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Postmarketing observational study on the safety of 2021/2022 and 2022/2023 influenza vaccination campaigns in Italy: TheShinISS-Vax|Flu study protocol

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ABSTRACT

Introduction The purpose of TheShinISS-Vax|Flu study is to examine the association between influenza vaccines and adverse events requiring hospital admission or emergency care during the influenza vaccination campaigns 2021/2022 and 2022/2023 in Italy.

Methods and analysis This is a Self-Controlled Case Series multiregional study using linked routinely collected data from regional healthcare databases of the participating regions. Study participants will be persons aged ≥6 months, unvaccinated or who have received influenza vaccine during the influenza vaccination campaigns in the seasons 2021/2022 and 2022/2023 in Italy and who have experienced the outcome of interest for the first time during the study period (1 September 2021–30 June 2022 and 1 September 2022–30 June 2023 for the first and second vaccination campaigns, respectively). Risk periods will be specifically defined for each outcome and further subdivided into periods of 7 days. The exposures will be the first or second dose of the influenza vaccines administered during the two vaccination campaigns. Statistical analysis will be conducted separately for the data of the two campaigns. Exposure risk period will be compared with baseline risk period defined as any time of observation out of the risk periods. The modified SCCS method will be applied to handle event-dependent exposure and mortality and fitted using unbiased estimating equations to estimate relative incidences and excess of cases per 100 000 vaccinated by dose, age, sex and type of vaccine. Calendar period will be included as time-varying confounder in the model, where appropriate.

Ethics and dissemination The study received the approval from the National ethics committee for clinical trials of public research bodies and other national public institutions (PRE BIO CE n.0036723, 23/09/2022). Results will be published in peer-reviewed journals and reports in accordance with the publication policies of the Italian National Institute of Health and of the Italian Medicines Agency.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large sample size and long follow-up for detecting rare adverse events of influenza vaccines.
⇒ An R-based statistical tool, TheShinISS, enabled distributed analyses on real-world data to overcome privacy issues.
⇒ Use of modified Self-Controlled Case Series method to handle event-dependent exposure and mortality, and to control for time-independent confounders.
⇒ It was not possible to validate outcomes through clinical records review.
⇒ Only serious adverse events requiring emergency care or hospital admission were included.

INTRODUCTION

Seasonal influenza is a viral respiratory disease in human, caused by A or B virus. Influenza epidemics occur annually worldwide with substantial burden of disease.

Influenza vaccination campaigns remain an important public health intervention to reduce influenza viruses' circulation during epidemic and pandemic. They are organised annually since the waning of immunity and the yearly changes in viral antigenic configuration requires annual updating of the vaccines.[1]

Vaccines are rigorously evaluated in preregistrative randomised clinical trials, but their wide scale introduction may provide the opportunity to identify rare adverse events that can be undetected in clinical trials. Therefore, it is essential to have continuous monitoring of adverse events potentially associated with influenza vaccines, using both passive and active surveillance systems, as a key element of any vaccination campaign.[2]

New safety concerns may arise since composition of influenza vaccines changes yearly according to WHO recommendations (https://www.who.

int/teams/global-influenza-programme/vaccines/who-recommendations).

The Italian National Institute of Health (Istituto Superiore di Sanità-ISS) and the Italian Medicines Agency (Agenzia Italiana del Farmaco-AIFA) coordinated TheShinISS-Vax|Flu study, a post-marketing active surveillance of the adverse events following immunisation of influenza vaccines in place in Italy. This is a collaborative project which aims to cover a large population using linked healthcare databases of the participating Italian regions.

ISS has a long history of monitoring the safety of vaccines using ad hoc studies to collect and analyse data, also involving networks of local health authorities, general practitioners and paediatricians.[3–6] These past experiences have offered the possibility to gain insights into areas where the existing surveillance system can be strengthened, and the development of large-linked database monitoring system has resulted a major challenge.

ISS has pioneered a new model to conduct active surveillances of influenza and COVID-19 vaccines in Italy. This model applies a distributed analysis framework using TheShinISS, an R-based open-source statistical tool that locally processes data collected and updated periodically from regional healthcare databases according to a study-tailored, Common Data Model (CDM).[7] The advantages of this model consist of: the inclusion of a large population; the timely access and ease of regional data sharing with a reduction of workload of health professionals; and the enhancement in the quality control of the regional healthcare data. Recently, multiregional studies have been conducted by TheShinISS using regional routinely collected and linked health data from vaccination registries, hospital discharges and emergency care admissions and pharmacy claims databases.[8 9]

In Italy, the Ministry of Health annually releases recommendations for the prevention and control of influenza. The recommendations on 2021/2022 and 2022/2023 influenza vaccination campaign[10 11] have expanded the vaccine eligible population comparing with the previous vaccination campaigns, also considering the challenges of the COVID-19 pandemic scenario.

The purpose of this study is to examine the association between rare, serious adverse events and adverse events of special interest and influenza vaccines during the 2021/2022 and 2022/2023 influenza vaccination campaigns in Italy.

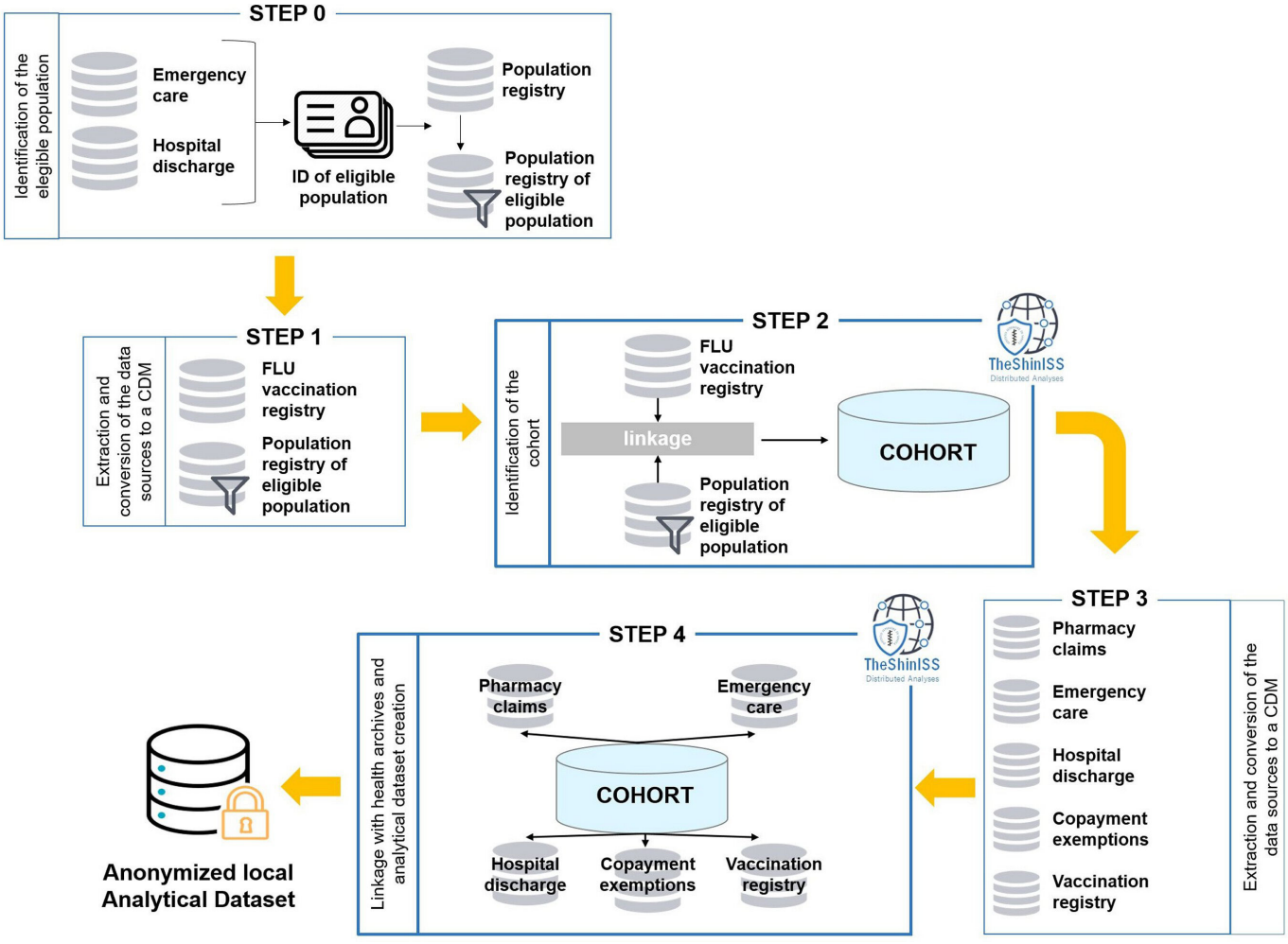

Figure 1 Diagram showing the data flow when using TheShinISS to locally process healthcare data structured according to a CDM. *Vaccination registry related to those registered in the regional population. CDM, Common Data Model.

Table 1 Definition of the adverse events potentially associated with influenza vaccines

Adverse events potentially associated with influenza vaccines	ICD-9-CM	Risk period (days after the vaccination)
Bell's palsy	351.0	60
Acute hepatitis	570; 572.2; 573.3; 573.9	60
Guillain-Barré syndrome	357.0; 357.8; 357.9	42
Encephalitis and encephalomyelitis	323; 348.3	42
Thrombocytopaenia	283.0; 286.5; 287 (excl. 287.39); V83.01; V83.02	42
Vasculitis	136.1; 273.2; 287.0; 446.0; 446.2; 446.4; 446.5; 446.6; 446.7; 709.1	42
Demyelinating diseases	323.81; 340; 341.0; 341.1; 341.2; 341.9; 377.3; 377.49; 377.9; 725	42
Convulsions	780.39	14
Anaphylaxis	995.0; 999.4	2
Neuritis (brachial neuritis, neuralgic amyotrophy)	353.5; 723.4	28
Narcolepsy	347	42
Swelling of limb	729.81	–
Syncope and collapse	780.2	–

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

METHODS AND ANALYSIS

Study population

Study population will include persons of ≥6 months of age of seven Italian regions (Piemonte, Friuli Venezia Giulia, Emilia-Romagna and Toscana of Northen Italy; Lazio of Central Italy; Puglia and Campania of Southern Italy), unvaccinated or who received influenza vaccine during the 2021/2022 and 2022/2023 influenza vaccination campaigns (from October to March), and who were admitted to emergency care or hospital for at least one of the outcomes of interest from the beginning of the vaccination campaigns to the end of the study periods. Participation in the study of the Italian regions is voluntary. AIFA invited all the Italian regions to participate in the study but participation depended on the availability of the healthcare databases, data update and personnel to be dedicated to the study.

Study period

For the vaccination campaign 2021/2022: 1 September 2021 –30 June 2022.

For the vaccination campaign 2022/2023: 1 September 2022– 30 June 2023.

Type of vaccine studied

All influenza vaccines were administered to the study population in the seven participating Italian Regions during the two campaigns, in accordance with the recommendations of the Ministry of Health[10 11] and the provision of AIFA decision.[12 13]

Data sources

The following healthcare databases will be used:

- Vaccination registry to identify influenza vaccination exposure and exposure to other vaccines which were administered from 1 September 2021 and 1 September 2022 for the first and second influenza vaccination campaigns, respectively, to the last data update.
- Population registry to identify information on age, sex, date of registration and deregistration (where applicable) in the regional healthcare system, and vital status (causes of death are not recorded in this registry) to the last data update.
- Pharmacy claims database to characterise the study population by obtaining information on the use of drugs (coded with Anatomical Therapeutic Chemical code) during the periods preceding the two influenza vaccination programmes (from 1 September 2020 and 1 September 2021 for the first and second influenza campaign, respectively, to the last data update).
- Hospital discharges database to identify the outcomes of interest prevaccination and postvaccination (from 1 September 2021 and 1 September 2022 for the first and the second influenza campaigns, respectively, to the last data update) and also to obtain information on the comorbidities of the study population in the 5 years preceding influenza vaccination (from 1 October 2016 and 1 October 2017 for the first and the second influenza campaigns, respectively, to the last data update) coded with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM).
- Admissions to the emergency care database to identify the outcomes of interest (from 1 September 2021 and 1 September 2022 for the first and the second

Table 2 Definition of comorbidities

	Hospital discharge code: ICD-9-CM (in the last 5 years)	Exemptions code	Pharmacy claim code: ATC (in the last 12 months)
Chronic pulmonary disease	480–488; 491; 495; 518.81–518.84	024	J05AH
Chronic obstructive pulmonary disease*	490; 492; 494; 496	057	R03
Asthma*	493	007	–
Cardiovascular and cerebrovascular diseases	390–398; 406–459	002; 021; 0A02; 0B02; 0C02; 036	B01AC; C01B; C01DA; C08DA; C08DB
Hypertension	401–405	031; 0A31	C02; C03; C07; C08; C09
Chronic kidney diseases	580; 582–585; 593; 753.12–753.14	023; 022; 061; 062	–
Dementia/Alzheimer's disease	290; 294.1; 331.2	011; 029	N06DA; N06DX
Diabetes	250	013	A10
Rheumatic diseases	446.5; 696; 710; 714; 720; 725	006; 028; 030; 045; 054; 067	L04
Haematological disease	280–289 (excl. 285.1)	003	B01AA; B01AB; B01AE; B01AF; B01AX; B02BD; B03
Neurological diseases	238.7; 296.3; 311; 332; 345; 340; 348.39	017; 038; 044; 046	N03A; N04B; N05A; N06A
Neoplasms	140–209; V10	048	L01
Metabolic disorders	272; 278	025	C10
Moderate/severe hepatopathy	456.0–456.2; 571–572; 573.0	008; 016	–
Cystic fibrosis	277.0	018	R07AX
Ulcer disease	531; 532; 533		A02B
Colitis	555; 556	009	–
HIV	042	020	J05AE; J05AF; J05AG; J05AR
Infections*	053; 599.0; 010–018; 031; 078.5; 052–054; 136.3; 117.5	055	J01; J02; J04; J05 (excl. J05AE; J05AF; J05AG; J05AH; J05AR)

*ICD-9-CM in 365 days.
ATC, Anatomical Therapeutic Chemical; HIV, Human Immunodeficiency Virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

influenza campaign, respectively, to the last data update) coded with ICD-9-CM.

- Exemptions from healthcare service copayment database to obtain information on comorbidities of the study population (to the last data update).

Table 3 Definition of drug use

	Pharmacy claims code: ATC (in the last 12 months)
Other vaccines	J07 (excluding COVID-19 and J07BX03 influenza vaccines J07BB)
Anti-COVID-19 vaccines	J07BX03
Glucocorticoids	H02AB
Non-steroidal anti-inflammatory drugs	M01A
Estroprogestinics	G03

ATC, Anatomical Therapeutic Chemical.

Study design

TheShinISS-VaxlInfluenza study will use a Self-Controlled Case Series (SCCS) design.[14–19]

The SCCS design is best suited to evaluate the safety of vaccines and other medicinal products when the relationship between transient exposures and acute events is investigated. This method requires only data on individuals, vaccinated and unvaccinated, who have experienced an event (cases). Estimation is within individuals and consequently, any time-invariant unknown or unmeasured potential confounders are controlled for.

Therefore, it represents a valid epidemiological design alternative to the cohort and case–control study in the research on vaccine safety, particularly in situations where it is difficult to identify an appropriate comparison group, for example when vaccinated population has different characteristics from unvaccinated or most of the population has received the vaccine.

The SCCS model was originally developed to investigate the association between vaccines and adverse events

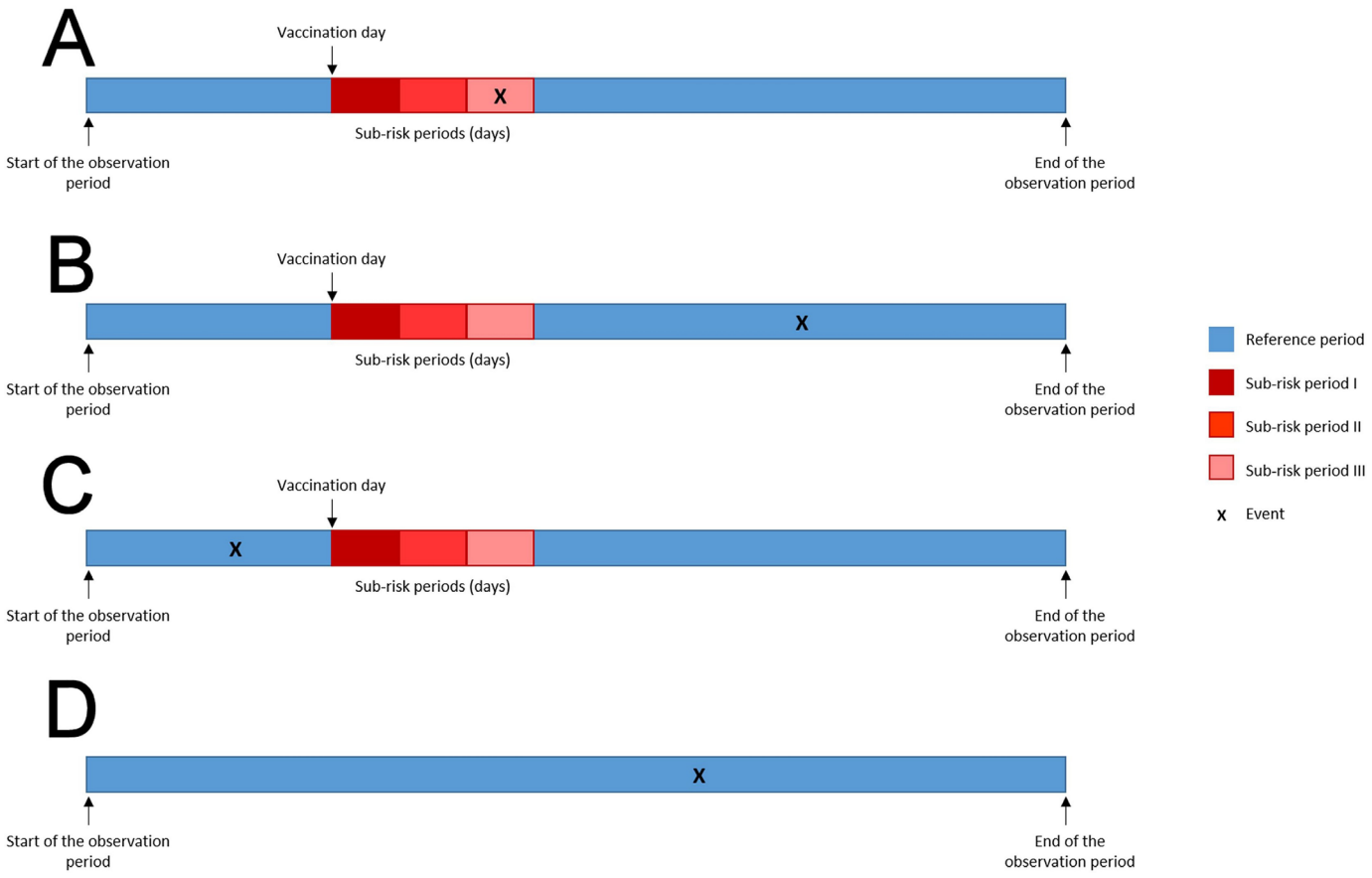

Figure 2 Schematic presentation of Self-Controlled Case Series method for hypothetical subjects included in the study. (A) Events occurring in vaccinated subjects during the risk period. (B) Events occurring in the reference period after vaccination. (C) Events occurring in the reference period before vaccination. (D) Events occurring in unvaccinated subjects.

with the key assumption that the occurrence of an event does not influence postevent exposures, for example by delaying or even cancelling the subsequent exposures. This assumption may be violated for vaccine safety studies when the occurrence of the outcome of interest is a contra-indication to vaccination. To handle event-dependent exposures a modified SCCS method has been developed.[17–19]

In the modified SCCS model for event-dependent exposures, unlike the standard model, it is essential to include unvaccinated cases. This is because the absence of vaccination may indicate cancelled vaccination that occurs more often for events that occur earlier. As a result, the absence of vaccination can be informative on the timing of the event, and excluding unvaccinated cases may introduce bias.[19]

TheShinISS-Vax|Flu is a multiregional study using routinely collected data from regional healthcare databases/registries linked in each region at individual level. The study applies TheShinISS, the R-based open-source statistical tool which was developed by the researchers of ISS.[7] The tool is currently maintained and customised by the 'TheShinISS Network' that includes researchers from ISS, the Department of Epidemiology of the Lazio Regional Health Service and the Universities of Verona and Messina. TheShinISS allows to carry out distributed analyses in multidatabase pharmacoepidemiological studies according to a CDM strategy which is study tailored.[20] It has been already employed in large real-world studies with different epidemiological designs.[8 9 21–25]

Going into further detail, figure 1 illustrates the relational scheme of the study, including all the steps, which use TheShinISS to locally process healthcare databases structured according to a CDM: Step 0—identification of the eligible population from the hospital discharges database and admissions to the emergency care database; Step 1—extraction and preparation of the CDM of the vaccination registry and the population registry related to the eligible population identified in Step 0; Step 2—identification of the study cohort by vaccination status, data quality control and descriptive analysis (by execution of TheShinISS); Step 3—extraction and conversion of healthcare databases, and preparation of the CDM related to the cohort; Step 4—execution of TheShinISS on CDM to perform: data quality control, linkage of the cohort with healthcare databases, anonymisation, aggregation and creation of a minimal set of exposure and outcome variables, and specific covariates of interest

for the study, which will constitute the local anonymised analytical datasets.

Definition of the study outcomes

We will focus on 13 different outcomes considering the guidelines issued by AIFA[26] and hypothetical concerns regarding analogous vaccines or complications associated with the disease itself.

The outcomes will be identified from the diagnosis of emergency care admission or hospital discharge using ICD-9-CM code.

The outcomes of interest will be ascertained during the study period. Each case will be followed up from the beginning of the vaccination campaign (1 September 2021 and 1 September 2022 for the first and second vaccination campaigns, respectively) to the date of last regional health data update, for each individual alive; conversely, when a case dies, the end of the observation period will be defined according to the SCCS methodology to deal with mortality.[19]

Cases will be defined as those patients who have experienced the outcome for the first time during the study period (incident cases). This means that patients who have an emergency care admission or a hospital discharge, for the same outcome, within the 5 years prior to the start of the study period (look back) will be excluded. A time window of 5 years provides a sufficiently look back period to selectively identify incident cases. Deaths for any causes will be also considered.

Table 1 lists the selected adverse events which are potentially associated with influenza vaccination and the corresponding ICD-9-CM codes and the risk period, which are derived from the Brighton Collaboration[26] and the AIFA report.[27] The list will be updated in case of emerging signals on new adverse events potentially associated with influenza immunisation and the participant Regions will be requested to provide further specific data.

Definition of comorbidities and drugs

Table 2 reports codes of hospital discharges, drugs use and exemptions derived from the local health care databases/registries which are necessary for definition of comorbidities. Table 3 shows codes of definition of drug use.

Definition of the exposure

The exposure variables will include the first or second dose of the influenza vaccines available in Italy during the vaccination campaigns 2021/2022 and 2022/2023.

The influenza vaccines will be categorised according to the available type of vaccines during the two vaccination campaigns: quadrivalent vaccine (egg-based and cell culture-based influenza vaccine), quadrivalent and trivalent with MF59 adjuvant vaccine, live attenuated influenza vaccine (the nasal spray influenza vaccine).

For each outcome of interest, we will define specific risk periods (table 1) which will be further subdivided into three subrisks periods.

All remaining time within the individual observation period will define the no-exposure period for each outcome of interest, and will represent the baseline period to which the exposure risk period will be compared (figure 2).

Methods of analysis

Statistical analysis will be conducted separately for the data of the two vaccination programmes 2021/2022 and 2022/2023. Where appropriate, a pooled analysis will be conducted.

We will describe the characteristics of the cases as frequencies, percentages, medians and IQRs, in terms of age, sex, geographical areas, Charlson Index (based on hospitalisation in the 5 years prior vaccination), length of hospitalisation, number of hospital admissions for any causes in the 5 years prior to vaccination, number of drug prescriptions in the year prior to vaccination, and comorbidities.

We will describe the data extraction process in a flowchart reporting number of individuals at each stage of the process, for example those individuals potentially eligible, included, analysed and those excluded with reasons, indicating also numbers of individuals with missing or incoherent observations.

We will use the SCCS methodology, modified to event-dependent exposures,[14–19] to examine the association between influenza vaccine and each outcome of interest in individuals aged ≥6 months during the observation period. The modified SCCS model addresses situations where the occurrence of an event affects the timing or the occurrence of subsequent exposures. It introduces a counterfactual scenario in which no exposure can occur after occurrence of an event.[17–19]

If patients died, the end of the observation period will be defined according to what is proposed by the modified SCCS methodology to handle mortality.[19]

The SCCS model will be fitted using unbiased estimating equations to estimate relative incidences (RIs) and their 95% CIs in the predefined risk periods compared with the baseline periods. Unbiased estimating equations theory generalises likelihood theory to estimate the parameters of interest and it is used when the likelihood function is difficult to obtain. Precision of the estimates can be calculated similarly to the methods of the maximum-likelihood estimate.[28]

To account for possible seasonal variation in the baseline incidence of each outcome, temporal effects will be included in the model as time-varying covariate.

We will estimate, for each outcome of interest, the excess of cases per 100 000 vaccinated (EC) as the ratio of the number of excess cases due to the vaccine {[(RI − 1)/RI] × no. events in the risks period} divided by the

number of vaccinated × 100 000[29]; while the 95% CI 95% calculated by non-parametric bootstrapping methodology (10 000 replications).

Subgroup analyses will be carried out by age group (<60 and ≥60 years), sex, and type of vaccine for each outcome of interest.

Several sensitivity analyses will be performed to assess the assumptions of the SCCS model regarding the event-dependent exposure and observation period, the seasonality and the pre-specification of risk periods. Moreover, we will carry out analyses on cases receiving only influenza vaccines, excluding those with both influenza and COVID-19 vaccines. This restriction will also be applied in cases where other vaccines are received concurrently.

Statistical analyses will be performed using R (R Core team 2021) with SCCS package[30] and STATA software.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Time schedule

Time schedule of the study is presented in online supplemental table 1.

Ethics and dissemination

The study received the approval from the National ethics committee for clinical trials of public research bodies and other national public institutions (PRE BIO CE n.0036723, 23/09/2022). Results will be published in peer-reviewed journals and reports in accordance with the publication policies of the Italian National Institute of Health and of the Italian Medicines Agency.

Adverse reaction management

The adverse reaction reporting is not required according to the Guideline on Good Pharmacovigilance Practices (GVP) VI rev. 2 (VI.C.1.2.1.2. Non-interventional postauthorisation studies with a design based on secondary use of data).[31]

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Contributors SSA, CM, FM-I, RDC, PF, PM, FP, ARM and MM were involved in conception and study design. SSA, CM and MM were involved in drafting of the article. FMI, RDC, PF, PM, FP and ARM were involved in critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. SSA, MM and CM provided statistical expertise.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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