relatively low. Indeed, only 23% of adult Italians would willingly accept concomitant immunization, while 17% would absolutely not; the remaining majority (approximately 60%) may be dubbed as hesitant to some degree. The number of co-administration-hesitant individuals proved to be higher than that of the SIV-hesitant subjects recorded in our previous studies (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021) on the acceptance of SIV alone. A similar tendency has been reported with regard to pediatric vaccinations: in Italy, vaccine-hesitant individuals are less favorable towards using combined vaccines and vaccine co-administration (Giambi et al., 2018). From the point of view of public health, co-administration strategies have several advantages; these, however, are less obvious to laypeople, and communication on the matter may lead to some challenges regarding acceptance. The main public concerns may be the belief that too many vaccines overload the immune system, may be less effective than the same vaccines administered at different time points and may cause a higher number of adverse reactions (Bonanni et al., 2020). It should also be borne in mind that concomitant COVID-19/SIV immunization is a novel recommendation/practice, and that even the medical community is not very familiar with this approach. The availability and dissemination of further experimental, observational and pharmacovigilance data, guidelines issued by scientific associations, and the personal experience of vaccinating healthcare professionals will probably contribute to increasing public acceptance and the rate of vaccine co-administration. In any case, effective communication tools and approaches will play a crucial role in improving the acceptance of vaccine co-administration.

A recent single-center study by Stefanizzi et al. (Stefanizzi et al., 2022) reported a very high rate of co-administration of the third COVID-19 dose and SIV among healthcare workers. In particular, a total of 60.0% were co-administered both vaccines, while 26.2% and 13.8% of subjects chose to get only the COVID-19 vaccine and SIV, respectively (Stefanizzi et al., 2022). This comparably high co-administration rate was likely driven by the selected study population of healthcare professionals who received an appropriate and effective counselling.

Concomitant vaccine administration is an opportunity to increase immunization coverage, provided that clear clinical guidelines and well-coordinated implementation programs are available. Otherwise, this goal will not be achieved. For instance, during the 2021 Southern Hemisphere influenza season, the COVID-19 immunization program had a negative impact on SIV uptake: in Australia, a marked drop (compared with the 2019 and 2020 seasons) in coverage was reported in all age-groups. The exclusion of co-administration was the likely reason for the decrease observed (Van Buynder et al., 2021). Unlike the Australian experience, during the ongoing 2021/22 Northern Hemisphere SIV campaign, clinical guidelines on COVID-19/SIV co-administration have been issued by several public health authorities, including the WHO (World Health Organization (WHO), 2021) and CDC (Centers for Disease Control and Prevention (CDC), 2022e). It has been suggested (Van Buynder et al., 2021) that one of the key actions to maximize the uptake of both COVID-19 and SIV vaccines is for public health authorities to issue clear, consistent, timely and repeated communications on the importance and urgency of having both vaccinations. Our results corroborate this suggestion: among the various information sources on SIV, only people's trust in public health institutions was associated with a greater likelihood of COVID-19/SIV co-administration. Trust in government and health authorities is a well-known facilitator of vaccine uptake (Larson et al., 2018), including SIV (Prematunge et al., 2012) and COVID-19 (Q. Wang et al., 2021) vaccines. The degree of trust/mistrust varies according to structural and contextual factors; most people may implicitly trust institutions, but at the same time question their competency (Jamison et al., 2019). It is therefore likely that an increase in laypeople's confidence in public health authorities will reduce vaccination hesitancy at the population level. To achieve this, institutional communication efforts on immunization should be based on best practices of risk communication science and social marketing, which rallies citizens around shared values (Udow-Phillips & Lantz, 2020).

We established that both COVID-19 and SIV were independent correlates of a positive attitude towards vaccine co-administration, and the main effect of each one did not depend on the level of the other (no significant interaction was found). The available systematic evidence suggests that previous SIV receipt is a strong predictor of subsequent COVID-19 vaccination acceptance (Cascini et al., 2021; Luo et al., 2021; Nehal et al., 2021). Similarly, SIV uptake in previous seasons is associated with subsequent SIV receipt (Kan & Zhang, 2018; Nagata et al., 2013; Yeung et al., 2016). Moreover, COVID-19 vaccination status is also a strong correlate of 2021/22 SIV receipt (Domnich et al., 2021). In California, a decreasing trend in intentions to receive both COVID-19 and SIV vaccines was observed once the first COVID-19 vaccines were available (Fridman et al., 2021). Finally, one Italian study (Gerussi et al., 2021) found that being hospitalized for COVID-19 during the first pandemic wave was associated with the willingness to receive SIV but not COVID-19 vaccine. Causal pathways of this bidirectional COVID-19–SIV relationship therefore appear very complex and deserve further investigation in a longitudinal modality.

Acceptance of vaccine co-administration was higher among participants who had actively searched for information on SIV in the preceding weeks. In this regard, it has been demonstrated that only active seeking for information is associated with greater SIV uptake, while simple passive exposure to such information is not (Cheung et al., 2017). We can speculate that, in our sample, active seekers of SIV-related information had a higher probability of finding evidence-based information on COVID-19/SIV co-administration. Indeed, the first search result displayed by Google on typing "Influenza vaccine 2021" shows that "*During the 2021/2022 season, the flu shot may be done together with the COVID-19 shot*"; this message is located at the website of the Italian Ministry of Health (Italian Ministry of Health, s.d.-a). Again, the role of public health institutions in keeping their websites updated and delivering not only unambiguous but also user-friendly information remains crucial.

Being offered a more personalized SIV was associated with a 55% increase in the odds of having a positive attitude towards COVID-19/SIV vaccine co-administration. The market of available SIVs is highly differentiated (Grohskopf et al., 2021; Italian Ministry of Health, 2021a) and some SIV types may be more appropriate for a given population group (Boccalini et al., 2019; Bonanni et al., 2018). Indeed, the immune response to SIV depends both on the vaccine type and on a variety of patient characteristics (Domnich et al., 2019). Similarly, the emerging evidence suggests that the available COVID-19 vaccine types (e.g., mRNA vs inactivated) present distinct immunogenicity profiles (McDonald et al., 2021), and this may form the basis of more personalized future vaccination schedules. Core theories in economics, psychology and social marketing underline the fact that decision-makers benefit from having more choice (Scheibehenne et al., 2009), and having more choice is associated with more positive patient outcomes than having no choice (Ogden et al., 2009). By recognizing that hesitant patients are amenable to modified interventions, personalization of the standardized immunization schedule and service may reduce non-compliance (Gofen & Needham, 2015).

With regard to COVID-9/SIV vaccine co-administration, an increasing number of randomized controlled trials report data on non-clinically significant inferences (from the point of view of both safety and immunogenicity) of co-administering the available COVID-19 vaccines with age-appropriate SIVs. As of December 2021, these data are available for the cell-based, recombinant, MF59-adjuvanted (when co-administered with either ChAdOx1 or BNT162b2) (Lazarus et al., 2021) and high-dose (when co-administered with mRNA-1273) (Izikson et al., 2022) SIVs. It is desirable that these co-administration data appear both in summaries of product characteristics (intended primarily for health professionals) and in package leaflets (intended primarily for patients) of both COVID-19 and influenza vaccines.

Other factors able to influence people's intention to receive COVID-19 and SIV vaccines concomitantly include perception of the risk of disease and its severity, the perceived risk–benefit ratio of vaccination, and some socio-structural determinants, such as age and sex. These factors have been extensively studied as modifiers of either COVID-19 (Cascini et al., 2021; Luo et al., 2021; Nehal et al., 2021; Q. Wang et al., 2021) or SIV (Kan & Zhang, 2018; Nagata et al., 2013; Yeung et al., 2016) vaccine acceptance/refusal. Thus, it is universally accepted that perceived disease susceptibility and vaccination benefits facilitate uptake. Much less clear is the effect of socio-cultural determinants on COVID-19 and SIV vaccination acceptance. The increasing age is usually associated with a higher vaccine acceptance (Cascini et al., 2021; Kan & Zhang, 2018; Luo et al., 2021; Nagata et al., 2013; Nehal et al., 2021; Q. Wang et al., 2021; Yeung et al., 2016). In our previous survey rounds (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021) both SIV uptake and acceptance were higher in older individuals. By contrast, in this study an inverse age–acceptance relationship was observed: each 1-year increase in age was associated with a 1.1% decrease in the odds of accepting simultaneous vaccine administration. In the above-mentioned study by Stefanizzi et al. (Stefanizzi et al., 2022), the effect of age on concomitant COVID-19/SIV vaccine administration among healthcare workers was not statistically significant. In England and Wales, SIV and pneumococcal vaccine co-administration was highest in working age adults, followed by the elderly and children (Selya-Hammer et al., 2015). In our opinion, the lower COVID-19/SIV co-administration acceptance in older subjects may be driven by general tendency of the latter to be more cautious about adopting novel health-related technologies and practices. Similarly, the effect of sex on vaccine acceptance is controversial although it appears that females tend to have lower acceptance rates for both vaccines (Cascini et al., 2021; Luo et al., 2021; Nagata et al., 2013). It is even more unclear whether this different acceptance (if any) may generate gender disparities in vaccination coverage. In line with our findings [reversed aOR males vs females of 1.78 (95% CI: 1.50–2.12)], COVID-19/SIV vaccine co-administration was more prevalent among male healthcare workers with an OR 1.43 (95% CI: 1.22–1.67) (Stefanizzi et al., 2022). SIV and pneumococcal vaccine co-administration more frequently (by approximately 6%) than women, and this difference was present in all age-groups, while the between-sex difference in the general pneumococcal vaccination coverage rate was not statistically significant (Selya-Hammer et al., 2015). In sum, the effect of age and gender on vaccine co-administration acceptance should be further investigated.

Last but not least, an increasing amount of experimental and observational research (Debisarun et al., 2021; Marín-Hernández et al., 2021; R. Wang et al., 2021) suggests that SIV may exert non-specific protective effects against SARS-CoV-2 infection by inducing trained immunity, whereby "*the long-term functional reprogramming of innate immune cells is evoked by exogenous or endogenous insults and leads to an altered response towards a second challenge after the return to a non-activated state*" (Netea et al., 2020). We believe that this is another argument that should be incorporated into the communication mix regarding the benefits of COVID/SIV vaccine co-administration.

This study may have several limitations. First, as in all web-based studies, we systematically excluded people with no Internet access. Although Internet penetration in Italy is relatively high, a considerable proportion of citizens still do not use the web. For instance, only 47.3% and 14.9% of the elderly (who are the main target of both COVID-19 and influenza vaccines) aged 65‑74 and ≥75 years, respectively, are Internet users (Italian Institute of Statistics, s.d.). Different patterns of exposure to vaccine-related information may generate some variability in KAP with regard to both COVID-19 and influenza vaccination between Internet users and non-users (e.g., Internet users are likely to be more exposed to anti-vaccination web content). Second, although the study participants were assured about the anonymity of their responses, the social desirability bias cannot be completely ruled out. For instance, in the COVID-19 era, SIV may be seen as more socially favorable, and this may explain the higher than officially reported (Italian Ministry of Health, s.d.-b) 2020/21 SIV uptake. Third, it is unclear whether our results can be generalized to other contexts. Indeed, as our search of the principal scientific databases did not produce any similar study, no direct comparisons could be made. Finally, the cross-sectional nature of the survey did not allow us to establish any causal relationship.

To conclude, as COVID-19/SIV co-administration is a novel public health practice, laypeople's hesitancy towards this practice is prevalent and seems to be higher than hesitancy towards either vaccine administered alone. Acceptance of vaccine co-administration is driven by a variety of socio-structural, individual and contextual determinants, which should be incorporated into a tailored communication mix, in which public health institutions will play the central role. As shown by the recent Australian experience (Van Buynder et al., 2021), correct, unambiguous, timely and multi-channel communication and training of healthcare providers in COVID-19 and SIV co-administration is essential in order to maximize the opportunity to vaccinate.

Chapter 4. Increasing Influenza Vaccination Uptake by Sending Reminders: A Representative Cross-Sectional Study on the Preferences of Italian Adults

Declarations

This chapter is a slightly modified version of the manuscript entitled "Increasing Influenza Vaccination Uptake by Sending Reminders: A Representative Cross-Sectional Study on the Preferences of Italian Adults" by Alexander Domnich, Riccardo Grassi, Elettra Fallani, Giulia Costantini, Donatella Panatto, Matilde Ogliastro, Marco Salvatore, Maura Cambiaggi, Alessandro Vasco, Andrea Orsi, Giancarlo Icardi (© 2023 by the authors) published in Vaccines (Domnich, Grassi, et al., 2023). The article is published in open access modality and distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), which permits any use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

4.1 Introduction

Seasonal influenza vaccination (SIV) is an important public health strategy to prevent severe disease and several population groups, including older adults, subjects with underlying health conditions, pregnant women, children, and healthcare workers may benefit from annual immunization (World Health Organization (WHO), 2022). Despite these direct benefits for healthcare systems and the overall welfare of society, SIV coverage is still insufficient in most industrialized and developing countries (Palache et al., 2021).

Strategies to increase SIV uptake may be broadly summarized as interventions that (i) increase community demand, (ii) enhance access, and (iii) target healthcare providers or systems (Thomas & Lorenzetti, 2018). The central role of improving people's demand for SIV (also through addressing vaccination hesitancy) may be exemplified by the effect of the ongoing COVID-19 pandemic on SIV coverage. During the first pandemic phases (and before COVID-19 vaccines became available) public acceptance of SIV increased and previously eligible but unvaccinated people received their SIV for the first time (Bachtiger et al., 2021; Domnich, Cambiaggi, et al., 2020). Conversely, once mass COVID-19 vaccination campaigns were rolled out, a significant decrease in SIV uptake has been reported (Leuchter et al., 2022). This polarizing effect may be easily traced in Italy: while the 2020/21 SIV coverage in older adults aged ≥ 65 years registered a relative gain of 20% (passing from 54.6% in the 2019/20 season to 65.3% in the 2020/21 season), in the 2021/22 season the SIV coverage dropped to 58.1% with an 11% relative decrease (Italian Ministry of Health, s.d.-b).

In Europe, some countries like the United Kingdom (UK) and the Netherlands are more successful in approaching the minimum required SIV coverage in at-risk populations of 75%, especially in older adults (European Centre for Disease Prevention and Control (ECDC), 2018). These two benchmark countries were the first to implement comprehensive national guidelines on the roll-out of SIV campaigns, which were developed with a strong endorsement of general practitioners (GPs) (Kassianos et al., 2016). The best practices from these two countries suggest that the identification followed by a personal written notification sent to all eligible individuals have the greatest effect on increasing SIV uptake (Kassianos et al., 2016). Accordingly, following a reform of the vaccination policy in the Netherlands, all individuals aged ≥65 years (and also those turning 65 between September and May) receive a personalized invitation letter for free SIV. Moreover, an additional stock of vaccines is provided to GPs to further increase opportunity to vaccinate all eligible people (Van Ourti & Bouckaert, 2020). A large UK survey of GPs (Dexter et al., 2012) has shown that sending personal invitations for all patients (not just catch-up invitations to those who did not respond to an initial general publicity campaign) was associated with the highest SIV uptake among older adults. Of note, interventions based on traditional paper-based or electronic invitations to attend for SIV have among the lowest total costs (Anderson et al., 2018).

In Italy, SIV is currently offered free-of-charge to older adults aged ≥ 60/65 years, pregnant women, subjects with underlying health conditions, children aged 6 months to 6 years, workers at high risk of exposure (e.g., healthcare workers) and other professionals of primary public importance and some other categories (Italian Ministry of Health, 2022b). SIV campaign usually starts in mid-October and most doses are administered by GPs, who are remunerated for each vaccination performed (Barbieri et al., 2017). On the other hand, there is no nationwide active invitation program, and such initiatives are mobilized only by some Regional Health Departments (HDs) and/or local health units (LHUs). Indeed, both SIV uptake and associated policies in Italian regions are highly inhomogeneous (Barbieri et al., 2017; Fallani et al., 2021).

The available implementation research converges on the idea that targeted and proactive interventions may increase SIV uptake (Rizzo et al., 2018). It is also known that public trust in SIV-related information varies by information source (Domnich, Cambiaggi, et al., 2020) and some people prefer one communication channel over others (Tam et al., 2018). In this study, we aimed to explore projected effectiveness and attractiveness of active invitation to undergo SIV, triggered by different sources and delivered by different communication channels, in a nationally representative sample of Italian adults. In particular, there were two main study hypotheses. Based on the above-described UK study (Dexter et al., 2012), we first hypothesized that subjects who had previously received any form of reminder to get SIV would show a greater vaccination uptake and that people's preferences regarding different reminder sources varies. Our second hypothesis was that people's preferences regarding different communication channels differ (Ilozumba et al., 2021; Murphy et al., 2021).

4.2 Methods

4.2.1 Study design and procedures

This cross-sectional study was conducted between October 24 and November 10, 2022 and represents the fourth wave of a longitudinal computer-assisted web interviewing (CAWI) survey, which was established in 2020 with the aim to monitor changes in knowledge, attitudes and practices (KAP) on influenza and SIV in a panel of Italian adults (Domnich, Cambiaggi, et al., 2020). The inclusion criteria were as follows: (i) age ≥ 18 years, (ii) Internet access, (iii) residence in Italy and (iv) voluntary informed consent. Each survey round aimed to reach at least 2,000 responses. For the present survey, a total of 3,247 invitations were sent. These were selected from a pool of approximately 60,000 well-characterized individuals registered in the SWG database. In order to be representative of the adult Italian population, the selection was performed in a two-stage probabilistic quota modality, the details of which may be assessed elsewhere (Domnich, Cambiaggi, et al., 2020). The questionnaires used for each survey wave were composed of both recurring core items on SIV-related KAP and novel items introduced each time in order to reflect changes in influenza epidemiology and preventive strategies. Both recurring questionnaire items and results of the previous survey waves may be assessed in our previous publications (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021, 2022). This study is instead focused on the items introduced for the first time during the fourth survey wave and are described later in the text. Participants, who were active members of the SWG dataset, were invited to participate via email. This letter contained general information about the study aim and execution modality and a direct link to the password-protected survey. Before starting the survey, all participants were informed that participation in the study was voluntary, the responses provided would be analyzed in anonymized form, and who the data processor and owner was. After that, all participants provided their written informed consent. The survey had no time limits, a clearly visible progress indicator, one item per screen, and all items were mandatory to reply. This non-interventional, opinion-based web survey was conducted in accordance with all applicable Italian laws and regulations, including the General Data Protection Regulation.

4.2.2 Study outcomes

The past experience with receiving reminders to get SIV was measured on a single-choice matrix item "Have you ever received an invitation to get a flu shot delivered to you by. . ." (i) your GP; (ii) other specialist physicians you are in contact with; (iii) your pharmacist; (iv) your LHU; (v) HD of your region; (vi) your relatives or friends. The responses were coded as (1) Yes and (0) No. For this item, the independent binary variable of interest was the past season (2021/22) SIV uptake (1 = vaccinated). To further confirm or reject the first study hypothesis, we also measured the participants' attitudes toward SIV and associated reminders for the upcoming 2022/23 season. In particular, we asked subjects to reply on a matrix/rating scale item entitled "How would you judge a personal invitation to get a flu shot delivered to you by..." with the same six response options. Each of these response options was ranked on a 5-point Likert scale (5: Strongly positively; 4: Positively; 3: Neither positively nor negatively; 2: Negatively; 1: Strongly negatively). For this item, the predictor of interest was the intention to receive the 2022/23 SIV (Do you intend to have a flu shot in the upcoming season?), which was measured on a 5-point Likert scale (5: Yes definitely; 4: Probably yes; 3: I don't know; 2: Probably not; 1: Definitely not). To test the second hypothesis on the different preferences regarding different communication channels, subjects were asked to indicate a preferred channel for this personal invitation, by selecting one of the following: (i) phone call; (ii) postal letter; (iii) email; (iv) text/instant message on mobile phone; (v) I don't want to receive any invitation.

4.2.3 Study variables

Sociodemographic characteristics included sex, age, place of residence and socio-economic status (SES). Regions of residence were categorized into three macro-areas of North (Aosta

Valley, Liguria, Lombardy, Piedmont, Emilia-Romagna, Friuli-Venezia Giulia, Trentino-South Tyrol and Veneto), Center (Lazio, Marche, Tuscany and Umbria) and South (Abruzzo, Apulia, Basilicata, Calabria, Campania, Molise, Sicily and Sardinia). SES was assessed on the dimensions of education background, personal income and occupation pattern. In particular, three levels of education were distinguished, namely low (middle school or lower), medium (high/secondary or vocational school) and high (university degree or higher). Perceived income was classified into low, lower than average, average, higher than average, high and no personal income. Finally, people's occupation pattern could be one of the following: employed, student, housekeeper, retired, unemployed or other.

4.2.4 Statistical Analysis

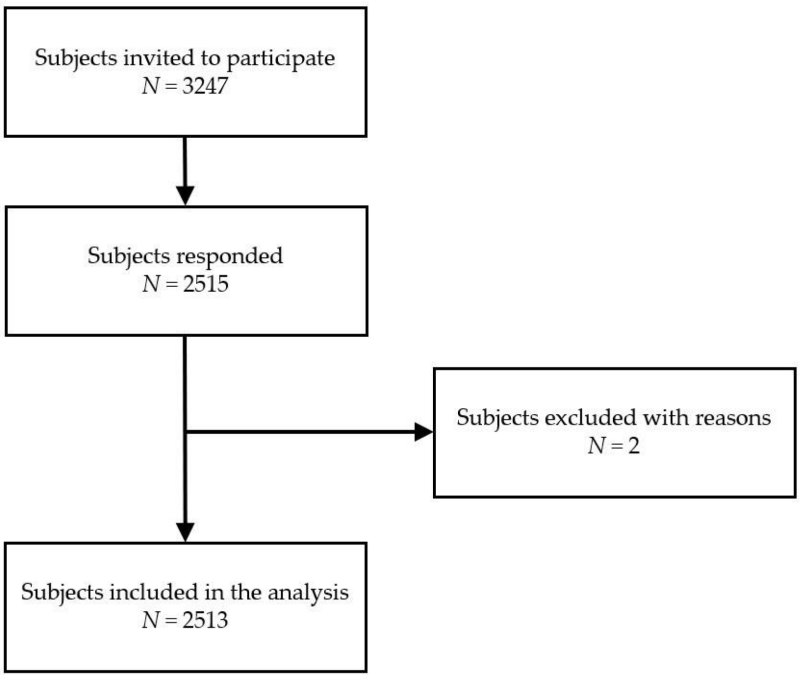
Categorical variables were expressed as percentages with Clopper–Pearson exact 95% confidence intervals (CIs), while continuous variables were reported as medians with interquartile ranges (IQRs). Proportions were compared by means of the Chi-square test. Cochran Q with Bonferroni-corrected post-hoc McNemar tests were used to verify the null hypothesis on the equal distribution of Likert scale-based variables. As SIV in Italy is currently recommended for all older adults aged ≥60 years (Italian Ministry of Health, 2022b), a subgroup analysis by age (18–59 vs. ≥60 years) was also conducted. To correct for potential confounders, multivariable logistic regression was used to obtain adjusted odds ratios (aORs) on the association between SIV uptake and past receipt or potential attractiveness of reminders to get vaccinated. During the model fitting, a strong collinearity (variance inflation factors > 10) was observed between the nominal variables of occupation pattern and perceived income. Considering that the latter explained more variance, we retained the variable of income in all adjusted models. When the Likert scale-based outcome variable of the likelihood of being administered the 2022/23 SIV was modelled in the ordinal logistic regression, a significant (Brant test: $p < 0.001$) violation of the proportional odds assumption was observed. This variable was therefore dichotomized into (0) will unlikely get vaccinated (responses "I don't know", "Probably not", and "Definitely not") and (1) likely get vaccinated (responses "Probably yes" and "Yes definitely"). The robustness of the base case model was verified in a sensitivity analysis by changing the classification rule, that is the response option "Probably yes" was moved to the category (0). All statistical analyses were carried out in R software (packages "stats", "PropCIs", "MASS", "car", "rstatix", and "brant") v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

4.3 Results

4.3.1 Characteristics of the study participants

Of 3,247 invitations sent, a total of 2,515 unique responses were received (response rate of 77.5%). Non-responders were similar to responders in terms of sex and macroarea of residence but were younger (60.3% of non-responders were 18–34 years). Two (0.1%) subjects were residing abroad and were excluded. In summary, responses from 2513 subjects were analyzed (**Figure 4.1**).

Figure 4.1. Flowchart of the study participants.



The principal sociodemographic characteristics of the study participants are reported in **Table 4.1**. Briefly, their median age was 51 (IQR 37-66, range 18-84) years and both sexes were approximately equally distributed. Most subjects resided in the Northern Regions, achieved at least middle school, were employed and declared average or higher income. A total of 46.4% reported receipt of the 2021/22 SIV. As expected, the self-reported 2021/22 SIV uptake was significantly ($p < 0.001$) higher in participants aged ≥60 years (68.2%; 95% CI: 65.0–71.3%) than those aged 18–59 years (34.4%; 95% CI: 32.1–36.7%).

Table 4.1. Sociodemographic characteristics of the study participants (N = 2,513).

Characteristic	Level	% (n)	95% CI
Sex	Female	52.01 (1,307)	50.03-53.98
	Male	47.99 (1206)	46.02-49.97
Age, years	18–24	8.16 (205)	7.12-9.30
	25–34	12.65 (318)	11.38-14.02
	35–44	15.60 (392)	14.20-17.08
	45–54	19.30 (485)	17.77-20.90
	55–64	16.87 (424)	15.43-18.39
	65–74	19.78 (497)	18.24-21.39
	≥75	7.64 (192)	6.63-8.75
Geographic area	North	46.24 (1,162)	44.28-48.21
	Center	20.06 (504)	18.51-21.68
	South	33.70 (847)	31.86-35.59
Education level	Low	9.91 (249)	8.77-11.14
	Medium	48.79 (1,226)	46.81-50.76
	High	41.31 (1,038)	39.37-43.26
Occupation status	Employed	56.39 (1,417)	54.42-58.33
	Student	6.84 (172)	5.89-7.90
	Housekeeper	7.84 (197)	6.82-8.96
	Retired	23.08 (580)	21.44-24.78
	Unemployed	4.38 (110)	3.61-5.25
	Other	1.47 (37)	1.04-2.02
Perceived income	Low	2.87 (72)	2.25-3.59
	Lower than average	8.04 (202)	7.00-9.17
	Average	33.19 (834)	31.35-35.07
	Higher than average	38.48 (967)	36.57-40.41
	High	1.71 (43)	1.24-2.30
	No personal income	15.72 (395)	14.32-17.20
2021/22 influenza vaccination	No	53.64 (1,348)	51.67-55.61
	Yes	46.36 (1,165)	44.39-48.33

4.3.2 Association between active invitation and influenza vaccination uptake

Approximately half of participants (52.16%, 95% CI 50.63-54.57%) had previously received at least one invitation to get vaccinated against seasonal influenza. Receipt of any reminder was significantly higher in older adults aged ≥60 years (68.8%; 95% CI: 65.6–71.8%) than in younger adults aged 18–59 years (43.7%; 95% CI: 41.3–46.2%). The 2021/22 SIV coverage among individuals who were invited (68.2%; 95% CI: 65.6–70.7%) to get vaccinated was about three times higher than among those who did not receive any reminder (22.2%; 95% CI: 19.8–24.6%) with an aOR of 6.47 (95% CI: 5.35–7.83). As shown in **Table 4.2**, most reminders came from participants' GPs (39.3%; 95% CI: 37.4–41.2%), followed by friends or relatives (22.8%; 95% CI: 21.1–24.5%) and specialist physicians (16.2%; 95% CI: 14.8–17.7%). Reminders from LHUs (13.0%; 95% CI: 11.7–14.4%), HDs (12.5%; 95% CI: 11.2–13.8%), and pharmacists (11.5%; 95% CI: 10.3–12.8%) were less prevalent. However, in the fully adjusted model, only invitations made by GPs, specialist physicians, and LHUs were associated with the past season SIV receipt (**Table 4.2**).

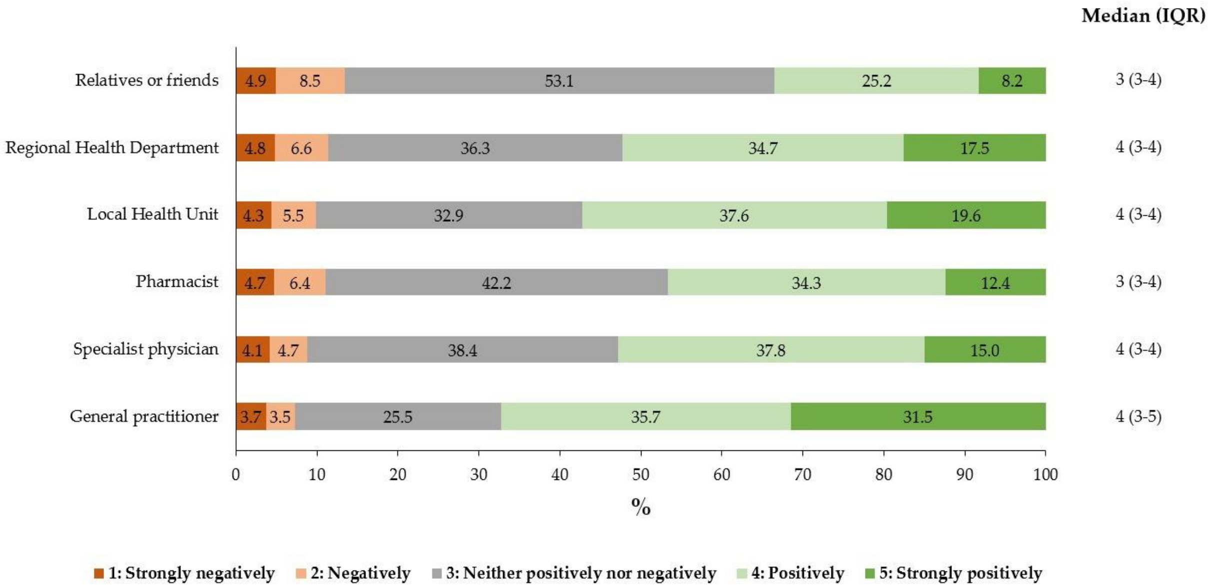
Table 4.2. Association between previous receipt of an invitation to get vaccinated and self-reported influenza vaccination in the 2021/22 season, by source of invitation (N = 2,513).

Received invitation to get vaccinated from		**Vaccinated, % (n)**	**Non vaccinated, % (n)**	**OR (95% CI)**	**aOR (95% CI)[a]**
General practitioner	No	36.91 (430)	81.31 (1,096)	Ref	Ref
	Yes	63.09 (735)	18.69 (252)	7.43 (6.20-8.91)	4.43 (3.60-5.48)
Specialist physician	No	73.65 (858)	92.51 (1,247)	Ref	Ref
	Yes	26.35 (307)	7.49 (101)	4.42 (3.47-5.62)	2.23 (1.64-3.05)
Pharmacist	No	81.97 (955)	94.14 (1,269)	Ref	Ref
	Yes	18.03 (210)	5.86 (79)	3.53 (2.69-4.37)	1.16 (0.80-1.67)
Local Health Unit	No	80.34 (936)	92.73 (1,250)	Ref	Ref
	Yes	19.66 (229)	7.27 (98)	3.12 (2.43-4.01)	1.54 (1.09-2.18)
Regional Health Department	No	81.20 (946)	93.03 (1,254)	Ref	Ref
	Yes	18.80 (219)	6.97 (94)	3.09 (2.39-3.99)	1.11 (0.78-1.59)
Relatives/friends	No	68.15 (794)	85.09 (1,147)	Ref	Ref
	Yes	31.85 (371)	14.91 (201)	2.67 (2.20-3.24)	1.26 (0.98-1.62)

[a]Adjusted for sex, age group, area of residence, education level, perceived income and other invitation sources.
aOR: adjusted odds ratio; OR, odds ratio.

Regarding the attractiveness (responses “positively” or “strongly positively”) of single invitation sources, people’s ratings were unequally distributed ($p < 0.001$) in the following descending order: GP, LHU, specialist physician, HD, pharmacist, relatives/friends (**Figure 4.2**). All pairwise comparisons were highly significant ($p < 0.001$) except that between specialist physician and HD ($p > 0.99$).

Figure 4.2. Distribution of the participants' judgements on the sources of personal invitations to get influenza vaccination.



A total of 46.92% (95% CI 44.95-48.89%) of respondents declared their willingness (29.13% and 17.79% replied "Yes definitely" or "Probably yes", respectively) to receive the 2022/23 SIV. Compared with younger adults (70.2%; 95% CI: 67.1–73.2%), this proportion was higher ($p < 0.001$) among ≥60-year-olds (34.1%; 95% CI: 31.8–36.5% As shown in **Table 4.3** (Model 1), each 1-point Likert scale increase in the perceived attractiveness of receiving an invitation from GP or LHU were associated with 81% and 51% increase in the odds of the likelihood of receiving the 2022/23 SIV. Other invitation sources did not reach $\alpha < 0.05$. The results of the sensitivity analysis, when only people who would definitely receive the 2022/23 SIV were considered as success (Model 2), were similar to the base-case, although invitation delivered by the own pharmacists turned statistically significant with an aOR of 1.30 (95% CI 1.02-1.68) (**Table 4.3**).

Table 4.3. Association between the likelihood of receiving the 2022/23 season influenza vaccination and attractiveness of single invitation sources to get vaccinated (N = 2,513).

Received invitation to get vaccinated from (reference category = No)	Model 1[a] aOR (95% CI)[b]	Model 2[c] aOR (95% CI)[b]
General practitioner	1.81 (1.44-2.28)	1.68 (1.32-2.15)
Specialist physician	1.00 (0.79-1.27)	1.12 (0.87-1.45)
Pharmacist	1.09 (0.86-1.38)	1.30 (1.02-1.68)
Local Health Unit	1.51 (1.17-1.95)	1.42 (1.08-1.88)
Regional Health Department	1.16 (0.92-1.47)	0.98 (0.76-1.28)
Relatives/friends	1.10 (0.89-1.36)	1.03 (0.83-1.27)

[a]5-point Likert-based outcome variable of the likelihood of receiving the 2022/23 season dichotomized and coded as (0) for the responses "I don't know", "Probably not" and "Definitely not" and (1) for the responses "Probably yes" and "Yes definitely".

[b]Adjusted for sex, age group, area of residence, education level, perceived income, past season influenza vaccination, previous receipt of invitations to get vaccination.

[c]5-point Likert-based outcome variable of the likelihood of receiving the 2022/23 season dichotomized and coded as (0) for the responses "I don't know", "Probably not" and "Definitely not" and "Probably yes" and (1) for the response "Yes definitely".

aOR: adjusted odds ratio.

4.3.3 Preferences on the invitation delivery mode

Digital communication channels, such as text/instant messaging (24.6%) and email (27.2%), were preferred by about half of respondents. Traditional postal letters (17.0%) or phone calls (8.6%) were less preferred. By contrast, 22.6% of individuals did not want to receive any reminder. When analyzed by age group, it emerged that compared with younger adults, significantly more ($p < 0.001$) subjects aged ≥60 years preferred text/instant messages (30.0% vs. 21.6%). Conversely, a significantly ($p = 0.005$) higher proportion of younger adults (24.4% vs. 19.4%) did not want to receive any reminder (**Table 4.4**). On considering that most individuals preferred digital communication channels, a post-hoc analysis on the comparison between subjects who preferred email and text messages was performed. When adjusted for the previously received communications and past season vaccination, subjects with the highest income (aOR high income vs. low income 4.56, p = 0.030) and those living in Central Italy (aOR Central Italy versus Northern Italy 1.54, p = 0.006) preferred email over text messaging. Of note, no differences between sexes, age groups, education level, and previous season SIV uptake emerged, suggesting that both email and text messaging would almost equally reach the target populations.

Table 4.4. Preferred communication channels to be invited to get influenza vaccination (N = 2,513).

Communication Channel	**Total (N= 2,513)**		**18–59 Years (N= 1,623)**		**≥60 Years (N= 890)**	
	% (n)	**95% CI**	**% (n)**	**95% CI**	**% (n)**	**95% CI**
Phone call	8.6 (216)	7.5–9.8	8.3 (135)	7.0–9.8	9.1 (81)	7.3–11.2
Postal letter	17.0 (427)	15.5–18.5	18.0 (292)	16.2–19.9	15.2 (135)	12.9–17.7
Email	27.2 (683)	25.5–29.0	27.7 (449)	25.5–29.9	26.3 (234)	23.4–29.3
Text/instant message	24.6 (618)	22.9–26.3	21.6 (351)	19.6–23.7	30.0 (267)	27.0–33.1
I do not want to receive any invitation	22.6 (569)	21.0–24.3	24.4 (396)	22.3–26.6	19.4 (173)	16.9–22.2

4.4 Discussion

This is the first Italian study to investigate public experience and perception of reminders to get vaccinated against seasonal influenza and some important correlates of this latter have been established. The main study strength is a large sample size of a representative and well-characterized cohort of Italian adults. Here, we demonstrated that half of Italian adults has been previously exposed to some form of reminders to get SIV and these individuals showed significantly higher odds of being vaccinated. Analogously, intentions to get the next season SIV were higher among subjects who perceived more attractive reminders sent by their GP, even when adjusted for the previous season vaccination, age, and other confounders. We therefore confirmed our first hypothesis. We also validated our second hypothesis on the differences in people's preferences regarding various communication channels: digital channels were favored by most participants.

The principal source of this invitation was participants' GP who, among other sources, showed the highest effect size on the past SIV receipt. This finding is in line with the results reported by Dexter et al. (Dexter et al., 2012) who documented the highest (P=.003) SIV coverage among older adults who received a personal invitation from their GPs. Indeed, a systematic review by Kohlhammer et al. (Kohlhammer et al., 2007) highlighted that the recommendation by GPs is among the strongest positive predictors of SIV. Analogously, GPs were attributed a comparably high ranking as a source of future reminders and subjects who assigned higher scores to GPs were more prone to be vaccinated in the next season. Although SIV hesitancy among Italian GPs seems uncommon and most of them implement some initiatives to engage proactively their patients (Levi et al., 2018; Vezzosi et al., 2019), influenza- and SIV-related knowledge among GPs may be suboptimal. For instance, Vezzosi et al. (Vezzosi et al., 2019) have reported that only 38.9% of GPs in Parma (Northern Italy) were aware of the minimal recommended SIV coverage rate in at-risk groups of 75%. Considering both a steady progress in the development of novel SIV formulations (Moore et al., 2021) and increasing availability of high-level evidence on the effectiveness and safety of SIV, national/regional public health authorities, scientific societies and GP associations should ensure effective forms of continuous medical education activities on the topic, in which a maximum number of GPs are incentivized to take part. In summary, our results confirm the central role of GPs in SIV-related decision making and underline that future health promotion and social marketing interventions to increase SIV coverage rates in Italy should not be planned or executed without endorsement of GPs.

Our second major finding is that the majority of Italian adults preferred digital channels like mobile phone messages (27.19%) or emails (24.59%), while the proportion of those who preferred more traditional phone calls (8.60%) or postal letters (16.99%) was substantially lower. This may also indicate acceleration in the communication paradigm shift towards digital technologies; indeed, the COVID-19 pandemic has sped up digital transformation of the Italian public service (Agostino et al., 2021). The available systematic evidence (Dumit et al., 2018; Frascella et al., 2020) converges on the idea that eHealth/mHealth reminders to increase vaccination uptake is overall effective and cost-effective when compared with "do noting" strategies. For example, a randomized controlled trial (RCT) on 12,354 at-risk subjects (Regan et al., 2017) has found that compared to the non-intervention group, individuals who received a text message showed a 39% increase in SIV uptake. However, when comparing effectiveness of single traditional and digital channels, some discrepancies emerge. Thus, vaccination completion rate among the United States (US) adolescents was 32.1% among those reached by text messaging, as compared with 23.0% and 20.8% contacted via postal letter or email, respectively. Of note, the average costs were $4.65 per postal letter and $3.09 per either email or text message (Morris et al., 2023). On the other hand, a recent large RCT (Mehta et al., 2022) has documented no detectable increase in COVID-19 vaccination uptake among US adults receiving text messaging compared with telephone calls only. These apparent inconsistencies are likely driven by a number of factors, including study design, healthcare model in which the study was carried out, type of vaccination, and target population. Interestingly, when individuals who preferred to be invited by email or text messaging were compared directly, no differences in terms of their sex, age, educational background or previous season vaccination emerged. This finding is of certain importance, especially for the universal healthcare models like in Italy, as it may signify an almost equal reachability of the principal target populations. Providing that both email and text messaging were preferred in similar proportions, we believe that based on the available infrastructure and operational complexities single Italian regions may opt for one or another channel. Although our study did not allow for establishing whether a simultaneous adoption of both email and text messaging could have an additive effect, the previous UK experience (Dexter et al., 2012) has shown that using two communication channels together was not associated with a further increase in SIV coverage. We speculate that the highest impact of sending emails or text messages on the SIV uptake would be seen in younger age groups (as compared, for example, with people aged ≥75 years, where SIV coverage is relatively high). Indeed, in Europe and Italy the older age is directly associated with higher GP consultation rates and most so-called frequent GP attenders are seniors (Welzel et al., 2017). In turn, two thirds of Italian GPs adopt opportunistic approach by offering SIV during a patient's unrelated visit (Levi et al., 2018).

Finally, our study highlighted a decreasing trend in SIV acceptance: compared with the past year (Domnich et al., 2021), the willingness of receiving SIV dropped from 48.6% to 46.9%. There is therefore an urgent need to implement effective strategies able to reverse this negative trend. Our results suggest that personal reminders, preferably sent by GPs via digital channels may be of aid. A similar decreasing trend (from the 2020/21 to 2022/23 seasons) in different target groups has been reported by the official statistics in both Italy (Italian Ministry of Health, s.d.-b) and the US (Centers for Disease Control and Prevention (CDC), 2023c). An initial increase observed in the 2020/21 season is likely driven by a higher effectiveness and reachability of the SIV campaign during the first months of the COVID-19 pandemic when no COVID-19 vaccines were available and there were concerns regarding SARS-CoV-2 and influenza virus co-circulation (Domnich et al., 2021; Giacomelli et al., 2022). It has been suggested (Nazareth et al., 2022; Pascucci et al., 2022) that the subsequent decrease in the 2021/22 and 2022/23 SIV uptake may be linked to safety concerns and mistrust of COVID-19 vaccines, which resulted in a more pronounced hesitancy toward SIV. Pascucci et al. (Pascucci et al., 2022) proposed that when COVID-19 vaccines had become available, some individuals expressed concerns over the administration of both SIV and COVID-19 vaccines within a short period and thus prioritized COVID-19 vaccination. Finally, it could also be that the 2021/22 and 2022/23 SIV promotional campaigns were less effective than that conducted during the unprecedented 2020/21 season and therefore SIV coverage rates started to return to the pre-pandemic levels. In summary, there is an urgent need to implement effective strategies able to reverse this negative trend. Our results suggest that personal reminders, preferably sent by GPs via digital channels, may be of aid. We noted three main study shortcomings that may affect the study results and their interpretation. The first limitation is the self-reported SIV status, which may have induced exposure misclassification bias. One the one hand, a validation study by King et al. (King et al., 2018) has demonstrated a high agreement (97.7% and 93.2% for the current and prior seasons, respectively) between the self-disclosed and registered SIV uptake. On the other hand, it has been also shown (Mac Donald et al., 1999) that while sensitivity of the self-reported SIV is as high as 100%, its specificity is substantially lower (79%). In other words, some people may overreport their actual SIV uptake owing to recall or social desirability biases. Indeed, SIV coverage observed in our study was higher than that officially reported (20.5% and 58.1% for general and elderly population, respectively) (Italian Ministry of Health, s.d.-b) and this was primarily driven by working-age adults. A similar discrepancy has been reported in another large Italian web-based survey (Giacomelli et al., 2022). Another possible explanation may be that out-of-pocket private purchase of vaccines (i.e., healthy adults for whom no reimbursement is currently provided) could be not registered in the official workflows. Secondly, as in all web-based surveys, our results may be prone to the coverage bias due to digital divide and therefore may not be representative of adults with no Internet access. While we have almost no concerns regarding working-age adults, older adults and especially the oldest old (≥75 years, 7.64% of the whole sample) in our sample of internet users may systematically differ from non-users. The relationship between Internet use and SIV uptake appears complex. In the US (Khanijahani et al., 2021), compared with non-users, those who use Internet but not for health information have 8% (aOR 0.92, 95% CI 0.88-0.96) decreased odds of being immunized with SIV. No difference (aOR 1.01, 95% CI 0.97-1.05) between non-users and subjects who used Internet for informal health information only has been found. Moreover, users who searched Internet for formal or formal health information were more likely to get vaccinated than non-users (aOR 1.52, 95% CI 1.45-1.59) (Khanijahani et al., 2021). Thirdly, for ethical considerations, we were not able to collect data and perform separate analyses stratified by the presence of single co-morbidities. In particular, this may be relevant to working-age adults, as in this population group, the free-of-charge SIV is offered to subjects with co-morbidities only. Future research should cover this specific population target.

4.5. Conclusions

The results of this representative survey suggest that vaccination reminders may contribute to contrasting the recently observed decline in SIV coverage rates. Reminders sent by a GP, who is the main and most influential source of SIV-related information, and using digital channels like text/instant messaging or emails may have the greatest impact on vaccine uptake.

Chapter 5. An exploratory study to assess patterns of influenza- and pneumonia-related mortality among the Italian elderly

Declarations

This chapter is a slightly modified version of the manuscript entitled "An exploratory study to assess patterns of influenza- and pneumonia-related mortality among the Italian elderly" by Elettra Fallani, Andrea Orsi, Alessio Signori, Giancarlo Icardi and Alexander Domnich, (© 2021 by the authors) published in Human Vaccines & Immunotherapeutics (Fallani et al., 2021).

5.1 Introduction

Worldwide, influenza is one of the leading infectious disease in terms of both incidence and mortality rates (Cassini et al., 2018; World Health Organization (WHO), 2012). Seasonal influenza vaccination represents the most effective public health intervention able to reduce the burden of disease (de Lusignan et al., 2016; World Health Organization (WHO), 2012). Indeed, the World Health Organization's (WHO) most recent position paper (World Health Organization (WHO), 2012) has listed several priority targets for annual influenza vaccination: pregnant women, children aged 6 months to 5 years, the elderly, subjects with specific chronic conditions, healthcare workers and international travelers. Among these, the elderly is probably the most recognized target group; indeed, as per the European Centre for Disease Prevention and Control (ECDC), (Mereckiene, 2018) all European Union (EU) Member States recommend seasonal influenza vaccination for older adults.

Influenza vaccine (IV)-induced immunogenicity and/or protection is often poor in the elderly as a result of immunosenescence (Haq & McElhaney, 2014). In order to circumvent this unmet need, alternative IV formulations have been developed. The first worldwide available IV specifically developed for the elderly was that formulated as a standard-dose egg-based subunit trivalent IV including MF59® (Seqirus UK Ltd.) adjuvant (adjuvanted trivalent influenza vaccine; aTIV) (Tsai, 2013). Italy was the first country to adopt aTIV in 1997 (Tsai, 2013), where it was still available during 2020/21 influenza season. Other historically or currently commercialized IVs may also address immunosenescence, including: (i) virosomal (Calcagnile & Zuccotti, 2010); (ii) intradermal (Bragazzi et al., 2016) and (iii) high-dose IVs (Wells & Grobelna, 2019).
The rationale for this study was primarily driven by a gap in the understanding of association between influenza vaccination coverage (IVC) rates and influenza-associated mortality. For instance, a previous Italian ecological study (Rizzo et al., 2006) did not find any meaningful association between the IVC rate and influenza excess mortality over time. However, the study by Rizzo et al. (Rizzo et al., 2006) did not distinguish between different types of available IVs at that time. Indeed, in the paper by Rizzo et al. (Rizzo et al., 2006), dating back to 2006, it has been stated that "In Italy, more immunogenic vaccine with novel adjuvants has been introduced since 1997… but it is too early to evaluate their population impact". On the other hand, a more recent study (Bellino et al., 2020) conducted in the Province of Treviso (northeastern Italy) found that the risk of all-cause death was significantly lower (by 33–39%) in the vaccinated elderly (as compared with unvaccinated subjects) in three consecutive seasons (2014/15–2016/17). Of note, aTIV was the most frequently administered IV in Treviso (Bellino et al., 2020).
In the context of Italian fiscal federalism single regions, the autonomous provinces of South Tyrol and Trento (henceforth referred to as "regions") are granted a certain level of freedom to achieve their own public health goals (Barbieri & Capri, 2016). Regarding influenza immunization, each year the Italian Ministry of Health issues a circular on the prevention and control of influenza (Italian Ministry of Health, 2020); each region may then fully adopt the national recommendations or provide its own circular/recommendations (Barbieri & Capri, 2016; Boccalini et al., 2019).
Diversity in the adopted policies may result in both (i) the so-called "jeopardization" (Barbieri & Capri, 2016; Boccalini et al., 2019) of IVC rates [up to double difference

reported in the observed 2019/20 season IVC rates among older adults aged ≥65 years (Italian Ministry of Health, s.d.-b) and (ii) different patterns of use for the available types of IV (Barbieri & Capri, 2016; Boccalini et al., 2019).

The primary aim of this study was to explore spatiotemporal patterns of pneumonia- and influenza (P&I)-related mortality observed in Italian older adults aged 65 years or above. The second goal was to investigate the epidemiological association between the observed local P&I mortality among subjects aged ≥65 years and IVC rates and IV policy patterns.

5.2 Materials and Methods

5.2.1 Overall Study Design

This is a typical ecological study: we investigated officially registered P&I-related mortality in the elderly (defined here as subjects aged ≥65 years) at the level (i.e., unit) of Italian provinces (N=110) and/or regions (N=21) over seven consecutive post-pandemic seasons (2010/11–2016/17). In other words, we analyzed population groups and not single individuals. Both exploratory and analytical approaches were considered.

Readers interested in both strengths and limitations of the ecological study design are invited to read the paper by Morgenstern (Morgenstern, 1995); moreover, the limitations specific to this exploratory study will be discussed later in the manuscript.

In this paper we considered only the post-pandemic period (i.e., starting from season 2010/11). This choice was based on the fact that the pandemic 2009 A/H1N1 (A/H1N1pdm09) virus completely replaced the so-called seasonal A/H1N1 (A/H1N1s) that circulated before 2009 (Gasparini et al., 2013; Italian National Institute of Health, s.d.). Data for 2018 onwards were not considered since no officially reported P&I-related mortality estimates were available at the time of data extraction (as of December 2020) (Italian National Institute of Statistics (ISTAT), s.d.-a, 2022).

5.2.2 Data Sources

Most data came from the official Italian data flows publicly available from the Italian Ministry of Health (Italian Ministry of Health, s.d.-b), National Institute of Health ((Italian National Institute of Health, s.d.), National Institute of Statistics (Italian National Institute of Statistics (ISTAT), s.d.-a, 2022), and National Institute for Environmental Protection and Research (Italian National Institute for the Environmental Protection and Research (ISPRA), 2020). Data regarding quotas for different types of IV were provided by Seqirus S.r.l., Italy (company database of regional demands for individual types of IV, i.e., data on tender allotments). The variables considered and corresponding data sources are reported in **Table 5.1**.

Table 5.1. Data sources used in the analysis.

Data	Source	Ref
Pneumonia- and influenza-related mortality rate in subjects aged ≥65 years	Italian Institute of Statistics	(Italian National Institute of Statistics (ISTAT), 2022)
Regional population, by age	Italian Institute of Statistics	(Italian National Institute of Statistics (ISTAT), 2022)
Influenza vaccination coverage rate in subjects aged ≥65 years and general population	Italian Ministry of Health	(Italian Ministry of Health, s.d.-b)
aTIV regional allotments to the total vaccine doses	Seqirus internal data	(Seqirus srl, s.d.)
Public health expenditure per capita	Italian Institute of Statistics	(Italian National Institute of Statistics (ISTAT), 2022)
Population density	Italian Institute of Statistics	(Italian National Institute of Statistics (ISTAT), 2022)
Average low winter temperature	Italian Institute for the Environmental Protection and Research	(Italian National Institute for the Environmental Protection and Research (ISPRA), 2020)
Virus (sub)type distribution	Italian Institute of Health	(Italian National Institute of Health, s.d.)

5.2.3 Study Outcome

The study outcome was the country-/province-/region- and year-specific estimate of P&I-related mortality in older adults aged ≥65 years as per the European Shortlist for Causes of Death (N=65 causes) compatible with the three most recent International Classification of Diseases (ICD) versions for influenza (ICD-8: 470–474; ICD-9: 487; ICD-10: J10–J11) and pneumonia (ICD-8: 480–486; ICD-9: 480–486; ICD-10: J12–J18) codes (European Commission, s.d.; Italian National Institute of Statistics (ISTAT), 2022). For this reason, we extracted the readily available dataset (Italian National Institute of Statistics (ISTAT), 2022) on the P&I mortality rate (per 10,000 inhabitants) until the last available year of 2017 for the whole country, regions and provinces.

5.2.4 Spatiotemporal Analysis of Pneumonia- and Influenza-Related Mortality

Depending on data availability (Italian National Institute of Statistics (ISTAT), 2022), the spatiotemporal analysis could be conducted at the level of single provinces (N=110). For this reason, first we visually explored the observed province-specific P&I mortality rates separately by year. This was done by plotting choropleth maps.

Moran's I global spatial autocorrelation coefficients (Moran, 1950) were then computed in order to measure the overall clustering pattern of the observed mortality rates. The interpretation of Moran's I is similar to that of Pearson's r correlation coefficient: positive statistically significant I values indicate geographic patterns of spatial clustering, negative significant I estimates show clustering of dissimilar values, while non-significant values at $\alpha<0.05$ indicate complete spatial randomness. Considering that Italy has the two islands of Sicily and Sardinia, for Moran's I statistics the k nearest neighbor spatial weights matrix was used (Anselin, 2002). As a "rule-of-thumb" (Nadkarni, 2016) we set the value of k as the square root of the total number of observations (N=110); this means the k-value used was 10.

Providing that all and year-specific global I coefficients were statistically significant, we then further investigated the local indicators of spatial association (LISA) (Anselin, 1995). Choropleth maps were created to visualize the four types of clusters/outliers, namely hot-hot (hotspots), i.e., observations that signified provinces with a higher than average mortality rate surrounded by provinces with a higher than average mortality rate, while

cold–cold (coldspots) signified provinces with a lower than average mortality rate surrounded by provinces with a lower than average mortality rate. Low–high and high–low outcomes represented outliers: these were provinces with low/high average mortality rates surrounded by provinces with high/low average mortality rates, respectively.
The spatiotemporal analysis was performed in R stats packages, version 2.15.2 (R Core Team, s.d.).

5.2.5 Spatiotemporal Analysis of Pneumonia- and Influenza-Related Mortality

The independent variables of interest were regional IVC rates and the proportion of aTIV doses to the total number of IV doses put into tender allotments. During the study period, IVC was recommended and fully reimbursed for all subjects aged ≥65 years, people ≥6 months affected by certain health conditions and some other categories. The Italian Ministry of Health routinely report region- and season-specific IVC rates for both the general population and older adults aged ≥65 years (Italian Ministry of Health, s.d.-b). Data on province-specific IVC rates are not publicly available. Therefore, the unit of this analytical part of the analysis was a region (N=21). The primary predictor of interest was IVC in older adults aged ≥65 years. However, a higher IVC rate in younger age groups may exercise some protective effect on the elderly owing to the phenomenon of herd protection. Indeed, some studies underlined the important role of children and adolescents in spreading influenza virus in their households (Brownstein et al., 2005; Glass & Glass, 2008; Viboud et al., 2004) and therefore to their grandparents. A model by Fumanelli et al. (Fumanelli et al., 2012) has suggested a significant social interaction between Italian elderly and younger individuals. For this reason and in order to account for the possible effects of herd protection, we also included a variable of IVC in subjects aged <65 years.
Another independent variable of interest was the proportion of potential aTIV users to the total number of IV doses put into tender allotments, and the data from the Seqirus Italy tender department. According to the latest Italian official recommendations (Italian Ministry of Health, 2020), aTIV may be used only for people aged ≥65 years. Therefore, we hypothesized that the higher local use of aTIV may be associated with better health-related outcomes among the Italian elderly.
To establish an association (or lack of association) between the region- and year-specific P&I mortality rates in the elderly and predictors of interest (i.e., IVC rates and share of

aTIV doses) panel regression analysis was undertaken. Briefly, the panel considered 21 spatial units (i.e., regions) followed over seven consecutive post-pandemic years and therefore consisted of 21x7=147 observations. However, an important assumption has to be highlighted here. P&I mortality data are routinely reported for the whole calendar year (Italian National Institute of Statistics (ISTAT), s.d.-a, 2022), while the IV campaign usually starts in mid-October/November and almost all IV doses are administered by the end of December. In Italy, according to the Italian National Institute of Health, most laboratory-confirmed influenza deaths occur between January and March (National Institute of Health, s.d.), and influenza-like illness (ILI) peaks were usually reached in late January or February (Table 2) (Italian National Institute of Health, s.d.). Moreover, considering the time lag of 2–6 weeks between IV administration and the peak of the vaccine-induced immune response (Fabiani et al., 2019), it is more likely that IV administered in autumn/winter of a year t-1 will mainly exercise its effect (if any) on bacterial influenza-related complications (that are the most frequent and require some time to be developed) leading to death in the first months of the following year t.

Both the fixed-effects (FE) and random-effects (RE) methods were applied. The FE approach may be useful in the context of causal inference: while standard regression techniques provide biased estimates of causal effects in case there are unobserved confounders, FE regression may provide unbiased estimates in this situation (National Institute of Health, s.d.; Rastogi et al., 1995). In other words, in our models, region-level FEs were included to absorb unobserved region-level heterogeneity in the observed P&I mortality rates not explained by other covariates in the model (Goldhaber-Fiebert et al., 2010). Indeed, unobserved effects are typical in ecological and social research (Brüderl & Ludwig, 2015). By contrast, the RE approach assumes that region-specific effects are not correlated with independent variables (Bell et al., 2019). In any case, the Hausman's specification test was applied (Hausman & Taylor, 1981) to formally differentiate between FE and RE models; the null hypothesis of this test is that the RE model estimates are consistent and efficient.

The following socioeconomic, environmental and virological variables were selected as potential confounders: public health expenditure per capita (€), population density (inhabitants per km^2), average winter temperature and the predominant influenza virus (sub)type(s). The reasons for inclusion of these variables are described below.

Public health expenditure per capita represents a proxy measure of regional welfare and is commonly used in health-related econometric studies (Hone et al., 2019; Moreno-Serra et al., 2019; Toffolutti et al., 2019; Yan et al., 2015). Indeed, this parameter varies substantially among the Italian regions (Italian National Institute of Statistics (ISTAT), 2022; Toffolutti et al., 2019) and has been found to be a significant predictor of regional measles, mumps and rubella (MMR) vaccination uptake in Italy (Toffolutti et al., 2019).

As per environmental factors, we selected two potential confounders, namely: population density and mean winter temperature regimens. The empirical idea for the former variable was that a higher population density would be associated with a higher virus transmission (Chandra et al., 2013; Goldhaber-Fiebert et al., 2010). In fact, the population density in Italy is highly non-homogeneous (Italian National Institute of Statistics (ISTAT), 2022). Second, single Italian regions lay in different climatologic areas with highly different daily temperature paradigms; this fact could have direct implications on the influenza-related outcomes since the so-called "cold waves" usually interfere with the mortality rate (Rosano et al., 2019). Moreover, Lytras et al. (Lytras et al., 2019) have concluded that in Greece the winter excess mortality rates attributable to cold temperatures were substantially higher than those attributable to influenza. Therefore, we proxied the cold waves in a given year and region as an average minimum temperature observed in the winter period. In our analysis, the winter period started at week 40 of the previous year and ended at week 20 of the next year, as per the FluMOMO model (Nielsen et al., 2018).

Finally, circulation patterns of influenza virus (sub)types (A/H1N1pdm09, A/H3N2 and B) may determine the magnitude of influenza-related outcomes. For instance, in Italy the predominance of the A/H3N2 subtype was associated with significantly higher excess mortality in the elderly (Rizzo et al., 2006). The predominance of a single virus (sub)type over other (sub)types was a priori set to 50% of the total national detections. This assumption was however, formally proved by performing a single-proportion z-test. Moreover, the adopted classification rule was compared with the previously published Italian studies (Affanni et al., 2019; Puzelli et al., 2019), meeting full agreement. Otherwise [i.e., when the most prevalent virus (sub)type was detected in <50% cases], the overall virological picture was dubbed as co-circulation (**Table 5.2**).

Table 5.2. Principal Italian influenza epidemic characteristics (Italian National Institute of Health, s.d.).

Season	Epidemic period, week/year*	Epidemic peak, week/year	Peak incidence, ‰	% virus (sub)types detections			
				A/H1N1pdm09	A/H3N2	A unsubtyped	B
2010/11	50/10–11/11	05/11	11.04	61.9	2.2	7.9	28.0
2011/12	51/11–11/12	05/12	9.64	0.2	89.3	7.0	3.5
2012/13	51/12–13/13	06/13	9.99	33.6	5.5	2.9	58.0
2013/14	52/13–13/14	06/14	6.67	34.0	56.3	6.8	3.0
2014/15	51/14–13/15	04/15	10.87	43.7	34.4	5.9	16.0
2015/16	52/15–14/16	08/16	6.14	15.1	24.1	3.9	57.0
2016/17	48/16–09/07	52/16	9.55	0.5	94.1	0.5	5.0

*Defined as influenza-like illness attack rate of ≥2‰ in the general Italian population (Calabrò et al., 2019; Di Pietro et al., 2017)

As recommended (Goldhaber-Fiebert et al., 2010; Wooldridge, 2013), in all panel regression models performed, the continuous variables (i.e., P&I mortality rates, public health expenditure per capita, population density, and average winter temperature) that were not percentages were transformed using natural logarithms (loge). The regression coefficients are therefore interpreted as elasticities. For instance, the model coefficient for IVC rate should be interpreted as the percent change in P&I mortality rate associated with a 1% change in coverage (Goldhaber-Fiebert et al., 2010; Wooldridge, 2013).
The following panel model specification was considered:

$$\log_e(\text{P\&I\_mort\_65+})_{i,t} = b_1(\text{IVC\_65+})_{i,t} + b_2(\text{IVC\_<65})_{i,t} + b_3(\text{aTIV})_{i,t} + b_4[\text{loge(PHexp)}]_{i,t} + b_5[\text{loge(Dens)}]_{i,t} + b_6[\text{loge(Temp)}]_{i,t} + b_7(\text{Virus})_{i,t} + \alpha(i) + \varepsilon_{i,t},$$

for $i = 1\ldots21$ and $t = 2011\ldots2017$, where “P&I_mort_65+” is P&I mortality rate in subjects aged ≥65 years; bs are regression coefficients; α is the unobserved time-invariant regional effect (in FE model) or constant intercept (in RE model); *i* is a region; *t* is a year; *ε* is the error term; “IVC_65+” is IVC in subjects aged ≥65 years; “IVC_<65” is IVC in subjects aged <65 years “PHexp” is public health expenditure per capita; “Dens” is population density; “Temp” is average low winter temperature; “Virus” is a dummy variable indicating the predominant virus (sub)type.

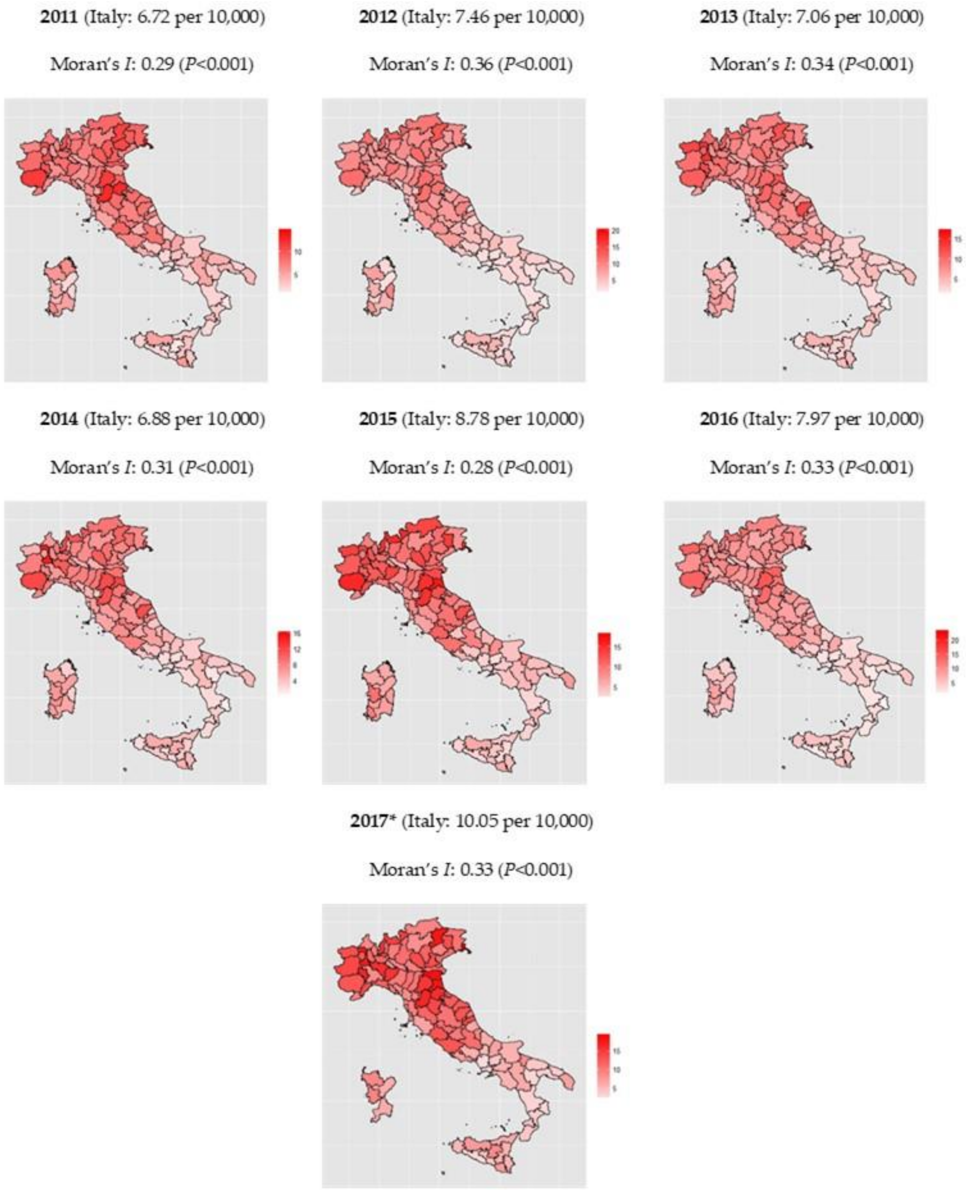
Taking into account a high probability of heteroscedasticity and/or autocorrelation, all models considered also the Arellano's heteroscedasticity-autocorrelation (HAC) robust standard errors (SEs). We performed the model diagnostics by applying the Breusch-Godfrey test for panel models to detect serial correlation for the errors and Pesaran cross-sectional dependence (CD) and Breusch–Pagan Lagrange multiplier tests for CD in the constructed panel models (Baiocchi & Distaso, 2003; Croissant & Millo, 2008).
All the modelling was made in R stats packages (R Core Team, s.d.).

5.3. Results

5.3.1. Exploratory Spatiotemporal Analysis of Pneumonia- and Influenza-Related Mortality in the Italian Older Adults Aged ≥65 Years

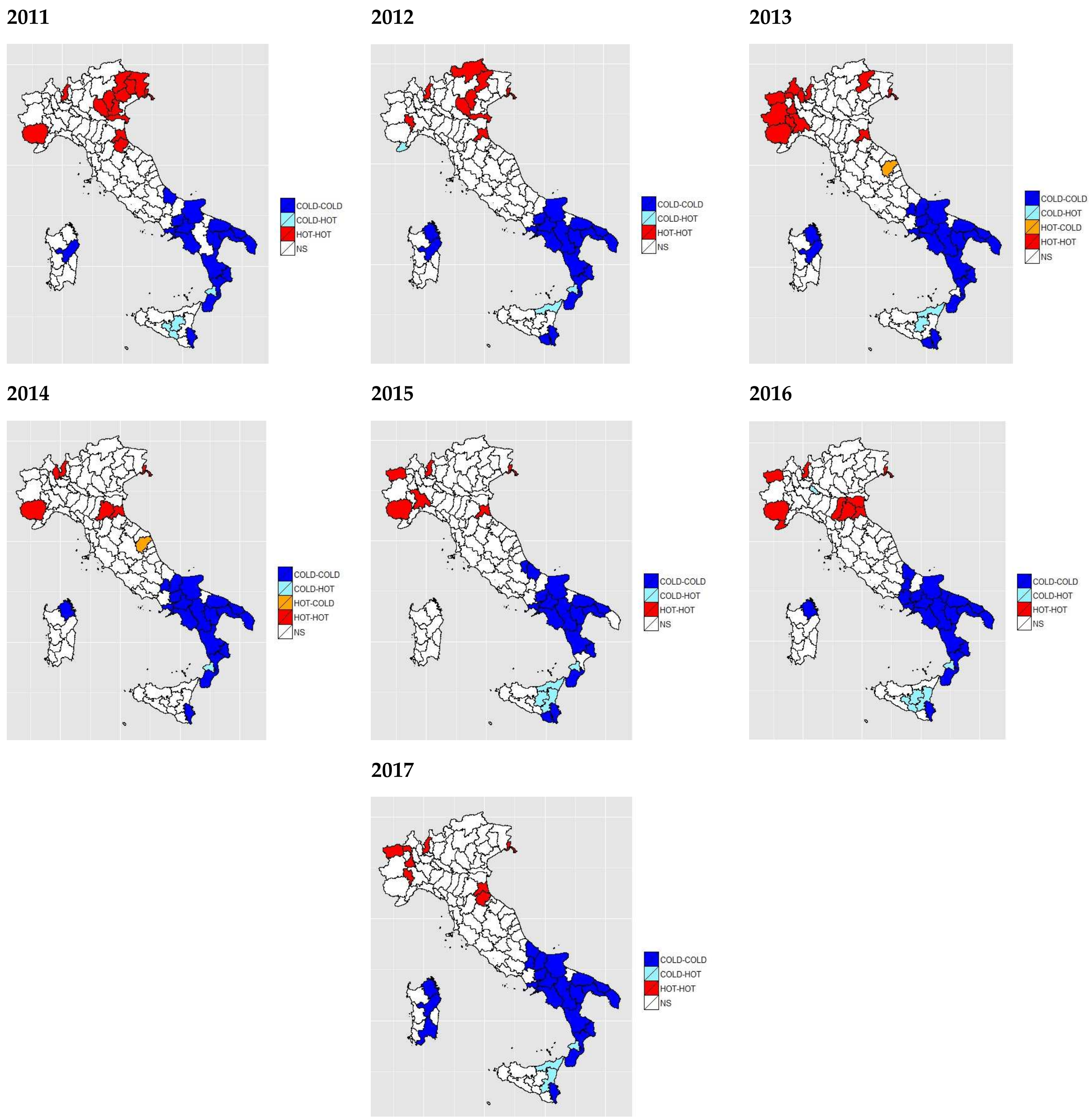
Over seven years (2011–2017) a total of 71,876 P&I-related deaths were reported in older adults aged ≥65 years. There was some variability in terms of P&I-related mortality rates observed between years. The highest rates were observed in years 2017 (10.05 per 10,000) and 2015 (8.78 per 10,000). In the remaining years the mortality rate was lower and 6.7<8 per 10,000 (**Figure 5.1**).
We then explored choropleth charts by mapping province-specific P&I-related death rates. A clear north–south gradient (especially in 2011, 2015 and 2017) was evident: compared with central and southern provinces, those located in the northern Italy displayed higher P&I mortality rates (**Figure 5.1**). As shown by Moran's Is, a significant ($P<0.001$) clustered pattern of the observed mortality rates took place in all years with the I-value ranging from 0.28 to 0.36.
The LISA analysis (**Figure 5.2**) confirmed the north-south gradient: most hotspots and coldspots were located among northern and southern provinces, respectively. The few outliers detected (mainly cold–hot) were located in Sicily.

Figure 5.1. Choropleth maps of pneumonia- and influenza-related mortality rates (per 10,000) in older adults aged ≥65 years, by year.



*Data from four provinces of Sardinia Region (Olbia-Tempio, Ogliastra, Medio-Campidano, Carbonia-Iglesias) were not available for year 2017.

Figure 5.2. Local indicators of spatial association (LISA) cluster maps of pneumonia and influenza-related mortality rates (per 10,000) in older adults aged ≥65 years, by year.



5.3.2. Association Between Pneumonia- and Influenza-Related Mortality and Influenza Vaccination Patterns

The total panel was composed of 147 observations and was balanced (i.e., no single space-time observations were missing). **Table 5.3** reports principal descriptive statistics of the continuous variables of interest. During the study period, an average IVC in the elderly was 55.0%. Two significant drops in IVC were observed: the first occurred in 2012 (from 62.7% to 54.2%), the second in 2014 (from 55.4% to 48.6%). During the study period, only one region reached the recommended target of 75% (Umbria in the 2010/11 season). The proportion of aTIV use was highly non-homogeneous with a range of 0–76% (**Table 5.3**).

Table 5.3. Summary statistics of the continuous independent variables considered.

Description	Mean	SD	Median	Min	Max	Ref
IVC in subjects aged ≥65 years, %	54.3	8.2	54.2	33.9	75.2	(Italian Ministry of Health, s.d.-b)
IVC in subjects aged <65 years, %	4.9	2.2	4.4	1.6	14.5	(Italian Ministry of Health, s.d.-b; Italian National Institute of Statistics (ISTAT), 2022)
aTIV regional allotments to total vaccine doses, %	28.3	18.0	28.6	0	76.3	Seqirus data
Public health expenditure per capita, €	1,885	148	1,854	1,652	2,283	(Italian National Institute of Statistics (ISTAT), 2022)
Population density, inhabitants per km^2	178.0	110.5	162.7	38.8	429.1	(Italian National Institute of Statistics (ISTAT), 2022)
Average low winter temperature, °C	6.9	2.7	6.8	1.0	12.9	(Italian National Institute for the Environmental Protection and Research (ISPRA), 2020)

Notes: aTIV: MF59®-adjuvanted trivalent influenza vaccine; IVC: influenza vaccination coverage

For what concerns the seasonal dummy variables, seasons 2011/12, 2013/14 and 2016/17 were dominated by A/H3N2, season 2010/11 by A/H1N1pdm09, seasons 2012/13 and 2015/16 by B type, while the remaining 2014/15 season was ascribed by a co-circulation of A/H1N1pdm09 and A/H3N2 (**Table 5.2**).

Results of FE and RE panel regression models are reported in **Table 5.4**. In the FE model, both IVC rate in the elderly, proportion of aTIV use, and average winter temperature were negatively associated with the observed P&I mortality rate in the Italian elderly. In particular, both FE and RE models predicted that each 1% increase in IVC rate in the elderly would be associated (P<0.001) with a 1.6-1.9% decrease in P&I mortality. Analogously, each 1% increase in aTIV use would be associated (P<0.05) with a 0.4% decrease in P&I mortality. By contrast, the co-circulation of type A virus subtypes was a significant positive predictor. No statistically significant association was observed for other independent variables. The output of the RE model was similar to that of the FE model. However, the Hausman's test suggested (P<0.001) that the FE model should be retained. The model diagnostics justified the use of both HAC robust standard errors (**Table 5.4**).

Table 5.4. Panel regression analysis on the association between pneumonia- and influenza-related mortality and potential predictors.

Variable	Fixed-effects model			Random-effects model		
	b	**SE (*P*)**	**HAC SE (*P*)**	***b***	**SE (*P*)**	**HAC SE (*P*)**
IVC in subjects aged ≥65 years	-0.019	0.004 (<0.001)***	0.004 (<0.001)***	-0.016	0.004 (<0.001)***	0.003 (<0.001)***
IVC in subjects aged <65 years	0.006	0.012 (0.61)	0.012 (0.63)	-0.006	0.012 (0.64)	0.011 (0.61)
Proportion of aTIV	-0.004	0.001 (0.013)*	0.001 (0.003)**	-0.004	0.001 (0.014)*	0.001 (0.006)**
Public health expenditure per capita (€ 1.000)	-0.714	0.656 (0.28)	0.869 (0.41)	0.287	0.574 (0.62)	0.906 (0.75)
Population density	-2.215	1.592 (0.17)	1.940 (0.26)	0.145	0.103 (0.16)	0.109 (0.19)
Average low winter temperature	-0.299	0.097 (0.003**)	0.072 (<0.001***)	-0.341	0.084 (<0.001***)	0.071 (<0.001***)
Predominance of A/H1N1pdm	Ref			Ref		
Predominance of A/H3N2	0.036	0.043 (0.40)	0.029 (0.21)	0.053	0.045 (0.24)	0.028 (0.062·)
Predominance of B	-0.059	0.055 (0.29)	0.040 (0.14)	-0.033	0.057 (0.56)	0.039 (0.40)
Co-circulation A/H1N1pdm09 and A/H3N2	0.108	0.068 (0.11)	0.049 (0.030*)	0.153	0.071 (0.033*)	0.047 (0.001**)
R^2, %	41.6			38.4		
Hausman test, *P*	<0.001***					
Breusch-Pagan test, *P*	<0.001***			<0.001***		
Pesaran test, *P*	<0.001***			<0.001***		
Breusch-Godfrey/Wooldridge test, *P*	<0.001***			<0.001***		

Notes: ·*P*<.10; **P*<.05; ***P*<0.01; ****P*<.001; aTIV: MF59-adjuvanted trivalent influenza vaccine; HAC SE: heteroscedasticity and autocorrelation robust standard errors; IVC: influenza vaccination coverage

5.4 Discussion

This study confirms that annual influenza vaccination in the elderly reduces overall P&I mortality rates and therefore that increased immunization rates are desirable. From the ecological and policy-making perspectives this study has also confirmed the usefulness of aTIV in preventing P&I-related mortality in the elderly Italian population. This is in line with a recently proposed concept of the appropriate use of IVs in Italy (Bonanni et al., 2018).

The protective effect of IV on (excess) mortality is still controversial. For instance, Rizzo et al. (Rizzo et al., 2006) and Simonsen et al. (Simonsen et al., 2005) have not documented any meaningful temporal association between IVC rate and winter excess mortality in Italy and the United States, respectively. By contrast, available meta-analyses of observational studies (Fukuta et al., 2019; Yedlapati et al., 2021) suggest a significant reduction in mortality among vaccinated individuals. Contrary to the previous Italian time-trend study by Rizzo et al. (Rizzo et al., 2006) we were able to demonstrate a protective effect of IVs on P&I mortality. The reasons for this discrepancy are likely to be multiple. First, two different and non-overlapping time periods with both different circulating viruses and available IVs were assessed. Second, two different proxy outcomes to quantify influenza-related mortality were used. Third, in the present study both time and space were incorporated in the analysis; this may provide additional benefits in countries like Italy with its "jeopardized" pattern of IVCs (Domnich, Cambiaggi, et al., 2020).

Our second main finding was that regions using a higher proportion of aTIV showed significantly lower P&I mortality in the elderly independent of IVC, virus circulation pattern, and other potential confounders. In the elderly population aTIV has systematically been shown to be both more immunogenic (Nicolay et al., 2019) and effective (Domnich et al., 2017) than standard-dose non-adjuvanted IVs. In particular, meta-analysis by Nicolay et al. (Nicolay et al., 2019) has shown that the use of aTIV was associated with significantly higher seroconversion rates and geometric mean titers against both vaccine antigen strains and heterologous strains, independently from the (sub)type analyzed. Analogously, the systematic review by Domnich et al. (Domnich et al., 2017) concluded that the available observational studies had usually displayed a greater effectiveness of aTIV against various influenza-related outcomes, as compared with non-adjuvanted counterparts. In this regard the ecological study design may confirm findings coming from primary experimental or observational research and may therefore be useful in the decision-making process.

The main strength of this study lies in the methodology adopted. While a limited number of time-space observations does not allow the model to be adjusted for “anything we want to” as well as the fact that some potentially useful data may be not available, the FE panel models provide unbiased estimates in situations when unobserved confounders are present (as in the case of this study) (Brüderl & Ludwig, 2015).

Apart from the well-known general limitations of ecological studies (ecological fallacy in primis) (Morgenstern, 1995), specific limitations apply to this study that must be considered. First, owing to data availability, the final regression models could be performed at the regional level only. A more space-detailed (e.g., provincial or local health unit level) evaluation is warranted. Second, the data on market share of single IVs come from regional tender allotments and therefore may not exactly correspond to effective IV administration. However, we believe that this limitation had a limited impact on the results since it is unlikely that the wastage/non-utilization rate differs among single IVs. Third, although we have no reason to believe that the automatic coding of causes of death may differ between regions, we could not completely rule out the between-region differences in reporting quality. However, this limitation may have only a small impact on the study results since the Italian National Institute of Statistics performs quality checks on a regular basis. Moreover, the FE panel model adopted may absorb this eventual heterogeneity.

To conclude, our analysis supports the increase in annual influenza vaccination in Italy and suggests that a higher IV uptake in the Italian elderly population would be beneficial. The use of aTIV in older adults is advised to reduce the burden of seasonal influenza disease.

Chapter 6. Time lapses between distribution of influenza vaccines to health authorities and their administration by General Practitioners (GPs) to older adults: a primary care study over five influenza seasons in Italy

Declarations

The manuscript by Francesco Lapi, Ettore Marconi, Elettra Fallani, Marco Salvatore, Maura Cambiaggi, Alessandro Rossi and Claudio Cricelli has been currently submitted to a peer-review scientific journal.

6.1. Introduction

Influenza causes one of the greatest vaccine-preventable disease burdens in Europe, accounting for an estimated annual average of 4–50 million symptomatic cases, approximately 15,000–70,000 deaths and 150,000 influenza-related hospitalizations (Cassini et al., 2018; European Centre for Disease Prevention and Control (ECDC), 2022; Rizzo et al., 2018). However, these complications are not equally distributed across populations, with some vulnerable subgroups, such as older adults, young children, pregnant women, and persons with chronic diseases or immunosuppressive conditions, experiencing an increased burden compared to the general population (Schmitt, 2016). Elderly individuals have an increased susceptibility to infectious diseases, as a consequence of the high prevalence of comorbidities and immunosenescence (Aiello et al., 2019; McElhaney et al., 2016). In Italy, excess mortality rates are more than 6 times higher among the elderly than in the general population, with influenza- and pneumonia-related mortality counting among the top 10 causes of deaths nationally (Giacchetta et al., 2022; Italian Ministry of Health, s.d.-b). Vaccination in older adults is therefore strongly recommended in European Economic Area (EEA) countries. In Italy, among older adults, a 1% increase in influenza vaccine coverage has been estimated to reduce the incidence of influenza from 2 to 4%. A statistically significant association was found between vaccine coverage declines observed between in the trienna 2005–2008 and 2014–2017 and an increase in influenza-like illnesses from 2.7% to 4.2% between the same 2 periods (Manzoli et al., 2018).

The window of opportunity for influenza vaccination is relatively brief, typically starting in September/October and ending in January or beyond in the Northern Hemisphere (Grohskopf, 2018; Italian Ministry of Health, s.d.-b). In Italy, annual influenza vaccination is recommended from the 1st of October continuing throughout the whole season. Vaccine coverage refers to the population proportion that has received the recommended doses of a vaccine. The Italian Ministry of Health has established a minimal effective target of 75% for influenza vaccination coverage for older adults and at-risk individuals of all ages, however, during the last 23 seasons (from 1999-2000 to 2021-2022), this objective has never been achieved (Italian Ministry of Health, s.d.-b).

The time lapse between vaccine delivery and administration can have an impact on vaccine coverage (Schmitt, 2016). In general, the shorter the time lapse between vaccine delivery and administration, the higher the vaccine coverage is likely to be, because delays in vaccine delivery or administration can create barriers to vaccine access and may cause people to miss their scheduled vaccine appointments (Bonanni et al., 2018, 2021; Luthy et al., 2016). Additionally, delays in vaccine delivery or administration can increase the risk of vaccine wastage or expiration, which can reduce overall vaccine coverage (Schmitt, 2016). In the 2000-2001 season in the United States, a 6- to 8-week delay of influenza vaccine delivery led to a sharp drop of 16% in vaccine coverage compared to the previous year. An analogous delay in the 2014–2015 season, along with antigenic drift, resulted in a shortage during the epidemic peak and the greatest numbers of hospitalizations and deaths over the previous 5 seasons (Lin et al., 2022). Hence, both the possibility of an intraseasonal waning in vaccine effectiveness and the risk of a decrease in influenza vaccine uptake due to late vaccine distribution must be taken into account to determine the best period of distribution and administration of the influenza vaccination.

Although there is limited qualitative information about how General Practitioners (GPs) judge vaccine delivery delays and how it affects their practice (Gray et al., 2017; Pyrzanowski et al., 2008), there have not been any studies that use actual data to measure the extent of this public health concern. We therefore measured the time it takes for vaccines to be distributed to regional health authorities and then administered to patients by GPs. Additionally, we investigated how the differential between the time of distribution and administration might increase the risk of all- and respiratory-cause hospitalizations. This investigation was conducted over 5 consecutive epidemic seasons.

6.2. Methods

This study was designed to examine the relationship between the rates of vaccine distribution and administration in doses/week to persons aged 65-95 years and to analyse the association between the differential speed of vaccine distribution and administration and rates of all-cause and respiratory-related hospitalizations in this population over 5 seasons from 2017 to 2022. The study protocol was approved by the Scientific Committee of the Italian College of General Practitioners and Primary Care. This study followed the principles of the Declaration of Helsinki and was compliant with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

6.2.1. Data Sources

We used the overall numbers of doses of adjuvanted trivalent or quadrivalent influenza vaccines (aTIV [Fluad®] and aQIV [Fluad® Tetra], respectively) as provided by the marketing authorization holder (MAH; i.e., Seqirus) to regional health authorities between 2017 and 2021. These data were provided on a regional and daily basis. Numbers of influenza vaccines administered to older adults aged ≥65 years by GPs were obtained from the Italian College of GPs health search database (HSD) over the same 5 influenza seasons. For both data sources, data were from 20 Italian regions of residence.

The HSD is a longitudinal observational database established in 1998 that contains electronic healthcare records (EHRs) of almost 1.2 million subjects under the care of approximately 1000 GPs distributed throughout Italy. The present study included computer-based patient records collected by a selected group of 800 GPs who met standard quality criteria regarding the levels of data entry (i.e., levels of coding, prevalence of selected diseases, rates of mortality, and years of recording). These GPs were selected on a geographical basis to include patients that would be representative of the whole Italian population. All diagnoses were coded according to the

International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM). To complement the coded diagnoses, GPs have the ability to add a free text. Information on drug prescriptions includes the name of the prescribed drug (i.e., active substance and/or brand name), the corresponding anatomical therapeutic chemical (ATC) code along with the related defined daily dose (DDD), the date of prescription, and the number of supply days. Vaccinations are registered in a dedicated section. HSD has been extensively used for retrospective and longitudinal research, including effectiveness investigations on influenza vaccines (Lapi, Domnich, et al., 2022; Lapi et al., 2019; Lapi, Marconi, et al., 2022).

6.2.2. Study Population

From the HSD, we identified all individuals aged 65-95 years and the regions where their GPs operated over the period between the 2017-2018 and 2021-2022 influenza seasons. A subject could be included in one or more seasons. Those aged ≥96 years were not considered, given the high rate of hospitalizations and/or institutionalization of these subjects, which suggests a reduced completeness of their EHRs in these settings. We therefore estimated the proportion of aTIV and aQIV (as reported in MAH data sources) doses distributed to regional Local Health Authorities (LHAs) and expected to be delivered to GPs (who may also have obtained doses from authorized pharmacies), weighting the population size of older adults served by each physician for the ratio between the actual number of delivered doses of aTIV/aQIV and the total number of older Italian residents (source: https://demo.istat.it/). These data were compared with the aTIV/aQIV doses being actually administered (as per EHRs) to older adults in the care of GPs belonging to the HSD network.

6.2.3. Outcome Definition

During the course of the 5 influenza seasons, we computed the velocity of vaccine doses distributed to regional LHAs and administration by GPs (or nurses belonging to the same clinics) on weekly basis. The term velocity describes the identification of doses of influenza vaccines delivered in a specific period of time (i.e., weekly). Specifically, the term distribution velocity refers to the doses of ordered influenza vaccine vials delivered from the MAH to the regional LHAs on a weekly basis, whereas the term administration velocity is used to define the number of influenza vaccines administered by GPs (or nurses belonging to the same clinics) each week. The mathematical difference between the distribution and administration velocities is used to indicate the lapses between distributed and administered doses on a weekly basis, thus providing a unique dynamic measure of the vaccine doses actually administered instead of remaining stocked by the regional LHAs and/or GPs. We investigated the potential relationship between these 2 velocities over the 5 seasons and determined the difference between the 2 velocities for each epidemic season and analysed the correlation between this difference and the rates of all-cause/respiratory-related hospitalization being registered during the epidemic seasons. We identified each hospital admission recorded in the database during the follow-up period. We also used free text to identify hospitalizations by searching for terms such as "recover*," "admiss*," and "hospit*" within 3 months before and/or after the exit date (i.e., death, end of the specific season, end of data availability). All records were reviewed and validated by an expert clinician to ensure the classification accuracy of the events, using the same approach as in prior studies (Lapi, Domnich, et al., 2022; Lapi, Marconi, et al., 2022). To maintain biological plausibility regarding the impact of the influenza vaccine on the risk of hospitalization, events occurring within the first 15 days of aTIV/aQIV administration were excluded from consideration (Rastogi et al., 1995).

6.2.4. Data Analysis

For each epidemic season, descriptive statistics were calculated. We plotted the trends of the cumulative vaccine doses expected to be received and those actually administered (according to EHRs) by GPs to immunize older adults over the 5 influenza seasons. To be consistent with the time frame of influenza season, weeks were the units of observation (Schmitt, 2016). To calculate vaccine coverage, we divided the number of older adults who received the influenza vaccine by the total number of persons aged 65-95 years under the care of GPs. The skewness of distributed and administered vaccine doses over seasonal weeks was proven through the Belanger and D'Agostino test (D'Agostino & Belanger, 1990). We therefore tested the potential presence of trend for both distribution and administration velocity among the 5 seasons using quantile (median) regression. With the same approach we investigated the possible relationship between the difference in velocities of vaccine distribution and administration (doses/week) and the occurrence of all-cause or respiratory-related hospitalizations. Operationally, the beta coefficients, with related 95% confidence intervals (CI), were calculated to quantify the proportional increase (or decrease) in the outcome for an increase of 1 dose/week of influenza vaccine (or differentials between doses distributed and administered; in this case, an increase indicates a slower allocation and administration of vaccines). Every regression analysis was clustered by region after identifying the presence of intraclass correlation ($p<0.001$). The estimates, which were obtained for every epidemic season, were pooled through meta-analysis. Heterogeneity was evaluated and tested using I-square and Q test, respectively.

To test the robustness of the results, we conducted two sensitivity analyses. First, our estimate of the number of doses expected to be delivered to GPs was derived by combining distribution data (sourced from the MAH) and regional census information. However, certain GPs who were affiliated with specific regional LHAs but who could not be identified in the HSD may have received additional aTIV/aQIV doses. Moreover, prior to the COVID-19 pandemic, some older adults may have independently purchased doses in pharmacies. As a result, the number of administered doses exceeded the expected quantities that were delivered to, or collected by, GPs during the initial 3 seasons. Second, we tested the effect of vaccine under-registration (i.e., false-negative vaccinations) on the results (Hempenius et al., 2021; Lapi, Marconi, et al., 2022), which can lead to bias because GPs are required to register vaccination twice: in a public regional registry and in their own EHRs. The additional GP workload might reduce the completeness of data collection, leading to underestimation of the ratio of doses/week. The primary analysis was therefore recalculated by limiting GPs to those reporting a vaccine coverage of ≥55%, which is consistent with the lowest coverage reported in official reports of Italian public health authorities for 1 of the included seasons (Italian Ministry of Health, s.d.-b). Utilizing a subset of GPs with more precise vaccine recording methods enabled the first sensitivity analysis to be revised as well, given that the number of older adults purchasing the influenza vaccine themselves should be minimized.

6.3. Results

Table 6.1 displays the characteristics of older adults forming the study population over the 5 epidemic seasons along with the actual number of residents in Italian regions where the overall number of aTIV/aQIV doses were delivered by MAH. The proportions of older adults registered in HSD were consistent with those calculated for the resident populations (ranging 26-27% vs. 27-28% for general and HSD population, respectively). This information enabled us to quantify the anticipated number of vaccine doses for administration to older adults: 78,455, 73,226, 78,973, 137,787, and 120,820 doses for the 2017-2018, 2018-2019, 2019-2020, and 2020-2021 seasons, respectively. More women than men received vaccines.

Table 6.1. Characteristics of the overall older adult population and the amount of influenza vaccine doses delivered and administered over 5 influenza seasons in Italy.

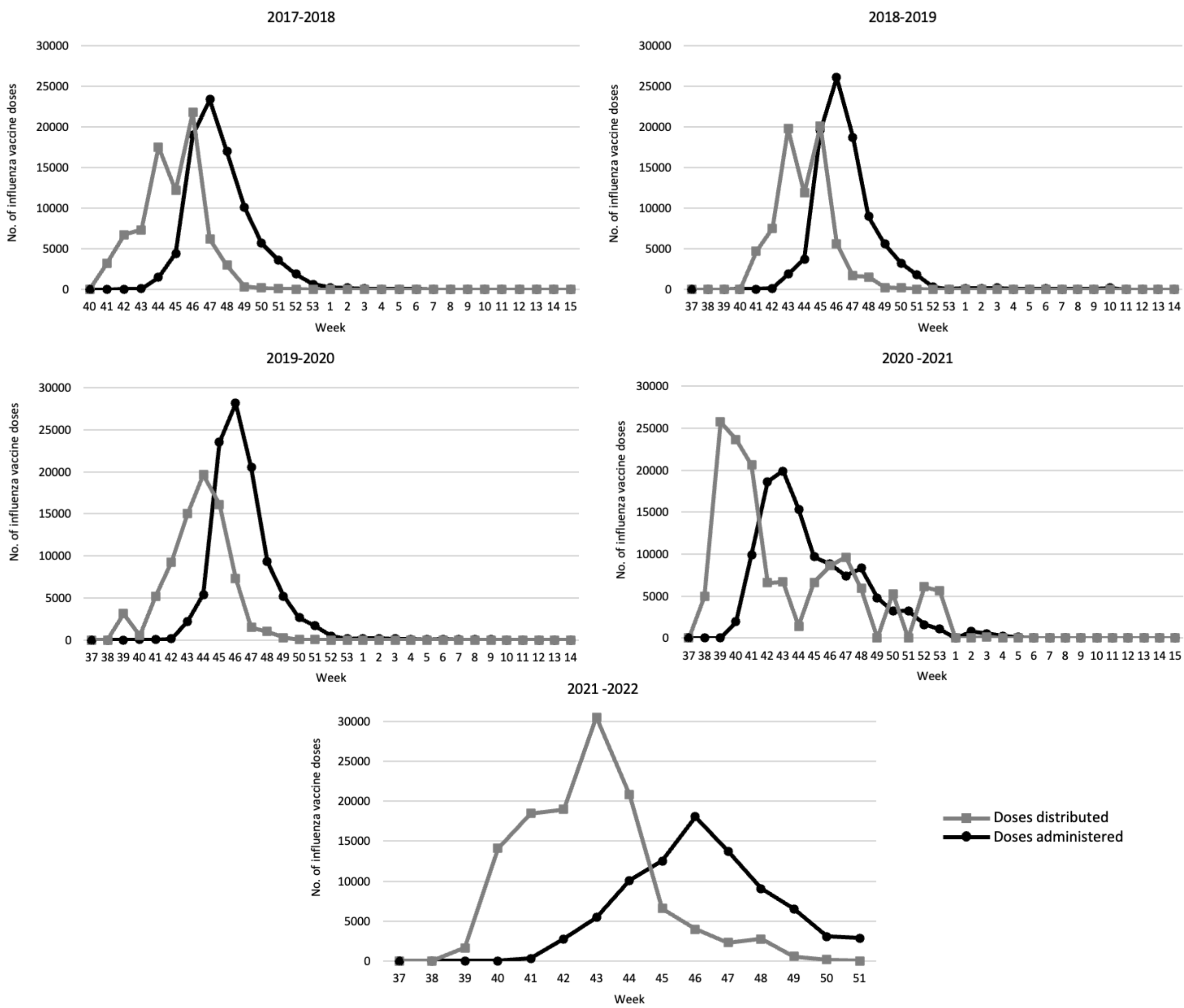
	Influenza season				
N	**2017-2018**	**2018-2019**	**2019-2020**	**2020-2021**	**2021-2022**
Total resident population (aged 15-95 years)[a]	51,862,355	51,833,341	51,794,400	51,479,434	51,540,338
Resident older adults (aged 65-95 years)[a]	13,487,719	13,581,770	13,739,556	13,821,297	13,927,447
Weeks	29	31	31	32	17
GPs in HSD	1129	1111	1096	1085	1064
Total population under care of GPs in HSD	1,346,465	1,287,476	1,223,344	1,174,423	1,058,289
Older adults under care of GPs in HSD	362,023	350,440	337,929	322,907	288,401
Male	160,320	155,634	151,480	145,928	133,103
Female	201703	194806	186449	176979	155298
Influenza vaccines					
Delivered doses	3,004,521	2,847,156	3,235,771	6,035,439	5,947,126
Expected doses[b]	78,455	73,226	78,974	137,787	120,821
Administered doses	87,316	89,955	99,384	114,253	85,815

Abbreviations: GP, general practitioner; HSD, health search database.
[a] As per https://demo.istat.it/

[b] The calculation involves, for each season, multiplying the number of older adults under the care of GPs by the ratio of doses delivered to the total number of older adults as indicated in official demographic reports on regional bases.

Figure 6.1 shows the patterns of distribution and administration of influenza vaccines for older adults in the 5 seasons under study. The pattern of distribution to the regional LHAs started from the first available dates related to the deliveries. The trend of the distribution and administration pattern represents the velocity (i.e., doses/week) of these actions in the weeks just preceding and overlapping the epidemic phase. In all influenza seasons, vaccine administration (presumably the first dose being injected) started 2-4 weeks after the first delivery. Over the seasons, the difference between the maximum (peak) distribution and administration was equal to 1, 1, 2, 4, and 3 weeks for 2017-2018, 2018-2019, 2019-2020, and 2020-2021 seasons, respectively. With the exception of the 2020-2021 season, in which there was an extended delay between distribution and administration patterns, the other 4 seasons were consistent in terms of differentials between distribution and administration patterns.

Figure 6.1. Trends in Influenza vaccine distribution to regional authorities and vaccine administration by general practitioners by influenza season.



Across the 5 seasons, the distribution velocity ranged from 341 to 833 median doses/week, the administration velocity from 152 to 270 median doses/week, differences between distribution and administration velocities from 289 to 622 median doses/week, and vaccine coverage from 23.65% to 36.53% (**Table 6.2**). All analyses were clustered by regions. The distribution velocity exhibited a rising trend over the 5 seasons, except for the 2018-2019 season, which decreased relative to its predecessor. A similar pattern was observed for the administration velocity across the 5 seasons, but no variance was noted during the initial 3 seasons. The fourth (2020-2021) season was marked by a more substantial increase in the differential between distribution and administration velocity. There was no trend for both distribution (quantile [median] regression, p = 0.421) and administration velocity (quantile [median] regression, p = 0.07) over the 5 seasons. In addition, no apparent trends were observed in the difference between distribution and administration velocities (quantile [median] regression, p = 0.189) or in vaccine coverage over the 5 seasons (quantile [median] regression, p = 0.142).

Table 6.2. Vaccine distribution and administration velocities and vaccine coverage over 5 influenza seasons in Italy.

Influenza season	Velocity, median doses/week (IQR)			Vaccine coverage (%)
	Distribution	**Administration**	**Difference[b]**	
2017-2018	518 (235-925)	176 (106-408)	395 (108-777)	23.65
2018-2019	341 (102-675)	209 (88-348)	289 (110-551)	24.51
2019-2020	466 (159-952)	152 (96-299)	304 (200-669)	28.49
2020-2021	740 (261-1360)	203 (102-351)	622 (216-971)	36.53
2021-2022	833 (242-1514)	270 (112-499)	431 (167-1068)	30.75
p value over 5 seasons[c]	0.421	0.065	0.189	0.142

Abbreviations: IQR, interquartile range (25th-75th percentile); MAH, marketing authorization holder; SD, standard deviation.

[a] From MAH data weighted by official demographics.

[b] Difference between distribution and administration rates (analyses are clustered by region of residence and then inferred to the Italian cohort).

[c] Test on median clustered by regions of residence.

In **Table 6.3** are reported the results on testing the variation between distribution and administration velocity and number of all-cause/respiratory-cause-related hospitalizations among older adults being vaccinated with aTIV/aQIV. We captured statistically significant association with a greater effect size, nominally 10%, 54%, and 12% increase versus the median number of all-cause hospitalizations for each differential dose/week between distributed and administered vaccines for the 2017-2018, 2018-2019, and 2020-2021 season, respectively. Although with a reduced effect size, we found consistent results when the analysis was restricted to hospitalizations likely due to respiratory causes. For what concerns the meta-analysis, using a random effect model (I^2=71%; Q test, p = 0.008), the pooled estimate was equal to a 10% increase (beta coefficient = 0.10 [95% CI, 0.01-0.20]) in all-cause hospitalization.

Table 6.3. Association between difference of distribution and administration velocities (doses/week of influenza vaccines) and hospital admissions over 5 influenza seasons according to quantile (median) regression.

	All-cause hospitalizations					**Respiratory-related hospitalizations**				
Influenza season	**Hospital admissions (n)**	**Vaccinees (n)**	**Cumulative incidence (%)**	**β[a] (95% CI)**	***p* value**	**Hospital admissions (n)**	**Vaccinees (n)**	**Cumulative incidence (%)**	**β[a] (95% CI)**	***p* value**
2017-2018	3303	87,316	3.78	0.10 (0.01-0.20)	0.034	179	87,316	0.21	0.01 (0.1-0.2)	0.014
2018-2019	3899	89,955	4.33	0.54 (0.10-1.20)	0.030	211	89,955	0.22	0.03 (0.01-0.06)	0.034
2019-2020	4373	99,384	4.40	0.45 (-0.12-1.01)	0.185	212	99,384	0.21	0.01 (-0.02-0.03)	0.524
2020-2021	4283	114,253	3.75	0.12 (0.01-0.22)	0.030	263	114,253	0.23	0.01 (0.001-0.013)	0.016
2021-2022	899	85,815	1.05	0.01 (-0.1-0.05)	0.854	21	85,815	0.02	—[b]	—
Pooled estimate[c]				0.10 (0.01-0.20)						

Abbreviations: CI, confidence interval.

[a] Proportional (%) increase or decrease versus the median value of the outcome for each individual vaccine dosage/day.

[b] Reduced analysis power for low number of hospital admissions (n=21).

[c] Meta-analysis using random effect model.

For the sensitivity analyses, when we adopted the subset of GPs reporting a vaccine practice coverage of ≥55% (**Table 6.4**), we found significant associations for both distribution (quantile [median] regression, p < 0.001) and administration velocity (quantile [median] regression, p = 0.009) over the 5 seasons.

Table 6.4. Characteristics of the five influenza seasons regarding overall older population and the amount of influenza vaccine doses both delivered and administered: general practitioners with influenza vaccine coverage of their older patients >=55%.

	Influenza season				
No.	**2017-2018**	**2018-2019**	**2019-2020**	**2020-2021**	**2021-2022**
Number of GPs (vaccine coverage of their older patients ≥55%)[a]	89	111	162	317	204
Total population under care of GPs	116,427	139,098	206,659	399,906	231,867
Older adults under care of GPs	32,110	38,967	57,766	115,410	68,217
Administered doses of influenza vaccines	20,112	24,548	36,538	76,355	43877

[a]Per official.

In addition, the difference between the distribution and administration velocities (quantile [median] regression, p = 0.001) was significantly different over the 5 influenza seasons (**Table 6.5**).

Table 6.5. Distribution, administration velocity, and their difference over the five influenza seasons: general practitioners with influenza vaccine coverage of their older patients ≥55%.

Influenza season	**Velocity, median doses/week (IQR)**		
	Distribution	**Administration**	**Difference[b]**
2017-2018	497 (139-537)	29 (58-128)	369 (125-408)
2018-2019	473 (94-582)	79.5 (39-105)	348.5 (87-479)
2019-2020	876 (123-1093)	90 (31-154)	721 (112-1008)
2020-2021	2293 (985-3938)	160.5 (77-305)	2133 (881-3561)
2021-2022	1537 (879-2428)	148 (84-299)	1438 (791-2033)
p value over 5 seasons[c]	< 0.001	0.009	0.001

Abbreviations: IQR, interquartile range (25th-75th percentile); MAH, marketing authorization holder; SD, standard deviation.

[a] From MAH data weighted by official demographics.

[b] Difference between distribution and administration rates (analyses are clustered by region of residence and then inferred to the Italian cohort).

[c] Test on median clustered by regions of residence.

The association between the median number of all-cause hospitalizations and each differential dose/week between distributed and administered vaccines for the 2019-2020 and 2020-2021 season was statistically significant, with 9% and 7% increases, respectively (**Table 6.6**). The pooled estimate stemming from the meta-analysis showed a 6% significant increase (beta coefficient = 0.06 [95% CI, 0.02-0.09]; I2=68%; Q test, p = 0.014) in all-cause hospitalization for each differential dose/week of influenza vaccine between distributed and administered doses.

Table 6.6. Association between difference between distribution and administration velocities of influenza vaccines (doses/week) over the 5 seasons according to quantile (median) regression: general practitioners with ≥55% influenza vaccine coverage of their older patients.

	All-cause hospitalizations				
Influenza season	**Hospital admissions (n)**	**Vaccinees (n)**	**Cumulative incidence (%)**	**β^a (95% CI)**	***p* value**
2017-2018	778	20112	3.9	0.03 (-0.014-0.70)	0.178
2018-2019	1076	24548	4.4	0.08 (-0.1-0.30)	0.331
2019-2020	1794	36538	4.9	**0.09 (0.05-0.13)**	**<0.001**
2020-2021	2807	76355	3.7	**0.07 (0.02-0.12)**	**0.015**
2021-2022	489	43877	1.1	0.02 (-0.02-0.05)	0.285
Pooled estimate[b]				**0.06 (0.02-0.09)**	

[a] Proportional (%) increase or decrease versus the median value of the outcome for each individual vaccine dosage/day.

[b] Meta-analysis using random effect model.

6.4. Discussion

To our knowledge, this is the first study quantifying the time lapses between distribution of influenza vaccine to regional health authorities and vaccine administration to older adults in a primary care setting. Over 5 epidemic seasons, we found a difference between velocities of vaccine deliverables to regional authorities and injections by GPs, although there was no significant trend. Instead, we found statistically significant increases between velocity variations and all-cause and respiratory-related hospitalization rates in 3 out of 5 seasons. Interestingly, when the analyses were restricted to GPs with greater accuracy in registering vaccine administration, there was a significant difference over the 5 seasons for both distribution and administration velocities. Overall, the findings from the sensitivity analyses were consistent with the results from the primary analyses. It may be expected that data from GPs with higher influenza vaccine coverage among their patients would corroborate the seasonal variations in the effective execution of the vaccination campaign.

The present study is the first quantitative evidence supporting qualitative observations reported in prior work. For example, a survey conducted among 448 primary care physicians in the US showed that the majority of physicians experienced delays in vaccine delivery during the 2009 H1N1 pandemic. Delays were attributed to insufficient vaccine supply, communication problems with vaccine distributors, and logistical issues related to vaccine distribution. The study also revealed that physicians who reported earlier delivery of vaccines had higher vaccination rates among their patients. The authors concluded that improving the vaccine delivery system is crucial to achieve higher vaccination coverage rates and reduce the impact of influenza on public health (O'Leary et al., 2011). Other authors claimed that multifaceted interventions that address both system-level and patient-level barriers are likely to be the most effective in improving influenza vaccination coverage in primary care practices (Pyrzanowski et al., 2008). Our findings did not show a direct association between velocity of distribution and administration and vaccine coverage, but the time to reach older subjects is still critical to ensure vaccine protection at patient and population levels. This dimension is clearly related to proper and on-time provision of vaccine supplies (Matrajt & Jr, 2010).

Our findings may provide valuable information on the efficiency of the administration and distribution of the substance or medication, allowing for further analysis and potential improvements in the process. In particular, we observed heterogeneity over the 5 influenza seasons concerning the time of allocation of doses to vaccinators, which was clearly identified among GPs with better recordings of influenza vaccines. In this respect, variation in how vaccine deliveries are organized by different regional and local health authorities may benefit from further study. After proving the presence of intra-class (region) correlation, we clustered by region for each regression analysis. Notably, as shown in **Figure 6.1**, starting in the 2019-2020 season, there appears to be a growing trend toward greater delays between the maximal distribution and maximal administration of vaccines. The difference between the distribution and administration peak passed from only 1 week in the 2017-2018 and 2018-2019 influenza seasons to 2, 4, and 3 weeks in 2019-2020, 2020-2021, and 2021-2022 seasons, respectively. The results of the present study provide evidence regarding the positive impact of minimizing the time period between vaccine distribution and administration. Therefore, the most favourable strategy is to order vaccines from MAH closer to the time regional LHAs deliver vaccines to GPs. Efficient vaccine distribution systems play a vital role in achieving high vaccination coverage rates and reducing the spread of vaccine-preventable diseases. In this respect, Manzoli and coworkers reported a significant association between influenza-like illness increase and decline in vaccine coverage. They also demonstrated that each 1% rise in vaccine coverage could prevent roughly 2,690 influenza-like illness cases among older adults in Italy (Manzoli et al., 2018).

Previous investigations have reported that improving vaccine distribution systems can lead to significant improvements in vaccination coverage rates and reductions in disease burden. For example, a study by Stockwell et al. found that the implementation of an EHR-based vaccine reminder system in New York City increased influenza vaccination coverage rates among adolescents from 5% to 34% (Stockwell et al., 2015). Similarly, a study by Fiks et al. indicated that the use of an EHR-based reminder system for paediatric influenza vaccination resulted in a 41.2% increase in vaccination coverage rates (Fiks et al., 2013).

Our study has several limitations. In the first 3 seasons, the number of administered doses was higher than the number estimated by distribution data. Given that we estimated the number of doses expected to be allocated to GPs using regional census data, some GPs operating under certain LHAs, not coded in HSD, could have received additional doses of aTIV/aQIV. In addition, in the period preceding the COVID-19 pandemic, some older adults might have autonomously purchased the vaccine from pharmacies, which were then injected by GPs. Nevertheless, this bias should have artificially reduced the difference between distribution and administration velocity, thereby further emphasizing the importance of logistic management in vaccine allocation to the final vaccinators. Furthermore, when we conducted the meta-analysis, the pooled estimate of beta coefficients was consistent with those obtained for seasons in which a significant association was captured. Based on this finding, we recalculated the analyses by limiting the GPs to those reporting a vaccine practice coverage of ≥55% - a group that administered an average of 79.8% of doses over the 5 seasons - the results of the quantile regression still captured an association for those seasons in which the differential velocity was particularly relevant. It appears this subset of GPs prioritized immunizing their patients sooner. The effect exerted by differential velocity in the 2021-2022 season is difficult to assess, given the poor circulation of influenza virus. Nevertheless, the two related curves of distributed and administered doses/week were those showing the minimum overlap, indicating the need to reduce this gap. A second limitation is that the administration velocity might be underestimated, given the availability of other vaccines in older individuals (excluding the high-dose vaccination which was not yet available in the included seasons). Nevertheless, the fact that our analysis of GPs who vaccinated ≥55% of their patients still captured a statistically significant association was reassuring. Furthermore, the specific use of aTIV/aQIV in the older adult population has become predominant over recent influenza seasons, and the assessment of distribution velocity should not be biased by the residual presence of other vaccines. Third, we used an ecological design that may have led to ecological fallacy. Confirmative studies using individual patient records are therefore needed. Nevertheless, we compared older adults being vaccinated for influenza who were likely similar in terms of comorbidities, as demonstrated in our previous studies using HSD (Corrao et al., 2014; Lapi et al., 2019). Fourth, for the last 3 seasons, the effect on the results of COVID-19 and its related vaccination cannot be excluded. Nevertheless, given that we examined cohorts of older adults being vaccinated for influenza, there is no reason to think about a differential effect exerted by concurrent vaccinations. Along this line, the absence of some associations in the 2021-2022 season is reassuring given the low circulation of influenza virus. Fifth, our definition of events was based on EHRs and may not have specifically captured influenza-related hospital admissions. However, the operational definition of this outcome has been largely adopted in prior investigations with consistent results (Lapi, Domnich, et al., 2022; Lapi et al., 2019; Lapi, Marconi, et al., 2022). Finally, the influenza vaccine uptake is also influenced by a variety of other factors, such as vaccine hesitancy, vaccine availability, vaccine accessibility, and public health policies related to vaccine distribution and administration (Mahroum et al., 2018). Therefore, reducing the time lapse between vaccine delivery to regional LHAs and actual allocation to GPs may not necessarily guarantee the greatest effectiveness of a vaccine campaign. A comprehensive approach that addresses all these factors is necessary to achieve high vaccine coverage rates.

In conclusion, the results obtained from this study emphasize the significance of a reduced time period between vaccine distribution and administration for reducing the incidence of all-cause and respiratory-related hospitalizations, in addition to other factors that influence vaccination barriers and hesitancy.

Chapter 7. The economic and fiscal impact of influenza vaccination for healthcare workers in Italy

Declarations

This chapter is a slightly modified version of the manuscript entitled "The economic and fiscal impact of influenza vaccination for healthcare workers in Italy" by Giovanna Elisa Calabrò, Filippo Rumi, Elettra Fallani, Roberto Ricciardi and Amerigo Cicchetti (© 2022 by the authors) published in Vaccines (Calabrò, Rumi, et al., 2022). The article is published in open access modality and distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), which permits any use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

7.1. Introduction

Influenza (or the flu) is an acute infectious viral respiratory illness that can annually lead to seasonal outbreaks and, rarely, pandemics (Breese et al., 2018). The global estimates of the World Health Organization (WHO) report 290.000-650.000 influenza-associated respiratory deaths every year. Moreover, influenza is reputed among the infectious diseases with the highest burden on population health in Europe (Cassini et al., 2018) where it causes 4–50 million symptomatic cases annually, approximately 15,000–70,000 deaths' and 150,000 influenza-related hospital admissions (Villani et al., 2022). The WHO divided vulnerable individuals who have a greater risk of contracting influenza, transmitting it and developing complications into five risk categories, namely, children under 5 years of age, pregnant women, people over 65, chronic patients and health care workers (HCWs) (World Health Organization (WHO), 2018). However, despite WHO recommendations, influenza vaccination policies are consolidated only in high-income countries and in a few low- and middle-income countries (Domnich et al., 2019), and in some risk categories, such as HCWs, suboptimal vaccination coverage is reported worldwide (Guillari et al., 2021). HCWs are at increased risk of exposure to influenza, posing a potential threat to their health and patient safety. exposure to influenza, posing a potential threat to their health and to patient safety. A systematic review and meta-analysis of the flu incidence among medical personnel and other healthy adults by Kuster et al.

(Kuster et al., 2011) (58,245 participants in total; influenza seasons 1957–2009) suggested that HCWs have a higher risk of symptomatic influenza infections (up to 2.5 times) compared to the population of healthy adults working in settings other than health care facilities. According to the estimates of Kuster et al. up to 22% of HCWs (especially those not vaccinated against influenza) can have influenza every epidemic season (Kuster et al., 2011). Furthermore, several studies reported data on presenteeism associated with influenza-like illness (ILI) among HCWs (Jędrzejek & Mastalerz-Migas, 2022; Perl & Talbot, 2019; Widera et al., 2010). Results of these studies show that a large group of physicians (even >75% (Jędrzejek & Mastalerz-Migas, 2022)) admit to carrying out their work despite having flu-like symptoms (the so-called presenteeism). For example, according to the results of an American survey (involving 1914 HCWs; influenza season 2014–2015), 41.4% of the respondents reported being present at work with influenza-like symptoms (a median of 3 days), while pharmacists and physicians were the ones who most commonly reported being present at work when sick (67.2% and 63.2%, respectively) (Chiu et al., 2017). In this way, HCWs can promote influenza virus transmission, putting patients at risk (Jędrzejek & Mastalerz-Migas, 2022). Globally, it is estimated that the HCWs influenza vaccination rates range from 2–44% and the recommended optimal influenza vaccination coverage rate for medical personnel to protect patients is about of 90% (Jędrzejek & Mastalerz-Migas, 2022). Nevertheless, suboptimal vaccination coverage is also reported in Europe (Dini et al., 2018). Although several European countries have specific vaccination programs for HCWs, a significant proportion of them remain susceptible to influenza because they are unvaccinated (Maltezou, Theodoridou, Ledda, & Rapisarda, 2019). The most recent European report about seasonal influenza vaccination coverage rate detected a suboptimal adherence among HCWs for the 2015-16, 2016-17 and 2017-18 seasons, ranging from 63,2% in Belgium to 15,6% in Italy (Mereckiene, 2018). Nonetheless, a considerable intensification of flu vaccine uptake was observed in Italy during the 2020–2021 influenza season, at least partly as a consequence of the SARS-CoV-2 pandemic (Domnich et al., 2021; Scardina et al., 2021). The maintenance of this positive trend is desirable, since HCWs model the health behavior to follow, advising patients and educating by example, and they have the responsibility to protect themselves to protect their vulnerable patients (Costantino et al., 2020). Therefore, vaccination is the most effective shield against influenza (World Health Organization (WHO), 2019b) both because it greatly increases the probability of not contracting the disease and because it lessens the severity of flu symptoms, which are generally, not followed by further complications. Furthermore, influenza vaccination represents an important protective measure not only for individuals, but also for the community (Villani et al., 2022). It reduces the probability of complications and consequently the impact in terms of health care burden (hospitalizations, outpatient visits, and medications) (Calabrò et al., 2020), and the impact on children's school absences and missed working days, either due to secondary illness in a caregiver or the need to care for a sick child (Villani et al., 2022), and on society, in terms of productivity losses and workers' absenteeism (Dini et al., 2018). Indeed, vaccine-preventable diseases (VPDs), such as influenza, have a significant impact not only on the health and social care system, but also on the production and economic systems. By decreasing the morbidity and mortality of VPDs, vaccinated workers are more likely to have improved productivity, work for more time, and remain active and prolific for longer in the job market than unvaccinated workers (Bloom et al., 2021). Moreover, flu immunization is recommended during seasonal epidemics to ensure proper functionality of health services and prevent presenteeism and absenteeism (Antinolfi et al., 2020; Jędrzejek & Mastalerz-Migas, 2022). An Italian study conducted in a large hospital in Rome during the 2017–2018 influenza season estimated a distinctly lower loss of productivity per capita in vaccinated HCWs compared to unvaccinated HCWs (respectively, €297.06 and €517.22), leading to a cumulative difference of 120.07 € for each undisposed day by applying the so-called human capital. approach. The same calculations have been performed using an alternative method, the friction cost model, achieving the same results, even if in a less pronounced way (Colamesta et al., 2019). The relevance of the economic burden of respiratory diseases in HCWs has been further highlighted by a prospective Swiss surveillance study (Kuster et al., 2021). The study, performed during two consecutive flu seasons (2015–2016 and 2016–2017), reported that nearly 90% of the health care professionals analyzed had manifested at least one influenza symptom, and 28% had missed one or more working days. In addition, 68% of the participants had gone to work despite the presence of influenza symptoms, introducing the problem of presenteeism with respiratory diseases, which represents a threat for colleagues and patients (Kuster et al., 2021). In contrast, a systematic review and meta-analysis found a non-significant influence of flu vaccination on ILI incidence among HCWs, although a strong benefit was observed when the outcome became more specific and analyzed only the laboratory-confirmed influenza case rate (Imai et al., 2018). Therefore, given the importance of appropriately allocating the available resources of the health care system, the development of new health economic models is needed to guide policy-makers in a value-based evaluation of immunization strategies that take into account the whole value of vaccination (de Waure et al., 2022). The economic impact of vaccinations should incorporate health and non-health benefits of vaccination in both vaccinated and unvaccinated populations, thus allowing for estimation of the societal value of vaccination (Wilder-Smith et al., 2017). When assessing the economic value of vaccines, decision-makers should adopt a full societal perspective that also considers the fiscal impact of an infectious disease (Ruggeri et al., 2020). The fiscal health model assumes that a higher productivity of HCWs translates into increased individual income, resulting in additional government tax revenues available to reinvest in health care services and the workforce. If an illness decreases the individual productivity, all the systems are negatively affected (Ruggeri et al., 2020). Ruggeri et al. (Ruggeri et al., 2020) assessed the fiscal impact of influenza, pneumococcus, and herpes zoster vaccines in Italy through the human capital approach, focusing on the general population aged 30 to 65. The study concluded that a flu vaccination program able to avert 200,000 influenza infections would increase the annual productivity by approximately €111 million and the fiscal revenue by approximately €18 million. Therefore, the main objective of the present study was to use the theoretical framework developed by Ruggeri et al. (Ruggeri et al., 2020) to estimate the economic and fiscal impact of an influenza vaccination program for HCWs in Italy.

7.2. Materials and Methods

We assessed the economic impact of an influenza vaccination program among HCWs in Italy by considering direct healthcare costs, productivity losses, and the fiscal impact. Specifically, the analysis applied the theoretical framework proposed by Ruggeri et al. in 2019 (Ruggeri et al., 2020). According to this framework, the accumulation of human capital and the increase in population health are key factors of economic growth in a country. Therefore, the investment in new health technologies capable of increasing population health correlates with the increase in workers' productivity. Increasing productivity increases incomes, and therefore consumption and tax revenues, which in turn could be used by governments to implement investments in health (Ruggeri et al., 2020).

We conducted the analysis in two-stage. First, we estimated the number of HCWs exposed to the flu, second we performed a cost analysis aimed to estimate the reduction of the indirect costs (productivity losses due to working days lost) and the increase in tax revenues deriving from the increase in the vaccination coverage among HCWs. For the estimation of social costs due to productivity losses and therefore to estimate the influenza fiscal impact, we used the human capital approach (Ruggeri et al., 2020). According to this approach, the individual "produces" in proportion to the income received, and the salary corresponds to the effective contribution of the worker to the productive activity (Ruggeri et al., 2020).

Epidemiological data were extrapolated from the literature. Finally, the analysis took into account a vaccination coverage among HCWs that ranges between 30% and 70%. Results were reported by number of HCWs exposed to the flu, indirect costs avoided and total increase in tax revenue.

7.2.1. Fiscal impact estimation

As reported by Ruggeri et al. (Ruggeri et al., 2020), we defined the fiscal impact as the decrease in tax revenue resulting from the reduction in individual income due to a specific condition / disease. Tax revenues are typically derived from individual income, which is correlated with productivity. Productivity in turn strongly depends on people's health. Therefore, the sustainability of healthcare systems may depend on their ability to ensure high levels of productivity through maintaining or improving health.

The purpose of our evaluation was to test the analytical framework developed by Ruggeri et al. 2019 (Ruggeri et al., 2020) to estimate the global impact (direct, indirect and fiscal) of a flu vaccination program for HCWs in Italy. Our assessment was consistent with the background of the theoretical framework and assumed that the accumulation of human capital and the increase in population health is the key driver of economic growth and the results of an endogenous process (Ruggeri et al., 2020). Therefore, according to this perspective, governments should invest in new health technologies in order to increase the population health, thus improving production growth. Increasing productivity increases incomes, therefore consumption, and tax revenues, which in turn can be used to increase investment in health. This process can be simplified with the following cause and effect formula:

$$+H \xrightarrow{yields} +y \xrightarrow{yields} +W \xrightarrow{yields} +T \xrightarrow{yields} +G,$$

where H represents the number of healthy individuals, y represents employer productivity, W represents employee income, T represents total tax revenue, and G represents public health expenditure (Ruggeri et al., 2020).

7.2.2. Costs Estimation

To determine the fiscal impact related to the increase in vaccination coverage among HCWs, a simulation was conducted to identify avoided productivity losses, tax revenues and social costs associated with the flu syndrome. The model considered an influenza attack rate in an unvaccinated cohort of 4.4% (Somes et al., 2018) and a vaccination coverage in the HCWs group of 30% (assumption). These two parameters were useful in defining the HCWs who could have contracted the influenza virus.

The model also assumed that HCWs receiving the vaccine did not contract the flu. Then, an average of the total number of working weeks and weekly working hours for Italian HCWs was estimated. Furthermore, an average number of weeks of work of 48 and a total of weekly working hours of 44 were assumed. The model has broken down the hourly cost for each professional of the National Health Service (NHS) by identifying the fixed part on the gross taxable amount (83%) and the variable part (17%). The cost of one hour of work for a HCW, considering both specialists and other HCWs (such as nurses, midwives, pharmacists) in Italy was of € 35.04. Therefore, a fixed part of € 29.08 and a variable part of € 5.96 were considered in the simulation. On the basis of this information, the model calculated the total weekly average gross taxable amount of € 1,541.76 and the annual average gross taxable amount of € 74,004.48. Considering an average duration of flu symptoms of two days (conservative assumption based on Italian National Institute of Health data (National Institute of Health, 2018b)), the productivity losses expressed in number of hours lost due to the flu syndrome (16 working hours) were calculated. Thus, flu syndrome could potentially generate an impact on the total annual taxable amount of € 73,909.17 (compared to € 74,004.48 that is the total annual taxable amount). The model calculated an average annual tax revenue of € 24,991.93 for the HCWs compared to € 24,950.94 among those who contract the influenza. Thus, the tax impact for HCWs was estimated of € 40.98 for flu syndrome episode. **Table 7.1** shows the estimates described above.

Table 7.1. Fiscal impact and indirect costs estimation.

Variable	Value	Source
Total working hours / HCWs	2,112	Italian National Institute of Statistics, 2022 (Italian National Institute of Statistics (ISTAT), s.d.-b)
Total working hours / week	44	Assumption
Hourly cost	€35.04	Calculated
Taxable Hourly Fixed Part	€ 29.08	Calculated
Taxable Hourly Variable Part	€ 5.96	Calculated
Total Weekly Taxable Amount	€ 1,541.76	Calculated
Total Annual Taxable Amount	€ 74,004.48	Calculated
Number of working days lost (flu syndrome average duration)	2	Italian National Institute of Health, 2022 (National Institute of Health, 2018b)
Number of working hours lost due to the flu syndrome	16	Calculated
Working hours considering an episode of flu / HCWs	2,096	Calculated
Impact of influenza complications on the total potential / man hours	2,112	Calculated
% people with flu complications	0%	Assumption
Impact of flu and complications among the HCWs total annual taxable income	€ 73,909.17	Calculated

Flu impact on the patient's total annual taxable income	€ 73,909.17	Calculated
Tax on personal income (Italy)		
€ 15,000	*23.00%*	Italian budget law 2021 (Gazzetta Ufficiale, s.d.)
€ 28,000	*27.00%*	Italian budget law 2021 (Gazzetta Ufficiale, s.d.)
€ 55,000	*38.00%*	Italian budget law 2021 (Gazzetta Ufficiale, s.d.)
€ 75,000	*41.00%*	Italian budget law 2021 (Gazzetta Ufficiale, s.d.)
€ 80,000	*43.00%*	Italian budget law 2021 (Gazzetta Ufficiale, s.d.)
Annual income (no flu)	€ 24,991.93	Calculated
HCW annual revenue	€ 24,950.94	Calculated
HCW tax impact	€ 40.98	Calculated
Annual social costs per HCWs	€ 560.64	Calculated

7.2.3. Eligible population

The eligible population were extrapolated from the latest available data referring to 2021 and provided by the Italian National Institute of Statistics (Italian National Institute of Statistics (ISTAT), s.d.-b).

Table 7.2 reports the type of HCWs, the incidence on 10,000 inhabitants and an average annual salary. The total number of HCWs in Italy was 753,658 in 2021. The model considered the total number of HCWs potentially exposed to flu. Assuming a percentage of vaccination coverage of 30% and an influenza attack rate for an unvaccinated cohort equal to 4.4% (Somes et al., 2018), the analysis considered a total of 23,213 flu cases among the HCWs using the following formula:

$$Total\ number\ of\ HCWs * (1 - vaccination\ coverage\ among\ HCWs) * attack\ rate\ among\ unvaccinated\ cohort$$

Table 7.2. Eligible population considered for the model (data referring to the Italian population for 2021 (Italian National Institute of Statistics (ISTAT), s.d.-b)).

	Type of HCWs	**Type of data Health Personnel**	**Health Personnel per 10,000 inhabitants**	**Average annual salary**
A	Anesthetists	12,226	2.06	76,900 €
	Cardiologists	13,706	2.31	98,000 €
	Surgeons	8,098	1.36	125,000 €
	Gastroenterologists	3,543	0.6	55,000 €
	Geriatricians	4,178	0.7	64,900 €
	Neurologists	6,658	1.12	64,900 €
	Oncologists	4,633	0.78	86,400 €
	Orthopedists	9,277	1.56	95,000 €
	Otolaryngologists	4,336	0.73	94,700 €
	Urologists	4,053	0.68	86,400 €
B	Other Medical Specialists	109,497	18.42	80,146 €
C	Pediatricians	16,569	2.79	64,900 €

	Free Choice Pediatricians (FCPs)	7,285	1.23	64,900 €
	Pediatricians (Excluding FCPs)	9,284	1.56	64,900 €
(A+B+C)	Medical Specialists	187,490	31.54	84,533 €
D	General Practitioners	50,354	8.47	105,000 €
	General Practitioners (GPs)	41,707	7.02	80,934 €
	Other doctors (Excluding GPs)	8,647	1.45	77,545 €
(A+B+C)+D	Total Doctors (General Practitioners and Specialists)	237,844	40.01	79,279 €
E	Dentists	51,678	8.69	77,000 €
	Midwives	17,239	2.9	33,600 €
	Nurses	373,064	62.76	26,400 €
	Pharmacists	73,833	12	26,500 €
(A+B+C)+D+E	**Total HCWs**	753,658	128	74,471 €

7.2.4. Sensitivity Analysis

A sensitivity analysis was provided by varying the vaccination coverage value among HCWs. This specific analysis allowed us to understand the implications from the point of view of (indirect) social costs and fiscal impact. In fact, vaccination coverage is potentially able to reduce the absenteeism of HCWs. This implies a reduction in productivity losses and at the same time an increase in tax revenues. The results of the model were presented starting from a vaccination coverage of 30% (base case) and assuming an incremental trend of 10% up to 70%.

7.3. Results

On the basis of the estimate of the fiscal impact carried out, an incremental increase in vaccination coverage among HCWs identified in the Italian setting was assumed in our model. Therefore, the model provided a simulation, starting from 30% of vaccination coverage, of 10% coverage increases in order to estimate the impact resulting from the increase in terms of additional tax revenue and indirect costs avoided. The objective of the simulation is, therefore, to estimate the reduction of indirect costs deriving from the lower number of professionals affected by the flu (expressed in lost working days), and from the increase in tax revenues that the reduction of working days lost due to flu symptoms was able to make (fiscal impact).

Table 7.3 shows the results of the analysis. We estimated that the 10% (from 30% to 40%) increase in influenza vaccination would be able to bring benefits (savings) in terms of social costs equal to -€ 1.301.394,93 taking into account cases of influenza avoided equal to 2,321. These results were estimated using the human capital approach. With regard to the fiscal impact, the same percentage of variation in vaccination coverage would be able to increase tax revenues of € 95.131,97. This revenue, consistent with the fiscal impact framework, could be used to finance interventions in the field of public health, generating more health which in turn could generate a population with less productivity losses and consequently with a higher tax revenue. The cumulative results assuming an incremental increase in vaccination coverage among HCWs of 10% per year over a 5-year time horizon, within the simulation conducted would lead to a total saving in terms of reduction of productivity losses expressed in the form of days of work lost due to the flu syndrome equal to -€ 4.475.497,16. In terms of the increase in tax revenues, the cumulative result estimated a value of € 327.158,84. **Figures 7.1-7.3** show the results of the analysis stratified by percentage of vaccination coverage.

Table 7.3. Main results of the fiscal impact of influenza vaccination for HCWs in Italy.

Year	Vaccine coverage	Number of HCWs exposed to influenza	Fiscal impact	Indirect costs	Total	Increase in tax revenues (cumulated)	Reduction in loss of productivities (cumulated)
1	30%	23.213	-€ 951.319,69	€ 13.013.949,29	€ 13.965.268,98	€ - *	€ - *
2	40%	20.891	-€ 856.187,72	€ 11.712.554,36	€ 12.568.742,09	€ 95.131,97	-€ 1.301.394,93
3	50%	18.802	-€ 770.568,95	€ 10.541.298,93	€ 11.311.867,88	€ 180.750,74	-€ 2.472.650,37
4	60%	16.922	-€ 693.512,06	€ 9.487.169,03	€ 10.180.681,09	€ 257.807,64	-€ 3.526.780,26
5	70%	15.230	-€ 624.160,85	€ 8.538.452,13	€ 9.162.612,98	€ 327.158,84	-€ 4.475.497,16

** Each year, the number of HCWs potentially exposed to influenza decreases by 10% (due to increased vaccination coverage). Therefore, the first year the increases are 0.*

Figure 7.1. Simulation - Fiscal impact (cumulated).

Figure 7.2. Simulation - Indirect costs (cumulated).

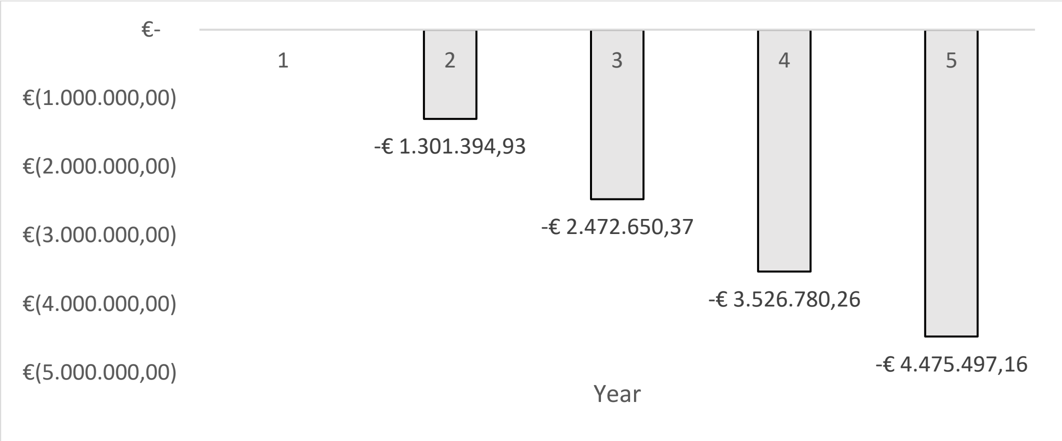
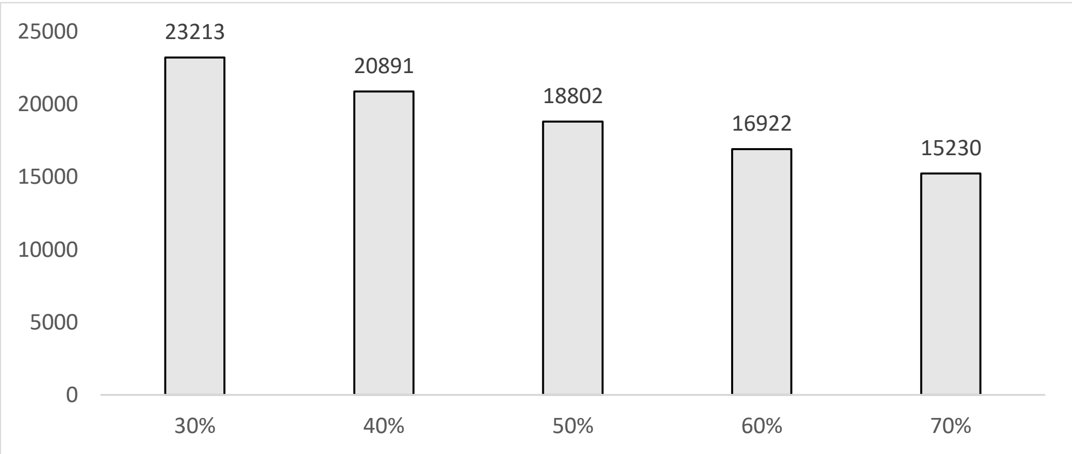


Figure 7.3. Simulation - Number of influenza cases among HCWs.



As seen in the analysis carried out, an increase in vaccination coverage on the one hand leads to an increase in terms of tax revenue deriving from the minor number of professionals affected by the flu virus, and at the same time involves a reduction in indirect costs (productivity losses) due to fact that professionals lose fewer days of work on average.

The model did not consider the direct health costs related to the acquisition and administration of the flu vaccination. In addition, within the simulation a vaccine efficacy in the prevention of influenza cases equal to 100% was assumed. However, in the light of the results obtained, it is possible to believe that an extension of the vaccination campaign among HCWs could represent a cost-saving strategy with a view to allocative efficiency of the resources available for the NHS. This is because direct healthcare costs are likely to be offset by using a broader perspective. We therefore believe that the savings in terms of indirect costs and the greater benefits deriving from the increase in tax revenues can amply offset the costs of acquiring and administering the influenza vaccines among the target population of our simulation.

7.4. Discussion

In our study, we implemented a theoretical framework on the fiscal impact (Ruggeri et al., 2020) to estimate the economic impact of an influenza vaccination program for HCWs in Italy by considering direct healthcare costs, productivity losses, and the fiscal impact. According to the proposed framework (Ruggeri et al., 2020), the increase in the productivity of vaccinated HCWs due to the absence of flu symptoms increases their incomes, and therefore consumption and tax revenues, which in turn could be used by governments to implement investments in health.

In our analysis, first we estimated the number of HCWs exposed to the flu, second we performed a cost analysis aimed to estimate the reduction of the indirect costs (productivity losses due to working days lost) and the increase in tax revenues deriving from the increase in the vaccination coverage among HCWs. Therefore, the analysis took into account a vaccination coverage among HCWs that ranges between 30% and 70%.

Assuming a percentage of vaccination coverage of 30% and an attack rate of influenza equal to 4.4% (Somes et al., 2018) the analysis considered a total of 23,213 HCWs exposed to seasonal flu virus. Estimating an increase in vaccination coverage among HCWs of 10% (from 30% to 40%), savings in terms of social costs of -€ 1.301.394,93 could be achieved. These results were estimated using the human capital approach. The same percentage of variation in vaccination coverage would be able to increase tax revenues of € 95.131,97. Furthermore, assuming an incremental increase in vaccination coverage among HCWs of 10% per year over a period of 5 years time horizon, total savings could be obtained in terms of reduction of productivity losses equal to -€ 4.475.497,16 and an increase of tax revenues of € 327.158,84. This revenue could be used to finance interventions in the public health field, generating more health which in turn could generate a population with less productivity losses and consequently with a higher tax revenue.

Therefore, an increase in vaccination coverage among HCWs on the one hand leads to an increase in terms of tax revenue deriving from the minor number of professionals affected by the influenza, and at the same time involves a reduction in indirect costs (productivity losses) due to fact that HCWs lose fewer days of work on average.

The optimization of the use of the limited resources available and the economic and financial sustainability of health systems have become central topics in the discussion of the health sector over the last few years (de Waure et al., 2022). In this context, flu vaccination in children, adults, and the elderly results in a reduction of hospitalizations, ambulatory care visits, and medical interventions, which leads to substantial savings in healthcare costs each year in Europe and worldwide (Largeron et al., 2015). Furthermore, this vaccination among the HCWs is associated with a substantial decrease in mortality for elderly patients and, therefore, the cost of not vaccinating HCWs can also be substantial in terms of missed benefits (Largeron et al., 2015). Still, influenza vaccination is associated with a reduction in indirect costs in terms of lost productivity and days of work lost due to illness (Dini et al., 2018; Villani et al., 2022), and reduces the potential fiscal impact caused by the disease (Ruggeri et al., 2020). Therefore, flu vaccination represents an exceptional opportunity to keep people healthy and it can contribute to the sustainability of healthcare systems by evading unnecessary use of financial and human resources and freeing resources for other health interventions (Largeron et al., 2015). These principles are perfectly in line with what is currently proposed within the Value-Based Healthcare (VBHC). Indeed, recently the Expert Panel on Effective Ways of Investing in Health (EXPH) of the European Commission (EC) proposed a value-based long-term strategy that provides a reallocation of resources from low to high value care in order to freeing resources for reinvestment in health [29]. In particular, the EXPH proposed to VBHC as a comprehensive concept built on four value-pillars: appropriate care to achieve patients' personal goals (*personal value*), achievement of best possible outcomes with available resources (*technical value*), equitable resource distribution across all patient groups (*allocative value*) and contribution of healthcare to social participation and connectedness (*societal value*) (Directorate-General for Health and Food Safety (European Commission), 2021). This approach has also been applied to vaccination field emphasizing the importance of evaluating and communicating the whole value of vaccines and vaccination (Calabrò, Carini, et al., 2022; de Waure et al., 2022). Understanding of value in health should be shared by all stakeholders and be geared towards the goal of maximizing social wellbeing. In fact, in recent years we are moving from the concept of a value-based healthcare to the concept of a value-based health system as it is the whole health system that contributes to the wellbeing of society, thanks also to prevention and health promotion (Smith et al., 2020). Nonetheless, despite the effectiveness and cost-effectiveness of prevention interventions, investment in prevention rests low in many countries (World Health Organization. Regional Office for Europe et al., 2018). Moreover, this is reflected, for example, with vaccination coverage still not optimal for the main VPDs, including influenza, in Europe and elsewhere. For this reason, health policies and immunization strategies based on the whole value of vaccination are needed. To achieve these ambitious goals, strengthening the generation of evidence and data is necessary in order to guarantee an evidence-based decision-making process also in the context of influenza vaccination. Furthermore, new evidence-based assessment frameworks and tools capable of recognizing the whole value of the flu vaccines and vaccination are indispensable (de Waure et al., 2022). This challenge evidently relates also to the need to better assess the impact of flu vaccination at societal level. The economic impact of influenza vaccination should incorporate the health and non-health benefits of vaccination, both in the vaccinated and in the unvaccinated population, thus also allowing estimating its societal value (Wilder-Smith et al., 2017). Therefore, the development of health economic models capable of capturing not only the cost-benefit of vaccination, but also the value of health itself is needed (Rappuoli et al., 2014).

Healthcare decision-makers and policy-makers should be aware of the limitations of traditional economic assessments for evaluating the vaccines value (Annemans et al., 2021). Future economic evaluations should pay more attention to the effect of vaccination on complications prevention, generation of health benefits for HCWs and benefits for the community beyond individual protection; besides, guidelines for the economic assessment of the whole value of vaccinations are needed, and economic analysis must be conducted taking into account the societal perspective as well as that of the health system, in order to underline and prove the whole value of vaccines (Annemans et al., 2021). From the societal perspective, influenza vaccination represents an important protection measure not only for individuals but also for the community, and it is cost-effective for children, pregnant and postpartum women, high risk groups, and healthy working age adults (Ting et al., 2017). Therefore, a complete social perspective should be adopted to assess the economic value of vaccines. Traditional methods to estimate the illness costs from a social perspective can also be improved by considering the fiscal impact, which explains the decline in diseases fiscal revenues. The potential reduction of the fiscal impact should be included in the evaluation of vaccines and vaccinations, adding a new dimension to this valorization (Ruggeri et al., 2020).

In our analysis, we have shown that increasing influenza vaccination coverage among HCWs can reduce productivity losses and an increase fiscal revenues that could be used to finance other health interventions such as the implementation of immunization strategies against influenza among HCWs.

Influenza vaccination among HCWs has been an important topic of study in Italy in recent years, particularly with the aim of evaluating the effectiveness of vaccination campaigns and increasing vaccination coverage (Barbara et al., 2020; Corsaro et al., 2017; Dettori et al., 2021; Gilardi et al., 2018; Panatto et al., 2020; Tognetto et al., 2020). Increasing vaccination coverage among HCWs is not always guaranteed and is often a difficult goal to achieve. In fact, it depends on several variables related to the availability and delivery of the flu vaccine, the presence of adequate and expert human resources, health education, and the promotion of well-structured communication campaigns (Dettori et al., 2021). A fundamental element to increase the adherence to influenza vaccination by health professionals appears to be linked to the effectiveness of vaccination campaigns. In particular, the use of different communication approaches such as posting explanatory leaflets and posters in each hospital ward, distributing information material, creating promotional spaces—through the use of social media and conveying correct communication through websites dedicated to vaccination (Dettori et al., 2021) - and using innovative methods such as forum theatre (Corsaro et al., 2017), have led to an increase in vaccination coverage against influenza among Italian HCWs. Other effective modalities were the organization of dedicated courses for HCWs, the active invitation to vaccination through e-mail, the on-site vaccination intervention, and the organization of dedicated units for the influenza vaccination of HCWs in the hospital setting (Barbara et al., 2020; Gilardi et al., 2018; Panatto et al., 2020; Tognetto et al., 2020). However, from the literature data it is clear that the best strategy to promote flu vaccination among HCWs should include multiple approaches in order to obtain an increasing coverage trend in all health care settings (Tognetto et al., 2020). On the other hand, the most recent literature criticizes the policy of mandatory flu vaccination among HCWs pointing to the lack of reliable empirical evidence on the real benefits for patients (Jędrzejek & Mastalerz-Migas, 2022). Mandatory vaccinations for HCWs have been in place in few European countries and for specific VPDs with varying success (Maltezou et al., 2011). In contrast, mandatory influenza vaccination policies were widely adopted by health care facilities in the United States the past decade with uptake rates of >90% among HCWs working in hospitals (Black et al., 2018). In Italy, the National

Vaccination Plan (PNPV 2017–2019) strongly recommends influenza vaccination of HCWs (Italian Ministry of Health, 2017). This condition allows each HCW to choose whether to get vaccinated or not. In addition, the individual Italian Regions have adopted different measures on vaccinations, especially in the workplace (Maltezou, Theodoridou, Ledda, Rapisarda, et al., 2019). Given the available and multiyear evidence in the United States, in terms of high uptake rates on one hand, and the fact that voluntary flu vaccination programs have failed to achieve high coverage rates, the implementation of mandatory flu vaccination policies could be justified in order to prevent the transmission of influenza through HCWs (Maltezou, Theodoridou, Ledda, Rapisarda, et al., 2019). Therefore, flu vaccination policies for HCWs will need to be reviewed and health care professionals will need to be prepared to address these issues in the next years.

In our analysis, we have shown that increasing influenza vaccination coverage among HCWs can lead to significant savings. These results are fundamental in view of the sustainability of health systems and of a value-based allocation of health resources.

Furthermore, our findings underscore the importance of investing in and using more effective flu vaccines. In fact, only by using more effective vaccines it is possible to obtain a greater impact of vaccination also in terms of economic savings for the health system and for society. In light of the results obtained, it is clear that promoting influenza vaccination strategies among HCWs is a priority to be implemented in order to increase vaccination coverage in this target population, guarantee health benefits for the health professionals themselves and their patients and contribute to sustainability of health systems through a value allocation of health resources.

Our study has some limitations, the main one being the fact that most of the data were determined only on the basis of scientific literature and assumptions. However, to overcome the lack of robustness associated with the values considered in the analysis, a sensitivity analysis was conducted. Furthermore, our results are conservative as, for example, we only considered two working days lost due to the flu, knowing that it could be even more (between 4 and 6 days according to literature data (Keech & Beardsworth, 2008)). The analysis also considered an average salary among HCWs without considering the differences between the various professional figures. The use of a weighted average and the retrieval of more specific information on professionals most exposed to contagion with the flu virus could provide more detailed information on indirect costs and the resulting fiscal impact.

Moreover, the model did not consider the direct health costs related to the acquisition and administration of the flu vaccination, but our goal was not to assess the economic and fiscal impact of specific flu vaccines. In fact, we wanted to determine the fiscal impact related to the increase in flu vaccination coverage among HCWs regardless of the vaccine used. In the light of the results obtained, it is possible to believe that an extension of the vaccination campaign among HCWs could represent a cost-saving strategy because direct healthcare costs are likely to be offset by using a broader perspective. In fact, the savings in terms of indirect costs and the greater benefits deriving from the increase in tax revenues can amply offset the costs of acquiring and administering the influenza vaccines.

However, in the future it will also be necessary to evaluate the fiscal impact of influenza vaccination strategies with specific vaccines also because the results of the model can be significantly influenced by their effectiveness.

Nevertheless, in our opinion, our economic model, which is the second, to our knowledge, to have applied the fiscal impact framework to influenza vaccination, may broaden the knowledge on the impact of influenza in the Italian setting and, therefore, support decision makers in defining vaccination health policies based on a broader value of available flu vaccines. In fact, new evidence of the value of the different available flu vaccines is crucial to promote their appropriate use and to support the implementation of value-based and evidence-based immunization strategies (Calabrò et al., 2020).

Among health technologies, vaccines are one of the most successful of contemporary era. Technological innovation can lead to high costs and severe financial pressure on health systems. However, health systems cannot give up on this innovation, but must take into account the point of view of all stakeholders: citizens and patients should be guaranteed quick and equitable access to more effective health technologies; research and development efforts should be encouraged when oriented towards the production of high value technologies; decision and policy makers should support innovation by using evidence-based tools for their assessment; and health systems should promote technological innovation while ensuring their sustainability (Domnich, Manini, et al., 2020).

Furthermore, in light of the important scientific progress of recent years and the countless health needs of the population, it will be necessary to focus on value-based but also personalized prevention. In fact, the principles of personalized medicine have already been applied in the vaccinomics and adversomics fields in order to well understand interindividual variations in vaccine-induced immune responses and vaccine-related adverse events (Traversi et al., 2021). New knowledge in these areas will also help determine the “right” type or dose of vaccine for the “right” person, and therefore these aspects will also need to be included in the evaluation of a broader value of vaccines.

7.5. Conclusions

Influenza has a significant impact not only on the healthcare system, but also on the production and economic one. Vaccinated workers are more likely to have an improved productivity, work for more time, and remain active and prolific for longer in the job market compared to unvaccinated ones. This also applies to healthcare professionals. In fact, flu vaccination is recommended during seasonal epidemics to ensure proper functionality of health services and prevent absenteeism of the HCWs.

Influenza prevention in children, adults, the elderly, risk groups and HCWs through vaccination represents an exclusive chance to keep people healthy and to reduce the economic impact of influenza on the health systems and society. In particular, considering vaccination among HCWs and workers in general, it is able to avoid cases of disease by reducing the loss of productivity of workers and the fiscal impact of the illness. Increasing productivity increases incomes, therefore consumption, and tax revenues, which in turn can be used to increase investment in health. Hence, flu vaccination among HCWs can contribute to the sustainability of healthcare systems by avoiding unnecessary use of health resources and freeing resources for other health interventions. Improving uptake of flu immunization programs is critical for current healthcare systems that are looking for solutions for more efficient and value-based healthcare resource use.

Therefore, the widespread promotion of influenza vaccination and the implementation of health policies aimed at increasing vaccination coverage in all target populations are key factors for the long-term sustainability of health systems around the world.

Chapter 8. Concluding Remarks

The evaluation of the best strategy for the use of commercially authorized vaccines is one of the World Health Organization strategic objectives (World Health Organization (WHO), 2019a). Addressing vaccine wrong beliefs and reluctance can facilitate the adherence to influenza programs (World Health Organization (WHO), 2019a). In this regard, the basis to support this policy is a continuous monitoring of the factors that can have a positive role in the acceptance of these measures and of the elements that are instead associated with hesitation (European Commission, 2020; Leask et al., 2014). This is the aim of Chapters 2,3 and 4, developed within the project Influenza Observatory.

The first survey related to this project has been performed in May 2020 (Domnich, Cambiaggi, et al., 2020), just after the onset of the COVID-19 pandemic, with the purpose of evaluating and elucidating the beliefs, attitudes, and practices of a representative sample of Italian adults concerning influenza vaccination. A deeper understanding of the beliefs, attitudes, and practices surrounding influenza vaccination among Italian adults is crucial for developing targeted interventions to improve vaccine acceptance and coverage, both from the standpoint of future vaccination campaigns against influenza and pandemic preparedness plans.

Several determinants can affect influenza vaccines uptake. These factors can be categorized into three main groups: structural social determinants, intermediary correlates, and healthcare system-related factors (Domnich, Cambiaggi, et al., 2020; Nagata et al., 2013).

I. Structural Social Determinants:

Structural social determinants refer to the demographic and socio-economic characteristics that may influence an individual's decision to receive influenza vaccination. The following factors fall under this category:

1. Age: Age has been consistently identified as a significant determinant of influenza vaccination uptake. Older adults, especially those aged 65 and above, are more likely to receive influenza vaccination due to their increased vulnerability to severe illness.

2. Sex: Research suggests that gender differences may exist in influenza vaccination uptake, possibly due to differences in health-seeking behaviors and attitudes towards preventive measures.

3. Socio-economic status: Individuals with higher socio-economic status tend to have better access to healthcare services, including vaccination. Financial barriers and lack of health insurance coverage can hinder vaccination uptake among those with lower socio-economic status.

II. Intermediary Correlates:

Intermediary correlates represent factors that mediate the relationship between structural social determinants and influenza vaccination uptake. The following factors are considered intermediary correlates:

1. Residential location: Geographic location can impact vaccination uptake. Individuals living in urban areas may have better access to healthcare facilities and vaccination campaigns compared to those in rural or remote areas.

2. Behavioral beliefs: Personal beliefs and attitudes towards influenza vaccination play a crucial role in the decision-making process. Positive beliefs about vaccine effectiveness and safety can increase vaccination uptake.

3. Social influences: The influence of family, friends, and healthcare providers can significantly impact influenza vaccination decisions. Social norms and recommendations from trusted individuals can motivate individuals to get vaccinated.

4. Vaccination history: Previous experience with vaccination, including past influenza vaccinations, can influence future uptake. Individuals who have received influenza vaccination in the past are more likely to continue doing so.

5. Perceived susceptibility: Perceiving oneself as susceptible to influenza and its complications can increase vaccination uptake. Individuals who perceive themselves at higher risk are more motivated to protect themselves through vaccination.

6. Sources of information: Access to accurate and reliable information about influenza and vaccination is crucial in making informed decisions. Individuals who receive information from trusted sources are more likely to get vaccinated.

III. Healthcare System-related Factors:

Healthcare system-related factors encompass aspects related to healthcare infrastructure, policies, and practices. The following factors fall under this category:

1. Accessibility: The availability and accessibility of vaccination services influence uptake. Convenient access to vaccination clinics, extended clinic hours, and mobile vaccination units can improve vaccination rates.

2. Affordability: Cost can be a significant barrier to vaccination. Affordable or free vaccination programs can increase uptake, particularly among individuals with limited financial resources.

3. Healthcare provider recommendations: Strong recommendations from healthcare providers can positively influence vaccination decisions. Healthcare providers can address concerns, provide information, and emphasize the importance of vaccination.

The project Influenza Observatory tried to capture how this complex mix of personal and external factors can influence influenza vaccine uptake over time, in the context of COVID-19 pandemic and the progressive passage to a post-pandemic situation (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021, 2022; Domnich, Grassi, et al., 2023).

The investigated study questions have been adapted and updated from time to time according to new needs and factors emerged (for example, at the beginning of the project, COVID-19 vaccination was not yet available, but it was developed in a second moment and, thus, included in the analysis).

The data collection methodology used has been the computer-assisted web interviewing (CAWI) (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021, 2022; Domnich, Grassi, et al., 2023). This approach leverages the power and convenience of internet to administer surveys and collect responses. This approach offers advantages such as accessibility, efficiency, anonymity, and the potential for more reliable data. Particularly, the CAWI methodology allowed a timing administration of the survey to participants, which could also take place 2-3 times per year. This frequency consented the collection of data at various points in time, providing a more comprehensive understanding of the subject being studied and allowing the identification any changes, trends, or patterns that may have emerged over time (Ball, 2019; Brancato et al., 2006; Ng, 2006).

The use of computer-assisted web interviews offers several advantages. Firstly, it provides a convenient means for participants to respond to surveys. With just a computer and internet access, individuals can participate from the comfort of their own homes or any location that suits them. This accessibility increases the likelihood of obtaining a diverse range of participants.

Secondly, CAWI allows for efficient data collection and management. Through web-based surveys, data can be automatically collected and stored electronically. This eliminates the need for manual data entry, reducing the chances of errors and saving valuable time. Researchers can easily access and analyze the collected data, facilitating quicker insights and conclusions.

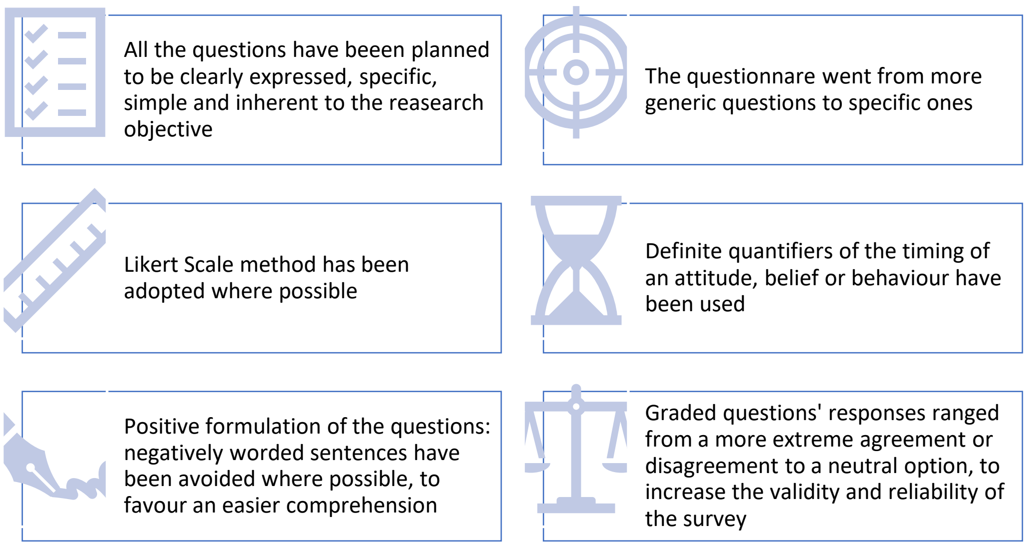
Furthermore, CAWI offers the advantage of anonymity. Participants can feel more comfortable providing honest and accurate responses when they are not required to disclose their identity. This anonymity helps to minimize any social desirability bias, resulting in more reliable and valid data.

However, CAWI also has its own disadvantages. Those with limited access to technology, are not suitable for self-administered questionnaires. Moreover, since participants are not required to disclose their identity, they may feel less accountable for their responses, which could lead to less honest and accurate responses. Additionally, because the researcher is not present to answer any questions or clarify any misunderstandings, participants may have difficulties in the survey comprehension, which could again lead to less reliable and valid data (Ball, 2019; Brancato et al., 2006; Ng, 2006).

Anyway, with a proper survey design and considerations for participant engagement, CAWI can be a valuable tool in gathering data for research and analysis.

The questionnaire design has been developed following specific precautions and rules (Lietz, 2010; Ng, 2006), summarized in **Figure 8.1**.

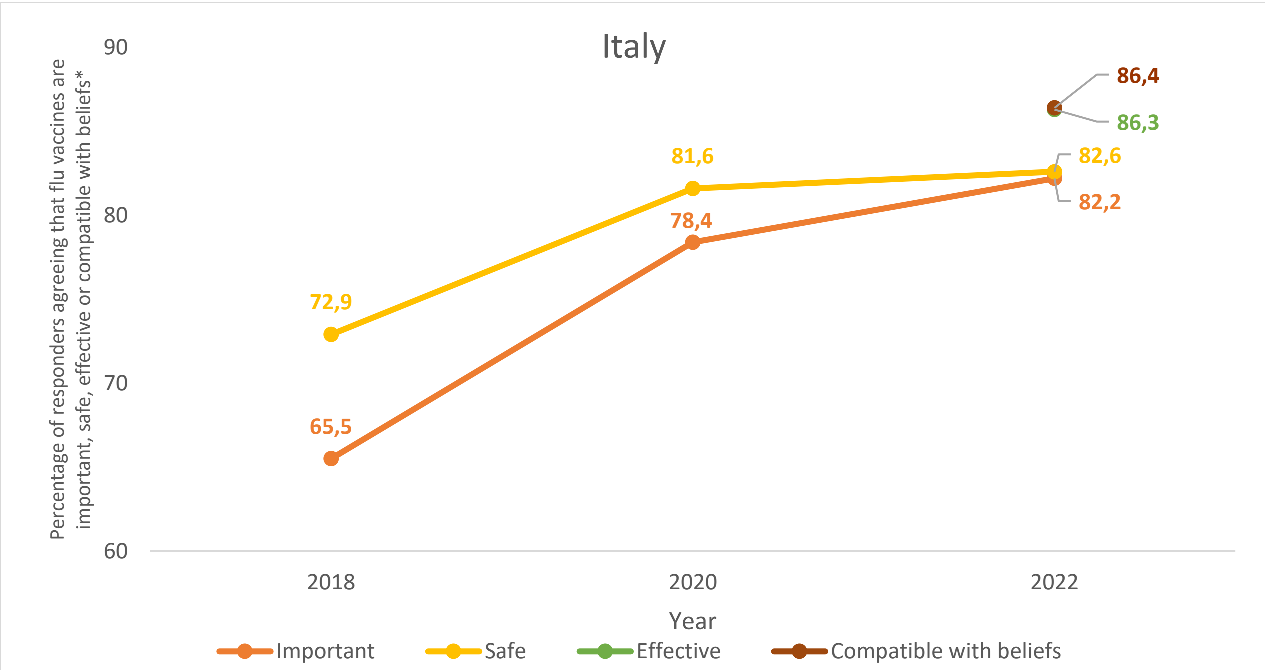
Figure 8.1. Questionnaire design method adopted in synthesis.



Cross-sectional surveys have been delivered to the panel at different times (2-3 times per year) during the evolution and development of distinct phases of the COVID-19 pandemic. Although the single questionnaire has been populated transversally and, thus, in a specific period, the administration of identical questions to the same population in exam allowed a longitudinal monitor of the responses. Some cross-sectional elements of innovations were eventually added time by time, according to changes in policy and technologies situation (for example, the arrival of COVID-19 vaccines or influenza and COVID-19 vaccinations co-administration). The presence of a longitudinal panel and, then, of the same persons questioned at each survey, was intended to remove the within-subject variation, leaving only the inter-person variability (Hillygus & Snell, 2015; Lynn, 2009; Schober & Vetter, 2018). The final aim was to try to monitor and associate, in the more reliable way, possible changes in attitudes, behaviors and beliefs to specific external changes or policies modifications occurred after SARS-CoV-2 appearance, excluding biases due to panel composition mutations.

Thus, different rounds of the Influenza Observatory project have provided different elements of input. According to the longitudinal study (Domnich et al., 2021), respondents' overall confidence in vaccines and willingness to receive the next seasonal influenza vaccination increased significantly after 1 year (from May 2020 to May 2021), specifically of 4.5 percentage points in the overall population. These data are aligned with the results of the European Vaccine Confidence project, which observed a positive trend from 2018 to 2020 and, then, 2022 in influenza vaccine trust (**Figure 8.2**) (European Commission, 2022). Of note, this trend was in contrast with that of overall vaccination, where no changes in safety beliefs have been monitored and a decrease in the perceived importance of vaccines has been detected (European Commission, 2022).

Figure 8.2. Trends in confidence (%) in the seasonal influenza vaccine between 2018 and 2022 for Italy (adapted from European Commission, 2022).



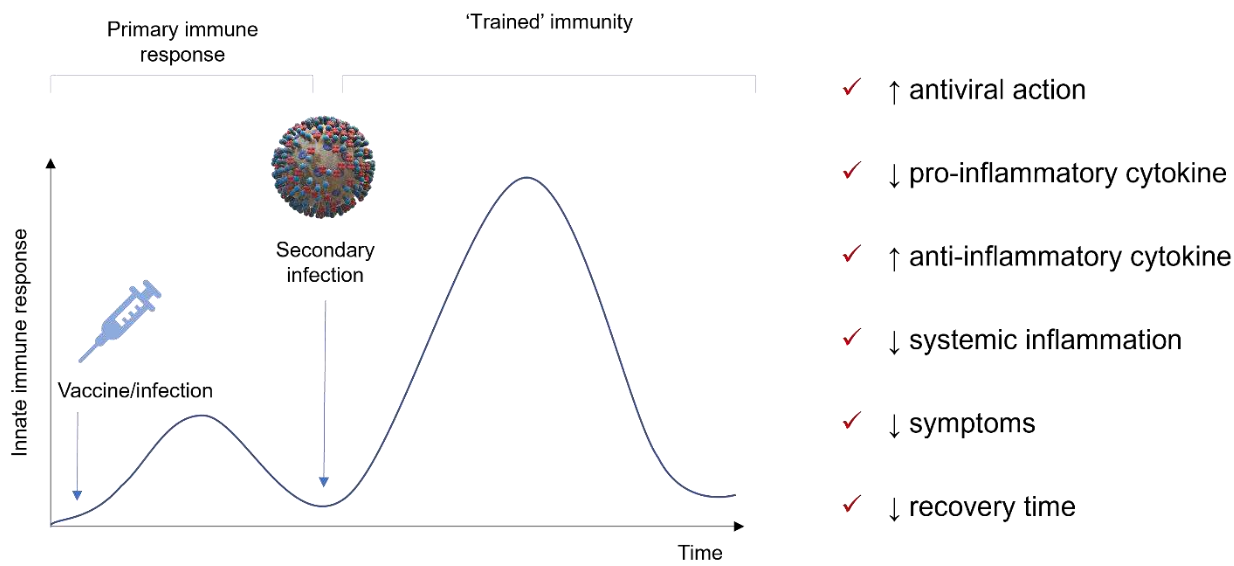
*questions about the influenza vaccine effectiveness and the compatibility with beliefs of the influenza vaccine were included only in 2022

This different fashion observed for the confidence toward influenza vaccination can be attributed to several factors. First of all, the alleviation of the burden on the health care system, saving medical resources and healthcare personnel for the treatment of other serious diseases (Italian Ministry of Health, 2021a; Paget et al., 2020; R. Wang et al., 2021). Secondly, influenza vaccination could facilitate the differential diagnosis with other respiratory viruses (Italian Ministry of Health, 2021a; Paget et al., 2020). Third, the possibility that the influenza and

SARS-CoV-2 co-infection may aggravate the patient prognosis (Alosaimi et al., 2021; Bai et al., 2021). Fourth, research published in 2020-2021 has shown that exogenous or endogenous stimuli may have a non-specific positive impact on the body's immune system. This phenomenon is known as "trained immunity" and involves boosting the innate immune response (Netea et al., 2020): innate immunity stimulation increases accessibility of pro-inflammatory genes in case of new infection, through epigenetic modifications. The response results increased and faster, facilitating the protection against the new pathogen (**Figure 8.3**). One potential benefit of trained immunity is the possible reduction of the incidence of COVID-19-related outcomes (Amato et al., 2020; Debisarun et al., 2021; Netea et al., 2020).

A systematic review and meta-analysis conducted by Wang et al. (R. Wang et al., 2021, p. 20) investigated the effects of influenza vaccination on the probability of testing positive for SARS-CoV-2. Based on the findings of the study, the risk of contracting SARS-CoV-2 infection was reduced by 14% (aOR 0.86, 95% CI: 0.81-0.91) in vaccinated individuals compared to unvaccinated ones. Further outcomes were specifically investigated in Italy by an ecological study (Amato et al., 2020) which estimated that each 1% increase in the IVC among individuals ≥65 years could protect by 78,560 SARS-CoV-2 seropositivity cases, 2512 hospitalizations with symptoms, 353 hospitalizations in intensive care and 1989 deaths in the whole Italian population. Nonetheless, when systematic reviews and meta-analysis focused on similar COVID-19-related outcomes (namely, hospitalization, intensive care unit admission, mechanical ventilation, mortality), rarely the outcome achieved the statistical significance, despite results tended to generally favour a benefit of influenza vaccination (Almadhoon et al., 2022; R. Wang et al., 2021; Zeynali Bujani et al., 2021). The overall body of evidence suggested that the positive impact of this preventive measure takes place particularly in the first phases of the infection, consolidating the hypothesis of the “trained immunity”.

Figure 8.3. Schematic and simplified representation of the "trained" immunity function and main positive theoretical effects.



Focusing on the structural social determinants examined in Chapter 2 (Domnich et al., 2021), a higher intention to receive the 2021/22 influenza vaccination has been associated with aging and male gender. A range of studies corroborates the relationship between the age increase and a better flu immunization behavior (Nagata et al., 2013; Okoli et al., 2021; Schmid et al., 2017; Yeung et al., 2016), whereas data surrounding the sex influence are less clear. La Vecchia and colleagues (La Vecchia et al., 2020), for example, founded an inverse trend, with better attitudes towards vaccination against influenza among female, suggesting the necessity to further investigate the effect of this variable.

A systematic review and meta-analysis reported a general global positive effect of COVID-19 on the acceptance of flu vaccination during COVID-19 pandemic (Kong et al., 2022). In this case, no associations with geographic location, age, sex or occupational status were observed, but previous vaccine acceptance, reinforced by a proper education on disease awareness and vaccine safety, demonstrated to be the main predictor (Kong et al., 2022). Similarly, in Chapter 2 (Domnich et al., 2021) an history of flu immunization and the vaccination or intention to get a COVID-19 vial have been founded to be among the major determinants in next season willingness to get vaccinated against flu. These results advocate a beneficial health-seeking behavior promoted by the pandemic situation, at least until 2021. However, the influence exerted by the pandemic could have both positive and negative effects. If on the one hand the maintenance of the acquired interest in a correct health status may promote an increase in vaccine coverage, on the other hand the association with an external evolving factor, such as the pandemic, could lead to unpredictable consequences. The alternance of COVID-19 waves overloaded the healthcare system to the detriment of other health services (EpiCentro, 2020) and a slowdown in vaccine uptake is possible once the state of alert and social responsibility has decreased (Stamm et al., 2023; Su et al., 2022). Moreover, the 2020/2021 influenza season has been characterized by a marked decline of influenza virus circulation (EpiCentro, s.d.-a), situation which affected even other respiratory pathogens (Olsen et al., 2021). That situation could be probably accounted to containment measures adopted to protect against an uncontrolled spread of the new Coronavirus, such as social distancing, lockdowns, suspension of global travel, mask use (Olsen et al., 2021). The 2021/22 influenza season has, indeed, seen a reappearance of flu, which gradually restarted to circulate, giving rise to a high-intensity season in 2022/23 (EpiCentro, s.d.-a). Nevertheless, the principal determinant of the 1-year reduction in willingness to receive 2021/22 flu vaccination was the very low circulation of influenza viruses in the 2020/2021 (Domnich et al., 2021; EpiCentro, s.d.-a), reinforced by the belief that influenza vaccination provides a suboptimal protection against the disease (Domnich et al., 2021). This mix may have affected 2021/22 Italian flu season, where a decline in influenza vaccine coverage rate was observed (i.e. drop down of 7.2 and 3.2 percentage points in ≥65 years and general population, respectively), but without achieving the pre-pandemic status (Italian Ministry of Health, s.d.-b).

A strategy to counteract this tendency is, thus, warmly advised, even since an improvement in attitudes and adherence to influenza vaccination seems to stimulate a better acceptance of other preventive measures (Domnich et al., 2021; Gatwood et al., 2021; Kong et al., 2022; Maltezou et al., 2021), suggesting that a better initial experience has a role in breaking down existing fears and barriers. As a consequence, the same relationship may exist between unwillingness to be vaccinated against flu or SARS-CoV-2 and hesitancy persistence.

The achievement of the full potential for health and well-being is a central concept pursued by the World Health Organization (World Health Organization (WHO), s.d.-c). The health sector must play a leading role in the surveillance of health inequalities, the monitoring of health outcomes and the delivery of health services, and collaborate with other sectors to monitor people's living conditions. The presence of high-quality, effective services together with an equal distribution of resources and the development of stratagems to remove barriers to vaccination access could improve the conditions of daily life, targeting a state of health equity (Centers for Disease Control and Prevention (CDC), 2022d; World Health Organization (WHO), s.d.-c).

An active invitation to get the flu shot, the so-called "chiamata attiva", may be one of initiatives to promote and adequate vaccination compliance and, for this reason, has been further investigated in the cross-sectional survey exposed in Chapter 4, the last currently carried out within the project Influenza Observatory (Domnich, Grassi, et al., 2023). The Italian Ministry of Health endorses the implementation of actions to arise influenza vaccination and requests the activation of an active offer of proven effectiveness towards people eligible for vaccination to Regions and Autonomous Provinces, with the involvement of general practitioners, pediatricians and pharmacies, to ensure that vaccination coverage is as high as possible (Italian Ministry of Health, 2021a, 2022b, 2023). 2513 have been then invited to express their opinion or provide their experience (always through a questionnaire delivered with CAWI methodology) about active reminders and the most appropriate sender and way to receive it. Referring to 2021/22 influenza immunization, the 52.2% (CI 95%: 50.6%-54.6%) of the participants previously experienced an active invitation. Among them, the flu vaccine uptake reported was 68.15% (CI 95%: 65.57%-70.66%), three times higher than subjects that did not receive any reminder (22.17%, CI 95%: 19.84%-24.63%) corresponding to an aOR of 6.47 (CI 95%: 5.35-7.83). This significant positive effect of interventions on influenza vaccination demand was identified in a 2018 Cochrane review too, in ≥60 years populations, increasing with the specificity of the intervention provided from a lower intensity (postcards) to medium and higher intensity with personalized reminders (i.e. phone calls) and the action of facilitators/home visits, respectively (Thomas & Lorenzetti, 2018). Several strategies of invitation to flu vaccination have been examined also in Chapter 4. The preferred way to receive the active invitation resulted to be mobile phone messages (27.19%) or emails (24.59%), whereas a lower percentage of Italian adults preferred postal letters (16.99%) or traditional phone calls (8.60%) (Domnich, Grassi, et al., 2023). A recent systematic review summarized the effectiveness of different information and communication strategies to improve influenza, pneumococcal, herpes zoster or COVID-19 vaccination coverage levels in older adults (Buja et al., 2023). Most of the studies concluded for a favorable effect of these gentle nudges to be immunized, albeit some studies did not observe any significant change. In contrast with Chapter

4 findings, the stronger effect size was reported by a randomized controlled trial (RCT) (Humiston et al., 2011) where patients in the intervention group received a letter/card reminder and, in some cases, phone calls to stimulate a vaccination appointment (flu vaccination rates 64% vs. 22%, $p<0.0001$, respectively, in the intervention and control groups). The difference in the outcomes may be explained by the different age of populations included in the two studies (all adults in Chapter 4 and only elderly individuals in Humiston and colleagues trial) and by the so-called digital divide that can affect all the online surveys: older adults involved in the online survey and, in particular, Internet users aged ≥ 75 years (7.64% of the total population in Chapter 4) may differ from non-users. Of note, even the provider received a reminder to contact the patient for the influenza vaccination within Humiston et al. trial, suggesting that not only a recipient but also a sender prompt could be the basis of a successful program (Humiston et al., 2011).

Some studies made their analysis even more specific, paying attention to the wording used in the message. These studies varied from randomized controlled trials to field analysis, but all concluded that a "reserved for you flu shot" text-message rather than a more generic one produces more effective results (Buttenheim et al., 2022; Milkman et al., 2021; Patel et al., 2023).

However, as mentioned above (Buja et al., 2023), some interventions reported non-effective results. Among them, one used automated calls achieving very low call completion rates (Stolpe & Choudhry, 2019) and another was a telephone-based study where the participants had already received an invite to get a flu shot the previous month (Kellerman et al., 2000), probably affecting the final outcome. A study conducted specifically on subjects with chronic obstructive pulmonary disease or asthma resulted ineffective both in the phone call and email intervention arms, compared to the control group (Klassing et al., 2018). In this case, the active invitation has been carried out by pharmacies. A large number of patients in the telephonic intervention arm preferred to discuss the vaccine recommendations with their physician before taking action (Klassing et al., 2018), suggesting that, particularly in the vaccination field and in frail populations, some active invitation providers may be more appropriate than others.

GPs, specialist physicians, Local Health Units, pharmacists, Regional Health Department and relatives or friends have been considered among possible sources of intervention to nudge vaccination in Chapter 4. The first three were significantly associated with an effective vaccination in the following season, with the GP representing the most convincing source of active reminder, with an aOR of 4.43 (CI 95%: 3.60-5.48) (Domnich, Grassi, et al., 2023). Health care providers vaccination recommendation has been found to be a powerful method to improve vaccine confidence and uptake, helping patients to understand the importance and safety of this preventive measure (Kohlhammer et al., 2007; Nguyen et al., 2021). However, influenza vaccination adherence among HCWs is suboptimal in most of European countries, fluctuating from 15.6% to 63.2% in the 2015-2018 time period (Mereckiene, 2018). Moreover, an Italian survey reported that only 58.9% of HCWs sustained to be prepared and updated on vaccinations (Sani et al., 2022), pointing the attention to the exigence to improve health care provider knowledge about flu vaccination to adequately support and engage the patient.

Another solution to this hesitancy may be a concomitant administration strategy. Results of Chapter 2 suggested, indeed, an encouraging attitude towards influenza and COVID-19 vaccines co-administration in May 2020 (Domnich et al., 2021). Nonetheless, the Chapter 3 investigation, conducted during the autumn of the following year, resulted in a hesitation for co-administration in Italy higher than that of vaccines taken individually. Only 23% of the population firmly accepted the co-administration, whereas 17% totally refused to adhere to this option and the 60% could be classified as more or less doubtful about this practice (Domnich et al., 2022), despite the positive recommendation provided by the Italian Ministry of Health the 2nd of October 2021 (Italian Ministry of Health, 2021b). Randomized controlled trials examined the safety and the preservation of immunogenicity/efficacy of both flu and COVID-19 vaccines alone and co-administered, reporting supporting data (Izikson et al., 2022; Lazarus et al., 2021; Toback et al., 2022). However, the newness and rapid development of SARS-CoV-2 immunization (Adu et al., 2023) and, even more, of concomitant dispensation strategies could have a role in the hesitation observed. Thus, a better confidence is anticipated after the dissemination of adequate information related to this routinary practice. Two monocentric Italian studies further examined the co-administration acceptance among HCWs, reporting, respectively, a 60.0% (Stefanizzi et al., 2022) and 33,6% (Lecce et al., 2022) compliance towards vaccine co-administration. These higher values may be related to the population selected, i.e. HCWs, which are on average better informed and, then, confident about concomitant administration. However, a recent Canadian survey reported again suboptimal flu and COVID-19 co-administration rates (26.2% on 3,000 individuals ≥18 years) in the

2022/2023 influenza season, despite a high knowledge (69.8%) regarding this practice (Roumeliotis et al., 2023). This awareness increases in older adults (83.0%), albeit followed by an even lower adherence (23.9%) (Roumeliotis et al., 2023). A similar pattern has been found in Chapter 3 (Domnich et al., 2022), leading to the conclusion that probably elderly subjects are less prone to accept novelties.

On this line, in the context of frequent debates and discussions on COVID-19 vaccines, even the so-called phenomenon of "vaccine fatigue" may have contributed to this outcome (Su et al., 2022). The “vaccine fatigue” is a sense of exhaustion or weariness that leads to a refusal to receive further information or guidelines concerning vaccination. The causes can space among a variety of antecedents, like the lack of trust in the government and the media, frequent requests of immunization, adverse events after vaccination, misunderstandings about the severity of the diseases/usefulness of preventive measures and medical dissensus. General public, caregivers and physicians can be all affected by it, experimenting this feeling of disaffection and disinterest towards vaccines (Stamm et al., 2023; Su et al., 2022). On this line, GPs placed at the first position as source of information for influenza vaccination in all the surveys, markedly highlighting the centrality of the physician-patient relationship (Domnich, Cambiaggi, et al., 2020; Domnich et al., 2021, 2022) (Chapter 2 and 3). A divergence in expert opinions may lead the patient away from vaccination (Stamm et al., 2023); on the opposite, a convergence in the medical counselling offered to the patient could improve the trust on influenza vaccination. In addition, traditional media (television and newspapers) showed the wider 1-year increase as a trusted information source in the Chapter 2 study (Domnich et al., 2021), despite frequently partial, ambiguous and incorrect messages (Bodemer et al., 2012; Dhanani & Franz, 2020) could have resulted in a loss of vaccine confidence. To counteract this trend, the Italian Ministry of Health tried to guide the citizen among the numerous and sometimes conflicting information through digital communication, developing a dedicated page to fight against misinformation (Lovari, 2020). Moreover, media trainings and publication of balanced and reliable information could revert this tendency, avoiding the need to discern among discordant news.

Personalized influenza vaccination was associated both in Chapter 2 (Domnich et al., 2021) and 3 (Domnich et al., 2022) with an intensification of the willingness to be vaccinated against flu alone or with COVID-19, suggesting that a more tailored prevention program could have a positive impact on vaccination coverage rates. In recent years, indeed, the evidence that specific vaccines can have a better performance, at least in certain categories, is becoming always more consolidated. Particularly, at present, the Advisory Committee on Immunization Practices (ACIP) carried out the more up to date institutional systematic review about benefits and harms of enhanced vaccines (i.e. MF59-adjuvanted, recombinant and high-dose vaccines) compared to non-adjuvanted, standard dose vaccines or among them in ≥65 year-olds, leading to a preferential recommendation of enhanced vaccines in all the older adults over conventional vaccination (*ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022; Grohskopf, 2022). No preference of an enhanced vaccine over the others has been expressed, basing on available evidence (*ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022; Grohskopf, 2022). Another systematic review and meta-analysis explored the matter even more deeply, gathering all head-to-head MF59-adjuvanted-influenza vaccine and high-dose influenza vaccine efficacy and effectiveness comparisons in elderly individuals up to the 7th of March 2022 (Domnich & de Waure, 2022). This new study drove to the same ACIP conclusions, reporting a similar effectiveness in preventing seasonal influenza in ≥65 years between the two flu vaccines (no randomized clinical trials have been found) (Domnich & de Waure, 2022). Direct comparisons are of particular importance in the field of flu, since influenza viruses are characterized by a marked seasonality. During their circulation, influenza viruses can undergo a gradual modification of the sequence of proteins' constitutive amino acids capable of stimulating an immune response. This phenomenon concerns both A and B viruses (but in A it occurs more prominently and frequently) and is responsible for seasonal epidemics. The new variants become sufficiently unrecognizable to antibodies in the majority of the population, making a large number of people susceptible to the new strain (Centers for Disease Control and Prevention (CDC), 2022f; National Institute of Health, 2018a). This process, called antigenic drift, may have a negative impact on vaccine effectiveness, leading to the so-called "mismatch" between circulating virus and virus included in the vaccine (Belongia et al., 2016; Tenforde et al., 2021). Seasons characterized by antigenic drift can result in very different effectiveness estimates compared to matched seasons. In addition to this, even an incorrect or impossible selection of the candidate vaccines strains can impair the protective effect of this preventive measure; similarly but distinctly, egg-specific adaptations can occur in viruses grown in eggs, often developing changes in the surface antigens epitopes, that change the virus binding specificity from the human-dominant receptors (α2,6-linked sialosides) to those dominant in the eggs (α2,3-linked sialosides) (Settembre et al., 2014).

This process, analogously to antigenic drift, can drive again to vaccine antigenic mismatch, impairing influenza vaccine effectiveness. In light of this premise, it is evident that a diverse plethora of factors affects the final vaccine effectiveness, showing the marked seasonality of the influenza virus. Consequently, a comprehensive analysis of several seasons is required to have an adequately complete framework on this pathogen and related preventive measures. RCT have a primary role in the flu vaccines pre-licensure phase, but they are typically conducted under ideal conditions and rarely over the course of multiple seasons. Real-world evidence (RWE) analyses in the post-marketing phase can assess influenza vaccine effectiveness and safety across sequential influenza seasons in real conditions, in larger populations and for patient-oriented outcomes, consolidating, perfecting or modifying what was observed in the clinical phase (Centers for Disease Control and Prevention (CDC), 2023a; Flannery & Fry, 2019; Halloran et al., 1997; Heneghan et al., 2017).

Among the evidence that could be generated in a real-world setting, ecological study can provide epidemiological information and insights to public health, allowing the analysis of associations among variables at a population level (Cataldo et al., 2019; Morgenstern, 1995). For this reason, Chapter 5 (Fallani et al., 2021) investigated spatiotemporal patterns of P&I-related mortality among Italian subjects aged ≥65 years and the epidemiological correlation between the observed local P&I mortality, IVC rates and IV policy patterns. The analysis found that influenza campaign features, environmental factors and virological characteristics of the season all contribute to the final outcome. Specifically, only an increase in IVC, proportion of aTIV used and average low winter temperature was significantly associated with a benefit in reducing P&I-related mortality in people aged 65 years or over, both in the FE and RE models analyzed, whereas co-circulation of different types of influenza A virus (i.e. co-circulation of A/H1N1pdm09 and A/H3N2 subtypes) was significantly related to a worsen outcome. Conversely, public health expenditure per capita, IVC in subjects aged less than 65 years, population density, predominance of subtype A/H3N2 and predominance of strain B did not show any statistically significant association with P&I-related deaths.

Notably, an improvement of 1% in IVC rate in older adults was associated with a 1.6-1.9% decrease in the P&I mortality. This means, considering a mean of 10,268 influenza and pneumonia-related deaths per year monitored during the period analyzed, that approximately a range of 164-195 P&I-related deaths could be avoided on average every year for each 1% IVC increase. In addition, each increase of 1% in aTIV proportion administered in older adults was associated with a 0.4% decrease in the P&I mortality in this subgroup of population, that implies about 41 further P&I-related deaths prevented per year, for a total of 205-236 P&I-associated deaths avoided per year in case of increase of 1% in IVC rate and aTIV proportion used.

These data are relevant, since, during the last season analyzed (i.e. influenza season 2016/2017), an IVC of 52.0% was reported in adults ≥65 years, that is a value definitely lower than the minimum target of 75% and the optimal goal of 95% established that season by the Italian Ministry of Health and by the Italian National Vaccination Prevention Plan 2017-2019 in this subgroup of population (Italian Ministry of Health, 2016, 2017), emphasizing how many P&I additional deaths could have been avoided in case of better adherence to this prevention measure.

Looking at the choropleth maps, a net increase in P&I-related mortality rate can be monitored in some years, moving from southern to northern Italy, in particular 2011, 2015 and 2017. A higher P&I-related mortality was detected in northern Italian provinces compared to southern and central ones. Basing on data obtained by our analysis, we can infer that a combination of IVC rates in central and southern Italian regions and the remarkable differences in average winter temperature between northern and southern Italy probably had a main role on these results (Rossi et al., 2017; Superior Institute of Health (ISS), s.d.). These observations were confirmed by LISA analysis too: all the coldspots were detected in southern Italy or islands, whereas hotspots were essentially reported in northern Italy regions. However, a significant clustered pattern, monitored by Moran's I value, was observed.

One Italian ecological study already valued general influenza vaccination benefits in Italian elderly without identifying a remission in influenza-related mortality in this category (Rizzo et al., 2006), emphasizing the problem of suboptimal response in elderly population due to immunosenescence phenomenon (Abedin et al., 2005; Haq & McElhaney, 2014; Rizzo et al., 2006). Immunosenescence is a physiological progressive immune decline that progresses with aging and involves innate and adaptive immunity, predisposing older people to infections, like influenza (Abedin et al., 2005; Haq & McElhaney, 2014). This is an especially relevant issue in Italy, because people over 65 are in continuous growth and represented more than 1/5 of the total population in 2019 (Italian National Institute of Statistics (ISTAT), 2018, p. 201):

adjuvanted formulations are a potential solution to overcome this problem (Nanishi et al., 2020; Soni et al., 2020) and for this reason they have been further investigated in our analysis.

Focusing on the impact of socioeconomic predictors, regional public health expenditure per capita does not seem statistically decisive for the outcome, even if it resulted significantly interrelated with a decrease in influenza-related deaths in other analysis (Nikolopoulos et al., 2011). Moreover, influenza vaccination was related to a remarkable reduction in public health and economic burden in Europe and United States (Preaud et al., 2014; Sander et al., 2009). Specifically, MF59®-adjuvanted TIV showed the best cost-effectiveness profile, with lower total costs and substantial health benefits compared to other vaccines available for elderly in Italy during 2016-2017 influenza season (Capri et al., 2018) and, in fact, in 2019/2020 exclusively aTIV remained available among the so-called "enhanced" influenza vaccines in Italy, recommended for people aged 65 or over (Italian Ministry of Health, 2019). Only during the following season, another IV, namely high-dose vaccine, was introduced in Italy, joining to the adjuvanted vaccine within this category (Italian Ministry of Health, 2020); however, high-dose influenza vaccine was not yet available in Italy during the study period (Fallani et al., 2021) and for this reason it was not possible to include it in the analysis. Thus, the not significant impact of the predictor regional public health expenditure per capita in our study may have been determined by some unconsidered confounders, by the wide range of health investments included inside this parameter and, reasonably, by the inclusion of not only influenza-focused health, therapeutic and preventive available proposals. This hypothesis is reinforced and supported by our analysis: a greater IVC was correlated with a lower influenza-related mortality, and, focusing on the use of aTIV, a major proportion of this specific kind of vaccine was associated with an additional protection from influenza-related deaths. Consequently, an investment in public health and, particularly, in influenza vaccination, may be at least partly associated to a decreased P&I-related mortality. Such discrepancy highlights the fundamental role of conscientious assignment of public capitals in the health sector, therapeutic appropriateness and, specifically, with regard to our analysis, vaccination appropriateness. An incorrect choice could be unproductive or even detrimental, whereas a correct allocation of direct regional public health funds is essential to obtain the maximum benefit. Consequently, a more careful selection of the type of vaccine administered, based on specific needs and peculiar conditions of the treated population groups, could lead to improved results. Focusing on aTIV use investigated in Chapter 5 and vaccination appropriateness, systematic reviews and meta-analysis support an improved relative effectiveness of aTIV compared to non-adjuvanted standard dose trivalent or quadrivalent IV for numerous outcomes and, according to the last available evidence, comparable effectiveness versus high-dose influenza vaccine, placing enhanced vaccines as the most appropriate immunization choice for older adults (*ACIP February 23-24, 2022 Presentation Slides | Immunization Practices | CDC*, 2022; Coleman et al., 2021; Domnich et al., 2017; Domnich & de Waure, 2022).

In the same way, Chapter 5 highlighted aTIV proper choice from a public health point of view in Italian adults ≥65 years during the 2011-2017 time-period. In recent years, several experts introduced the term of "precision vaccinology" and, in this context, placed a specifical advantageous use of adjuvanted vaccines within more vulnerable population, such as elderly and immunocompromised (Nanishi et al., 2020; Soni et al., 2020). Adjuvanted vaccination was associated with a better stimulation of immunogenicity in subjects with a weakened immune system, enhancing both innate and adaptive immunity (Nanishi et al., 2020; Soni et al., 2020). The adjuvant system is, in fact, able to confer a wider persistence and magnitude of the immune response compared to non-adjuvanted standard-dose immunization measures (Kavian et al., 2020; Tregoning et al., 2018) and to potentiate the immunity related to a greater cross-protection against influenza viruses, reducing disease severity (Li et al., 2021; Sridhar et al., 2013).

This kind of immunity could protect elderly from clinically relevant influenza illness and, then, from its potential complications. The value of this technology in these population groups was, indeed, acknowledged both in Italian and extra-Italian realities in the flu field (Australian Technical Advisory Group on Immunization (ATAGI), 2021; Italian association of medical oncology (AIOM), 2021; Italian Society of Hygiene, 2019; Joint Committee on Vaccination and Immunisation (JCVI), 2020).

Going into specifics of influenza-related mortality outcome, Fabiani et al. reinforced Chapter 5 main findings, revealing a stronger capacity of prevention of influenza-related hospitalizations and deaths of aTIV compared with other types of vaccines (22% vs 18%), namely intradermal and non-adjuvanted trivalent or quadrivalent vaccine, in people over 74 in 2016/2017 season. Effectiveness differences became even more evident focusing on subjects aged 90 or over (Fabiani et al., 2020). 2016/2017 influenza season stood out for its considerable excess of mortality: it was dominated by A/H3N2 subtype and marked by a lack of match between circulating strains and vaccine virus (Fabiani et al., 2020; Rosano et al., 2019), highlighting the adjuvanted technology's peculiar aptitude to cope with mismatch events.

Applying this concept to our analysis, it was possible to identify any mismatch phenomena occurred during the seasons examined, collecting data from some Italian studies, elaborated at a regional level (Northern Italy) or throughout Italy. It emerged that 2010/11 was characterized by match (predominance A/H1N1pdm09), 2011/12 by mismatch (high predominance A/H3N2), 2012/13 by match (predominance A/H1N1pdm09 and B), 2013/14 by match (predominance A/H3N2 and A/H1N1pdm09), 2014/15 by A/H3N2 mismatch (predominance A/H3N2 and A/H1N1pdm09), 2015/16 by A/H3N2 and B mismatch (predominance B), 2016/17 by A/H3N2 mismatch egg-adaptive and B mismatch (high predominance A/H3N2) (Affanni et al., 2019; Mannino et al., 2012; Pariani et al., 2015; Rosano et al., 2019; Superior Institute of Health (ISS), s.d.). Although some available data were related only to specific Italian zones, it appears that approximately 4 of 7 seasons considered, which could possibly affect our analysis, were characterized by antigenic mismatch between circulating influenza virus and strains included in administered vaccines in specific Italian regions or throughout Italy. Of these, 3 reported A/H3N2 predominance and 2 co-circulation of A/H3N2 and A/H1N1pdm09. Notwithstanding the remarkable mismatch rate and the not always easy features of the examined seasons, influenza vaccination in elderly individuals was associated to a protective benefit against P&I-related mortality, intensifying with the increase of the proportion of aTIV used. Cases of antigenic match and single strain circulation seems to be related with a better outcome than mismatch and co-circulation of A/H3N2 and A/H1N1pdm09 subtypes, as confirmed by P&I mortality data reported in Chapter 5. The virological characteristics of the season may affect regional influenza-related mortality, in fact, according to the analysis: co-circulation of A/H3N2 and A/H1N1pdm09 viruses has been associated to a worsen outcome.

Referring to viral prevalence, a smaller proportion of strain B is more commonly detected in adults, if compared to minors (Panatto et al., 2018). Most infections in these individuals are caused by influenza A virus and, then, they may be more frequently at risk of A/H3N2 and A/H1N1pdm09 dangerous infections. This, coupled with immunosenescence phenomenon, hinders and complicates flu prevention in elderly individuals. Nonetheless, our analysis associated a larger proportion of enhanced vaccine administered in older adults to a higher benefit, supporting this preventative practice. Furthermore, a prolonged influenza vaccination effect can contribute to mitigate the deaths attributable to pneumonia and influenza. In this regard, some influenza vaccines, like recombinant and MF59®-adjuvanted vaccine reported a notable immunogenicity protracted for one year (Kavian et al., 2020).

IVC in subjects aged less than 65 years doesn't seem a significant predictor of P&I-related mortality in the elderly in our analysis, although a general potential benefit on some influenza outcomes is possible (Italian Ministry of Health, 2020). The same observation was made for population density: in fact, other studies reported controversial data about a possible association between population density and influenza mortality (Chandra et al., 2013; Chowell et al., 2008).

The exploratory spatiotemporal analysis reports the highest rates of regional P&I-related mortality in years 2017 (10.05 per 10,000) and 2015 (8.78 per 10,000). This is in line with the excess of all-cause mortality observed in Europe and, more specifically, even in Italy, during 2014/2015 and 2016/2017 winter seasons season (Molbak et al., 2015; Rosano et al., 2019; Vestergaard et al., 2017). The abrupt decline in IVC monitored in 2014 and the co-circulation of A/H1N1pdm09 and A/H3N2 during the 2014/15 season could have a role in the outcome detected, like, maybe, the substantial predominance of A/H3N2 infections during the 2016/17 (Italian National Institute for the Environmental Protection and Research (ISPRA), 2020; Rosano et al., 2019; Vestergaard et al., 2017). Our analysis underlines a possible positive association between A/H3N2 infection and P&I-related deaths, but we didn't get statistically significant results. Nonetheless, the prevalence of A/H3N2 is often associated with higher severity infections and increased influenza morbidity and mortality and then its possible role on the outcome can't be completely excluded (Adlhoch et al., 2018; Belongia et al., 2016; Superior Institute of Health (ISS), s.d.; Vestergaard et al., 2017). A recent ecological study conducted in Italy was able to gather all the data at a Province/Metropolitan Area level across 17 consecutive seasons, getting data at a more granular level and, indeed, founding a statistically significant association between A/H3N2 predominant circulation and P&I-related deaths (Domnich, Orsi, et al., 2023). Moreover, winter 2014/15 saw a sharp drop of vaccine coverage (particularly of aTIV) and this, combined with a season characterized by high influenza activity, was followed by an alarming increase of complications, hospital admissions and deaths in Italy (Bonanni et al., 2018). On the contrary, the average winter temperature was higher than the normal reference climate value 1961-1990 in all three cases, suggesting that it has not a central position in the greater influenza related-mortality observed (Superior Institute for Protection and Environmental Research (ISPRA), s.d.-c, s.d.-a, s.d.-c). Nonetheless, a connection among temperature, influenza epidemic and excess of mortality in 2016-2017 influenza season in Italy, in Milan, was found (Murtas & Russo, 2019). An explanation to this reported evidence was provided by a study conducted by Qi et al. (Qi et al., 2021), which demonstrated that a temperature below 18°C can enhance consistently influenza activity, boosting host susceptibility, survival and transmissibility of influenza virus and, besides, more in detail, a highly efficient transmission was verified at 5°C in guinea pigs (Lowen & Steel, 2014). Therefore, even if the average winter temperature was not particularly low compared to the normal reference climate value, it was cold enough to promote the spread of influenza virus. An increase in minimum temperature was inversely associated with influenza-related influenza-like-illness (ILI) or Acute Respiratory Infection (ARI) in temperate countries, in fact (Soebiyanto et al., 2015). An ecological study conducted in United States proved that temperature modestly influenced influenza-related deaths: it was calculated that influenza mortality during the cooler months (December to March) was at least 40 times higher than in warmer months (June to September) (Barreca & Shimshack, 2012). In the same way, our analysis confirmed a relationship between average low average winter temperature and P&I-related mortality in the Italian context.

The lowest values of P&I-related mortality was reported in two of the years in which the rate of IVC has been higher, namely 2011 and 2014. 2011 was characterized by the predominance of A/H1N1pdm09 virus. 2014 saw a co-circulation of A/H3N2 and A/H1N1pdm09 subtypes. This is significant, because, despite unfavorable virological characteristics of the 2013/2014 influenza season, a good match between the circulating viruses and the strains included in the vaccine characterized the years 2011 and 2014 in Italy (Pariani et al., 2015; Rosano et al., 2019; Superior Institute of Health (ISS), s.d.). Therefore, probably, a better vaccination protection was guaranteed. 2014 had a particularly warm winter: this factor may have contributed to the final outcome reported as well (Superior Institute for Protection and Environmental Research (ISPRA), s.d.-b).

At the best of our knowledge, this is the first study which analyzed public health expenditure per capita, population density, proportion of adjuvanted trivalent influenza vaccine, average low winter temperature and co-circulation of different influenza A viral subtypes as potential predictors of P&I-related mortality in a regional Italian setting. A 2023 study consolidated

Chapter 5 main findings at a more granular level, founding a milder effect size, and associated a mean of 0.6% (95% CI: 0.3–0.9%, P < 0.001) decrease in P&I-related deaths in ≥65 years-olds to each 1% growth in IVC (Domnich, Orsi, et al., 2023). However, it was not possible to get data at Province/Metropolitan City grade for specific influenza vaccines (Domnich, Orsi, et al., 2023): public health impacts of specific vaccination types on influenza-related outcomes should be ideally further explored in future ecological studies.

Each year, the ideal period for this delivery process and, then, the flu immunization is ruled by the complex interaction of the binomial 1) potential decline in vaccine-induced immunity during the season and 2) risk that a delay in the vaccination may result in an overall decrease of influenza vaccination coverage and in an unprotected population when the influenza outbreak begins (Bonanni et al., 2018, 2021). Indeed, if on the one hand a recent systematic review and meta-analysis conducted by Young et al. (Young et al., 2018) reported a significant decline in the vaccine effectiveness (VE) against A/H3N2 (-33%) and, more modestly, against B type (-17%) from 15-90 days to 90-180 days after vaccination, on the other hand it seems that a postponement in vaccine delivery and administration may negatively affect the influenza vaccine protection exerted on the overall population throughout the flu season.

The situation becomes even more elaborate in the setting of the Italian fiscal federalism, where regions and the autonomous provinces of South Tyrol and Trento may entirely assimilate the national recommendations or adopt a personalized strategy to achieve the public health objective. These decisional differences may result in a "jeopardization" of influenza vaccine coverage in Italy, with differences in distribution timing and, consequently, causing a possible impact on influenza-related outcomes (Fallani et al., 2021).

Therefore, in a prospective of an appropriate management of the resources in Italy (Expert Panel on Effective Ways of Investing in Health (EXPH), 2019), Chapter 6 had the objective to investigate the time lapse between distribution of influenza vaccines to regional LHAs and the administration to patients through the GPs and how different timings of distribution/administration can affect the risk of respiratory- and all-cause hospitalizations. In this regard, the Italian National Vaccine Prevention Plan 2017-2019 (Italian Ministry of Health, 2017) reputed an efficient logistical management, from the supply to the distribution and administration, as a crucial element for the achievement and maintenance of an adequate influenza vaccine coverage and consequent protection. Although different studies have already tried to estimate a possible effectiveness waning 3-6 months after influenza vaccination (Young et al., 2018), as well as the risk of unprotected population in case of a delay in flu vial administration (Lin et al., 2022), at the best of our knowledge, this is the first study that quantitatively analyzed the impact of different flu vaccine distribution and administration velocities in ≥65 year-olds in a primary care setting.

For a question of data availability both at MAH and GPs level, our analysis examined the distribution modality of MF59®-adjuvanted TIV/QIV in Italian elderly population. Nonetheless, the main findings of the study are intended to provide a general indication to overall influenza vaccination distribution patterns, albeit probably varying in the effect size depending on the vaccine type considered.

Chapter 6 found a relationship between vaccine dispensation velocities and all-cause and respiratory-related hospitalization frequency in 3 seasons out of the total 5 analyzed, without a significant velocity difference among Italian regions. Specifically, a higher velocity of distribution and then vaccination of the patients has been associated with a reduction of respiratory-related and all-cause hospitalizations, with a 10% pooled reduction of the median number of all-cause hospitalizations for each increase in the differential dose/week between distributed and administered vaccines. Similar results have been found by economic studies conducted in United States (US) both in children and older adults. Accelerating childhood vaccinations to conclude by the end of October seems to offer significant advantages for society, both in terms of economics and public health outcomes (Lee et al., 2009, 2010; Morris et al., 2023). By doing so, society can save between $6.4 million and $9.2 million, additionally gaining 653 to 926 quality-adjusted life-years (QALYs) (Lee et al., 2010). Analogously, vaccination after October of persons ≥65 years has been associated to losses in terms of money and utilities, even making incentives ≤$2.50 still cost-effective to get vaccinated within that date (Lee et al., 2009).

Focusing the attention on the use of adjuvanted influenza vaccine, recent analysis has modeled the impact of an enhanced flu vaccines (i.e. MF59®-adjuvanted, high-dose and recombinant influenza vaccines) preferential recommendation on influenza-related burden in US elderly individuals (Morris et al., 2023). The increase of enhanced vaccines usage could reduce up to

4% deaths and hospitalizations in case of absence of vial administration delays, at the same conditions of IVC. The same outcome could, instead, worsen by over 7% in case of injections postponements of 3 or 6 weeks and/or a drop of 10%-20% in IVC rates (Morris et al., 2023). These findings underscore the importance of prioritizing timely childhood and elderly vaccination as a valuable investment in the well-being of these subjects and the overall health of society. Available data seem to support the hypothesis that, despite a possible waning in vaccine effectiveness over the season, an earlier vaccination is anyway able to protect a wider range of population, leading to a favorable overall outcome. However, Lee et al. estimated that influenza vaccination is still a cost-effective solution in older adults until February, despite becoming increasingly less advantageous as the season advances, supporting the value of protecting late vaccinees (Lee et al., 2009).

The differential between distribution and administration rates seems to do not affect significantly the IVC across the 5 seasons in Chapter 6. The achievement of an optimal distribution/administration rate is worthwhile, but the positive potential of this result is limited by several bottlenecks. The doses in the time unit delivered to GPs for administration to the patients, in fact, is strongly influenced by: (i) the initial vaccine availability, dependent on the quantity of vials initially ordered and the provision of that doses to regional LHAs and, then, to physicians in a timely manner, (ii) transportation capability and (iii) local storage capacities at LHAs and GPs level (Assi et al., 2012). All these factors must be implemented jointly to observe a supply process improvement: otherwise, the slower determinant (or that has achieved its maximum possibility) will affect the efficiency of the whole process, resulting in a plateau upon reaching its maximum capacity. The presence of these bottlenecks may have a role in the seasonal final IVC rate detected, in conjunction with other external factors that may influence the adherence to influenza vaccination campaign (Assi et al., 2012; Domnich et al., 2021). A vaccination program more diluted over time may resolve these logistical issues, until eventual chokepoints are improved.

In this regard, evidence elaborated in Chapter 6 supports a benefit related to a closer vaccine distribution and administration. Hence, an efficient flu vaccination programme should plan a strategy based on vaccination commitment to MAH, shortly followed by regional LHAs delivery to physicians and ready GPs influenza vaccine administration to patients, avoiding the bottlenecks saturation.

Given the importance of correctly and productively allocate available healthcare system funds, reliable analysis able to allow and drive this decision are required to support policymakers in a completely conscious evaluation and prioritization of their strategies. Cost-effectiveness analyses are essential from a point of view of access and reimbursement, testing the value of different vaccination options, but a fiscal impact model can support in understanding how and where allocate efficiently government tax revenues to get an adequate return (Mauskopf et al., 2022).

The fiscal health model developed in Chapter 7 (Calabrò, Rumi, et al., 2022), basing on Ruggeri et al. theoretical framework (Ruggeri et al., 2020), assumes that a higher productivity translates into an increased individual income, resulting in additional government tax revenues available to re-invest in healthcare services and workforce. If an illness decreases the individual productivity, all the system is negatively affected (Ruggeri et al., 2020).

Two main methods are available to perform a fiscal impact analysis. The first is the human capital approach, which considers the missed production related to the period of absenteeism due to the disease, commensurately to the salary perceived by the employee. The second is the friction cost method that is more focused on private company prospective and considers both the short-term lost productivity and replacement at work. Influenza vaccines are provided free-of-charge from the Italian National Health Service; therefore, a friction cost model would not include direct costs in a sanitary setting (Colamesta et al., 2019; Pike & Grosse, 2018; Ruggeri et al., 2020).

Since the intent was to have a comprehensive analysis, investigating the overall impact of all the different domains of a vaccination strategy, namely fiscal impact, direct and indirect costs, the human capital approach has been reputed the most appropriate for the analysis shown in Chapter 7 (Calabrò, Rumi, et al., 2022).

Policymakers have recognized a positive relationship between job satisfaction and active ageing, in order to extend the working lives of people (Eurostat, 2020). To do so, the implementation of policies aimed at promoting a better working environment is central. A study conducted prospectively drew the attention to both the problem of absence from work due to illness (namely, absenteeism) and presence at work despite the illness (the so-called presenteeism), exposing colleagues and, possibly, patients, to the risk of contagion. The analysis estimated that adult workforce could lost about 1-2 working days for influenza-like illness and attend work for a minimum of 4 days, even if symptomatically sick (Nichol et al., 2009). Influenza like-illness was considered responsible of about half of the total days of presenteeism and of approximately the 39% of absenteeism reported by the population in study (Nichol et al., 2009). Focusing on HCWs, a systematic review found an even wider average absence from work for influenza-like illness, ranging from of 0.5 to 3.2 days (Zumofen et al., 2023). All this evidence underscores the importance of proactive measures, such as vaccination campaigns, workplace policies, and public health interventions, to minimize the impact of these infection on productivity and to preserve the well-being of the working-age population. Furthermore, healthcare personnel impersonate the health behavioural model to follow, giving counsel to the patients and educating through their actions. As a consequence, they have the responsibility to protect themselves to preserve their vulnerable patients safety, since they are involved in public services of primary collective interest and are able to transmit the flu, through their activities, to those at high risk of flu complications (Costantino et al., 2020; Italian Ministry of Health, 2022b; Mereckiene, 2018). HCWs are, indeed, included among the subject to which seasonal influenza vaccination is actively and freely offered in Italy (Italian Ministry of Health, 2022b). However, last available data report a net inadequate IVC rate in this category (European Centre for Disease Prevention and Control (ECDC), 2018).

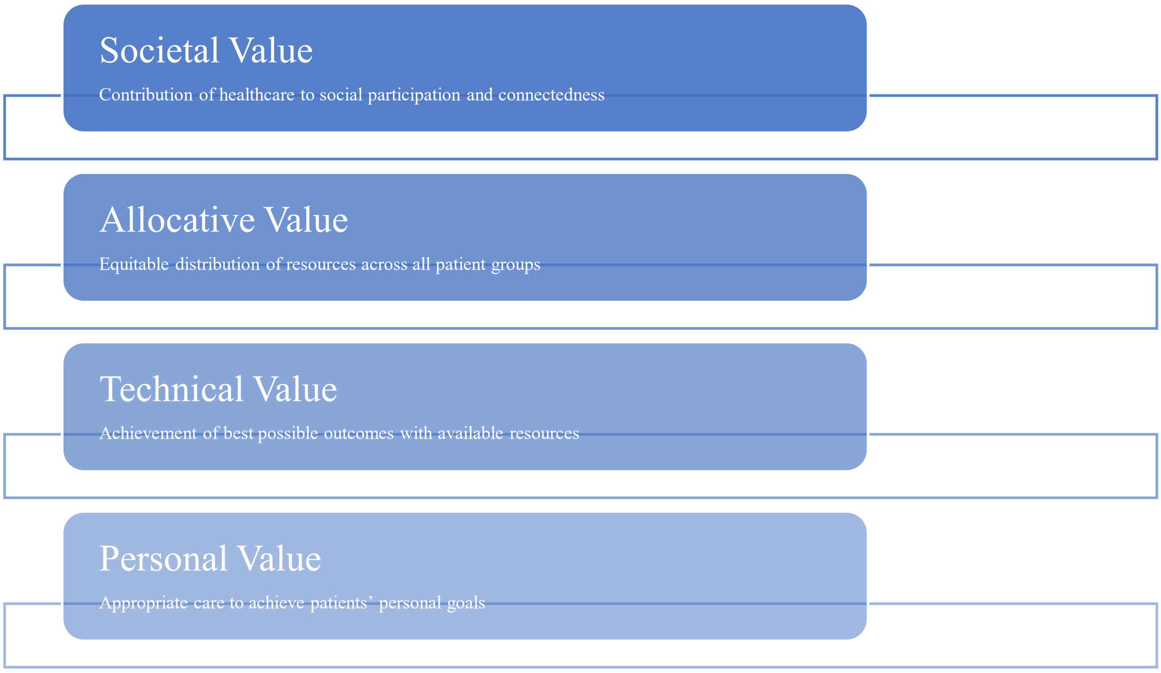
From a broader societal value point of view, through the decrease of morbidity and mortality of vaccine-preventable diseases, vaccinated adults are more likely to have an improved productivity, work for more time and remain active and prolific for longer in the labour market compared to unvaccinated ones (Bloom et al., 2021). Moreover, flu immunization is recommended during seasonal epidemics in order to ensure the correct functionality of healthcare services and prevent absenteeism (Antinolfi et al., 2020; Italian Ministry of Health, 2020). A recent systematic review searched in the literature all the economic analyses evaluating the impact of preventive measures on working adults (Ofori et al., 2022). The main findings support influenza vaccination on worksite as a profitable investment to limit the diffusion of flu infections, but adherence to this measure is fundamental to achieve the final objective (Ofori et al., 2022). On this line, Chapter 7 (Calabrò, Rumi, et al., 2022) estimated the economic and fiscal impact of a better IVC rate in Italian HCWs. The results of this analysis sustain that a passage of a IVC rate from 30% to 40%, considering a cohort of 23,213 Italian HCWs and an influenza attack rate of 4.4% (Somes et al., 2018), could lead to €1,301,394.93

and €95,131.97 social and fiscal savings, respectively. Besides, a flu vaccination strategy able to achieve a 10% growth in IVC rate each year, along a time trend of 5 years, may lead to a total improvement of €4,475,497.16 in the annual productivity and of €327,158.84 in the fiscal revenue (Calabrò, Rumi, et al., 2022). Ruggeri et al. considered the whole 30-65 age group, estimating approximately a €18 million increase in tax revenues and a €111 million improvement in annual productivity through a flu vaccination program able to avoid 200,000 influenza infections (Ruggeri et al., 2020). Chapter 7 (Calabrò, Rumi, et al., 2022) results are, thus, in line with Ruggeri et al. observations (Ruggeri et al., 2020), although in a more moderate way, since limited to a specific segment of the population.

Our work used a static model to perform the analysis, to first exploratively investigate the impact of increasing IVC rates on the fiscal and economic burden of influenza in the healthcare professionals sector (Calabrò, Rumi, et al., 2022). Influenza transmission follows different pathways and intensities between general population and HCWs and, indeed, there is a lack of studies applying dynamic transmission models, despite HCWs are subject to a significantly higher risk of influenza compared to adult working in other settings (Italian Ministry of Health, 2022b; Kuster et al., 2011). Further elements of complexity could be introduced within this variable, since it may differ among HCWs categories (and contact patterns) and diverse health departments (for example, Intensive Care Units, surgery area, geriatric sector…) (Gustin et al., 2023). Thus, Chapter 7 results are probably underestimated and a model able to dynamically estimate the herd immunity effect of influenza vaccination in this particular population may lead to an even larger economic and fiscal benefit. On this line, a dynamic Belgium cost-benefit analysis seems to corroborate this hypothesis, estimating that seasonal influenza vaccination could generate a return of investment (ROI) in working adults able to be cost-saving up to a mean value of approximately €10 for each vaccinated employee (Verelst et al., 2021). Decidedly more moderate results have been found by a ROI analysis conducted in an Italian setting in older adults (Barbieri & Boccalini, 2023), although the differences in flu attack rates among HCWs and elderly individuals and the use of a statistic model may represent a sufficient explanation to this waned final outcome. In addition, it may be possible that different working age groups may experience a diverse influenza-related burden, as investigated by a recent systematic review (Marchi et al., 2023). In the 1979–2001 and 2005-2008 period several studies (Dao et al., 2010; El Guerche-Séblain et al., 2022; Kim et al., 2023; Moa et al., 2022; Thompson et al., 2004) conducted in US, Australia and Brazil detected a statistically significant increase in hospital admissions frequency with the age. Even the median duration of stay for primary pneumonia and influenza hospitalizations increased with the same trend, passing from 3 and 4 days in <5 years and aged 5-49 years to 6 days in the 50-64, 65-69 and 70-74 age groups, reaching its maximum with 7 days in the aged 75+ (Thompson et al., 2004). As seen during the COVID-19 pandemic, performance of the healthcare systems is strongly influenced by resources, healthcare professionals availability and bed capacity. An overwhelmed hospital may impair an adequate assistance to patients, resulting in an aggravation or slower resolution of health conditions and reducing the number of available beds for eventual new admitted patients (Sen-Crowe et al., 2021). Moreover, persons aged from 50 to 64 years seems to systematically report a larger economic burden in terms of influenza-related hospitalizations compared to younger adults (i.e.18-49 years) (de Courville et al., 2022). Future analyses may, therefore, attempt to evaluate the fiscal impact of influenza vaccination, taking into account the different flu burden at diverse workforce ages.

Starting from 2019, the Expert Panel on Effective Ways of Investing in Health (EXPH) of the European Commission is bringing forward a new way to approach to health, based on solidarity and healthcare of good quality, reasonably priced, called “value(s)-based healthcare” (Expert Panel on Effective Ways of Investing in Health (EXPH), 2019). This new multifaceted approach is structured through 4 pillars summarized in **Figure 8.4**, taking into account that the concept of value is personal and can deeply vary according to the perspective considered, i.e. patients, HCWs, policymakers or company stakeholders (Expert Panel on Effective Ways of Investing in Health (EXPH), 2019).

Figure 8.4. Value(s)-based healthcare 4 constitutive pillars.



Although studies considering a value-based approach are increasing, there is still work to be done to achieve full recognition of the value of influenza vaccination to get an IVC improvement in each specific category of population (Calabrò, Carini, et al., 2022; Calabrò, D'Ambrosio, et al., 2022; de Waure et al., 2022). Following this guidelines, Chapter 7 study tried to expand the societal dimension of value applied to an economic analysis, including the fiscal impact of influenza on working subjects (Calabrò, Rumi, et al., 2022). The reallocation of resources is one of the main "action points" of the value-based methodology (Expert Panel on Effective Ways of Investing in Health (EXPH), 2019): the evaluation of the fiscal impact in HCWs supports both an optimal use of resources, in a prospective of reinvestment of the saved economic resources, and a more efficient healthcare system, suggesting solutions to improve the productivity of its workforce.

In conclusion, evidence developed within this PhD project highlights the importance of increasing seasonal flu vaccination coverage rate in Italy. Higher IVC rates have been associated to an improvement of influenza health-related outcomes in population aged ≥65 years and to profits in terms of economic impact and fiscal revenue in the working age population (specifically, in the HCWs category). In an optic "value(s)-based healthcare", a wider usage of enhanced vaccines, such as MF59®-adjuvanted seasonal influenza vaccine, joint to an optimization of distribution and administration velocity in elderly individuals, is advised to mitigate the burden of seasonal flu infection. However, to achieve this final goal, a continuous monitoring of public attitudes towards vaccines and immunization is essential. A notable proportion of adults, indeed, still report some elements of hesitation towards influenza vaccination, particularly if concomitant with COVID-19 immunization. Thus, pro-active public health campaigns and actions are required to effectively improve vaccine confidence and acceptance in the long-term. Further research is needed to assess the effectiveness of different types of interventions in increasing vaccine uptake, but the development of health policies to guide towards a high value care are the way to achieve durable and sustainable implementation of IVC in Italy.

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