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Original article

# Comparing two case definitions for including severe acute respiratory infection patients in influenza and COVID-19 vaccine effectiveness studies among older adults using the test-negative design: VEBIS hospital network, seven European countries, 2023/24

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ABSTRACT

*Introduction:* Two severe acute respiratory infection (SARI) case definitions (CDs) are often used in test-negative design (TND) hospital-based vaccine effectiveness (VE) studies. SARI-CD1 requires ≥1 symptom (cough, fever, shortness of breath, anosmia, ageusia, or dysgeusia); SARI-CD2 requires both fever and cough. Using VEBIS hospital network end-of-season 2023/24 data, we compared the effect of these CDs on influenza and COVID-19 VE estimates in Europe.

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*Methods:* Using the TND, we restricted analysis to seven countries recruiting patients using SARI-CD1; we created a subset of SARI patients also meeting SARI-CD2. Cases were RT-PCR-positive for influenza A(H1N1)pdm09, A (H3N2), or SARS-CoV-2; controls were influenza or SARS-CoV-2 RT-PCR-negative. We estimated VE among patients ≥65 years using logistic regression adjusted for country, onset date, age, sex, and chronic conditions. We estimated VE overall, by age group (65–79, ≥80 years) and time since vaccination (14–59, 60–119, ≥120 days). Absolute VE differences ≥10% were considered relevant.

*Results:* Patient characteristics and outcomes were similar across CDs. SARI-CD1 had slightly more vaccinated cases, with little difference in controls between the two CDs. For influenza, the absolute VE difference between SARI-CD1 and SARI-CD2 was 10% for influenza A(H1N1)pdm09 (34% vs 44%), 19% among those aged ≥80 years (21% vs 40%) and 18% at 60–119 days post-vaccination (4% vs 22%). For SARS-CoV-2, absolute VE differences were 11% overall (29% vs 40%), 11% among ≥80 years (33% vs 44%), and 12% at 60–119 days (34% vs 46%). All other absolute VE differences were < 10%.

*Conclusions:* VE was similar for influenza A(H3N2), adults 65–79 years and 14–60 days post-vaccination. We observed signals of higher VE with SARI-CD2 for influenza A(H1N1)pdm09 and SARS-CoV-2, particularly among adults ≥80 years and ≥ 60 days post-vaccination, although 95% CIs overlapped. These signals suggest CDs may contribute to VE variability and VE studies should clearly indicate CDs used.

## 1. Introduction

The frequent genetic and antigenic changes in influenza and SARS-CoV-2 viruses have led many countries in the European Union (EU) to implement annual vaccination programmes for both COVID-19 and influenza, with yearly recommendations for vaccine composition [1,2]. In general in the EU, influenza and COVID-19 vaccination are prioritised for older adults, specific occupational groups, individuals with chronic health conditions, and those at elevated risk of complications and severe illness [3].

Monitoring vaccine effectiveness (VE) is an important component of evaluating immunisation programmes and informing public health recommendations. Since 2022, the Vaccine Effectiveness, Burden, and Impact Studies (VEBIS) hospital network has been performing both influenza VE (IVE) and COVID-19 VE (CVE) studies within the same integrated platform across 12 sites in 11 EU countries. These studies follow a common generic protocol [4] and use the test-negative design (TND) [5], where hospitalised patients are recruited based on a clinical case definition (CD) for severe acute respiratory infection (SARI) and tested for the pathogen of interest. Those testing positive are classified as cases, and those testing negative as controls; the proportion vaccinated is then compared between these two groups.

Beyond VE studies, CDs also serve different purposes. In surveillance, their main role is to harmonise recruitment of populations, allowing disease trend monitoring and burden of disease estimation. Broader definitions with higher sensitivity are favoured to maximise case ascertainment, although this comes at the cost of reduced specificity [6,7].

The choice of CD is a critical element of TND studies, as it determines who is included and helps to ensure that cases and controls originate from the same source population, thereby minimising confounding from differences in health-seeking behaviour [8]. However, if the symptoms required for inclusion are associated with both case and vaccination status, the CD itself may introduce selection bias and affect VE estimates [9]. For example, stricter definitions may result in higher VE by excluding vaccinated cases with attenuated symptoms, whereas broader definitions may result in lower VE by including them [10].

Since the COVID-19 pandemic, different SARI CDs have been used across Europe for both surveillance and VE studies [11], typically based on symptoms collected via questionnaires or, where unavailable, diagnostic codes as a proxy sourced from electronic health records [12]. In some countries, VE studies are embedded within routine SARI surveillance systems, whereas in others, they are conducted separately. The VEBIS core protocol for hospital-based TND VE studies, commissioned by the European Centre for Disease Prevention and Control (ECDC), encourages alignment with existing SARI surveillance where feasible [4]. The protocol was initially developed to measure COVID-19 vaccine effectiveness and the definitions used reflect the importance to be able to include COVID-19 cases at the initial stage of the study. The protocol defines a patient with SARI (SARI-CD1) as an individual admitted to hospital for ≥24 h with at least one of the following symptoms: cough, fever, shortness of breath, anosmia, ageusia, or dysgeusia [4]. In contrast, other studies [13,14] use the less sensitive World Health Organization (WHO) SARI definition (SARI-CD2), which identifies a SARI patient as an individual admitted to hospital with both fever and cough [7]. SARI-CD2 is a subset of SARI-CD1, i.e. all patients meeting SARI-CD2 also meet SARI-CD1.

In this study, we assessed whether the use of SARI-CD1 and SARI-CD2 affected the estimates of IVE against laboratory-confirmed influenza A(H1N1)pdm09 and A(H3N2), and CVE against laboratory-confirmed SARS-CoV-2, during the 2023–24 season, in order to inform interpretation and comparison of VE studies that apply different SARI CDs.

## 2. Methods

We used end-of-season 2023/24 data from the VEBIS hospital network, a multicentre, hospital-based TND study conducted in 12 study sites among 11 EU countries, for which methods have been described previously [9]. We restricted analysis to countries recruiting patients using SARI-CD1 or a similar case definition and collecting individual symptom data, allowing retrospective reconstruction of both SARI-CD1 and SARI-CD2. Four study sites did not meet these criteria and were therefore excluded. Country-specific CDs and reasons for exclusion are provided in Supplementary Table S1. We further restricted our analysis to SARI patients 1) aged ≥65 years, 2) in vaccine target groups as recommended by each country (Supplementary Table S1); and 3) admitted to hospital ≤14 days after symptom onset (to ensure symptoms reflected the acute episode leading to admission).

For IVE, we focused on subtype-specific analyses for influenza A (H1N1)pdm09 and A(H3N2), as influenza B circulation was limited in Europe during the 2023/24 season. We defined cases as SARI patients testing RT-PCR-positive for influenza A(H1N1)pdm09 or A(H3N2) (for IVE) or SARS-CoV-2 (for CVE). We defined controls as SARI patients testing RT-PCR-negative for all influenza types (A and B) for IVE, and for SARS-CoV-2 for CVE. We classified patients as vaccinated if they had received the 2023/24 influenza (for IVE) or COVID-19 (for CVE) vaccine ≥14 days before symptom onset, and as unvaccinated if they had not received the 2023/24 vaccine or were vaccinated on or after symptom onset.

The analysis period was defined separately for each VE analysis by country. For IVE, the start week was based on the first subtype-specific detected case or 14 days after the start of the 2023/24 influenza vaccination campaign, whichever occurred first. For CVE, the start week was defined as the first week when the JN.1 (BA.2.86 sublineage) became predominant. We focused on this period as this sublineage had become

predominant and was associated with potential immune escape. This period occurred after the start of the XBB.1.5 vaccination campaigns across Europe and aligns with the published 2023/24 VEBIS CVE results [15]. Further details on how the predominance period was determined are available elsewhere [15]. Both analysis periods ended on 19 May 2024.

We described key characteristics (age, sex, comorbidities), vaccination status and clinical outcomes (intensive care unit (ICU) admission, in-hospital death) among patients meeting each case definition to explore potential differential inclusion.

We estimated VE as $(1 - \text{aOR}) \times 100$, where aOR is the confounder-adjusted odds ratio of vaccination among cases and controls from logistic regression. Separate estimates were obtained for SARI-CD1 and SARI-CD2. We adjusted the OR for age, sex, at least one chronic condition (diabetes, heart disease, asthma/lung disease, or immunodeficiency), onset date, and country. Age was modelled as a categorical variable (65–74, 75–84, 85–94, ≥95 years), a linear term, or a restricted cubic spline (RCS) (3–5 knots). Onset date was modelled as a RCS (3–5 knots) or a categorical term based on month. We selected the best functional form using Akaike's information criterion.

We estimated VE overall and stratified by age group (65–79, ≥80 years) and compared the effect of SARI CDs on IVE and CVE by calculating the difference in VE point estimates between SARI-CD2 and SARI-CD1. We defined differences of VE point estimates ≥10 percentage

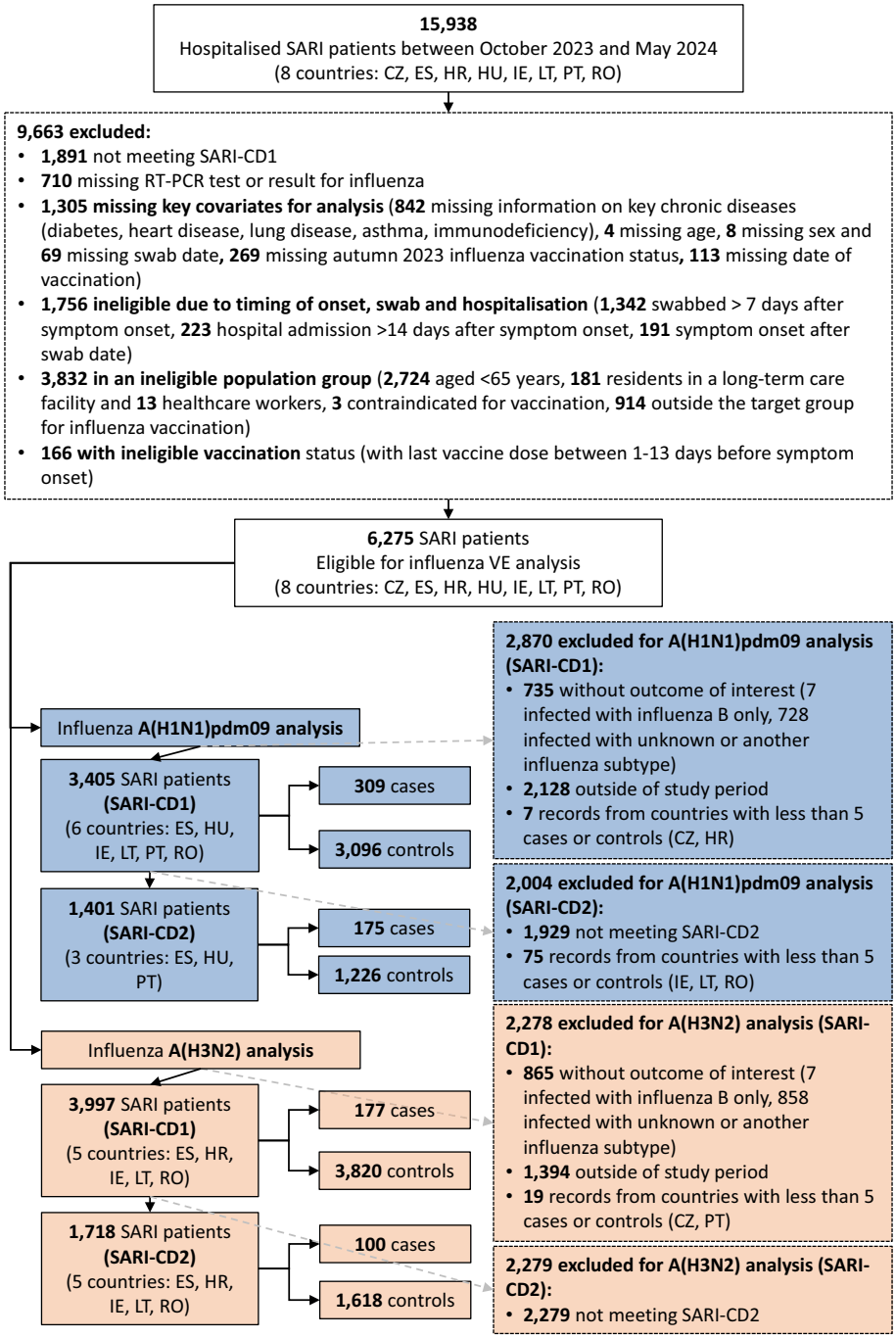



**Fig. 1.** A. Patient exclusion flowchart for influenza A(H1N1)pdm09 and A(H3N2) vaccine effectiveness analysis, VEBIS hospital network, eight European countries, 2023/24. B. Patient exclusion flowchart for COVID-19 vaccine effectiveness analysis, VEBIS hospital network, eight European countries, 2023/24. Abbreviations: CZ: Czechia, ES: Spain (national), HU: Hungary, HR: Croatia, IE: Ireland, LT: Lithuania, PT: Portugal, RO: Romania

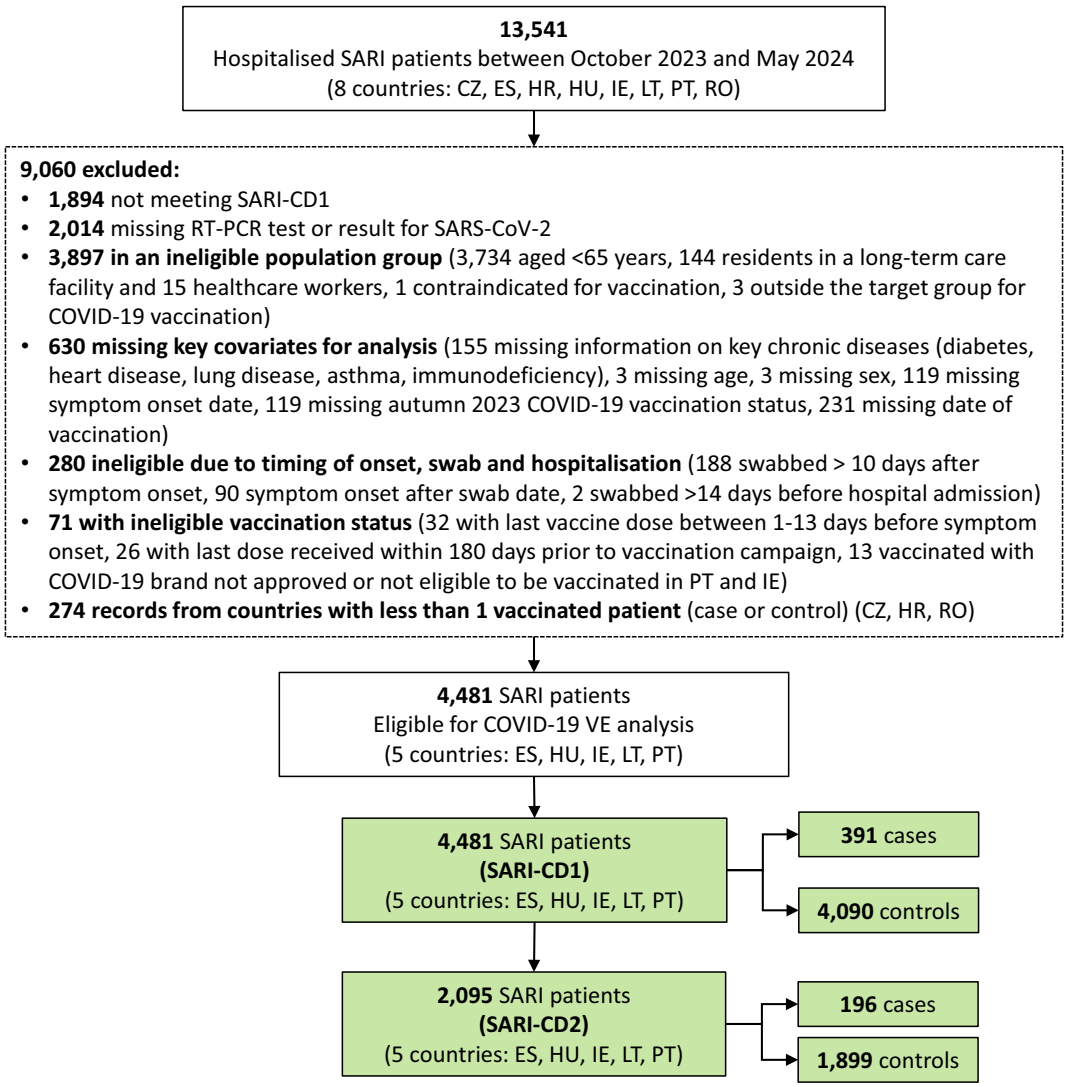



**Fig. 1.** (*continued*).

points as potentially relevant, using this threshold to aid interpretation. In addition, we estimated VE within three time since vaccination (TSV) bands (14–59, 60–119 and ≥ 120 days) to assess whether CD-related differences varied over time, accounting for potential waning immunity and changes in circulating strains.

When there were < 10 events per logistic regression parameter [16], we used penalised logistic regression (Firth's method) [17] to assess potential small-sample bias. VE estimates were not reported if the absolute difference between standard and penalised logistic regression estimates exceeded 10%, or if any cell in the case-by-exposure status table contained fewer than five patients.

We conducted sensitivity analysis to account for correlated vaccination behaviour [18] by excluding SARS-CoV-2-positive controls from IVE and influenza-positive controls from CVE, along with those with missing test results.

All data analyses were performed using R statistical software (v4.4.0, R Core Team).

## 3. Results

A total of eight countries met the eligibility criteria for inclusion. After applying the study and pathogen-specific restrictions, data from seven countries were included in at least one influenza or SARS-CoV-2 analysis. After exclusions, 3405 patients from six countries were included in the influenza A(H1N1)pdm09 analysis using SARI-CD1, of whom 1401 (41%) patients from three countries were included using SARI-CD2. For VE against influenza A(H3N2), 3997 patients from five countries were included using SARI-CD1 and 1718 (43%) using SARI-CD2 (Fig. 1A). For VE against SARS-CoV-2, 4481 patients were included from five countries using SARI-CD1 and 2095 (47%) using SARI-CD2 (Fig. 1B).

The proportion of patients aged ≥80 years was 53–55% using SARI-CD1 and 50–51% using SARI-CD2. Among SARI-CD1 patients, fever and cough were the most common symptoms (43–47%), followed by cough only (39–45%). Across pathogens, comorbidities were reported in 86–89% of patients under both CDs. ICU admissions occurred in 3–4% and in-hospital deaths in 6–7% of patients with both CDs. Laboratory-confirmed cases ranged from 4 to 12% across influenza A(H1N1)pdm09, A(H3N2) and SARS-CoV-2, with higher swab positivity under SARI-CD2 (Table 1).

Similar patterns were observed when stratifying by cases and controls (see Supplementary Tables S2–S4). Across pathogens, cases and controls peaked in late December to early January (weeks 49–3), reflecting a season with co-circulation of influenza A(H1N1)pdm09, A(H3N2), and SARS-CoV-2. The timing of peaks was consistent between SARI-CD1 and SARI-CD2 (Fig. 2).

Vaccination among cases was 56% with SARI-CD1 vs 53% with SARI-CD2 for influenza A(H1N1)pdm09, 59% vs 56% for A(H3N2), and 46%

**Table 1**
Characteristics of patients included in analysis by pathogen and SARI case definition among adults aged ≥65 years in the target group for vaccination, VEBIS hospital network, seven European countries, 2023/24.

| Characteristic | Influenza A(H1N1)pdm09 analysis | | | | Influenza A(H3N2) analysis | | | | SARS-CoV-2 analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SARI-CD1 (*n* = 3405) | | SARI-CD2 (*n* = 1401) | | SARI-CD1 (*n* = 3997) | | SARI-CD2 (*n* = 1718) | | SARI-CD1 (*n* = 4481) | | SARI-CD2 (*n* = 2095) | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Age group (years) | | | | | | | | | | | | |
| 65–79 | 1568 | 46 | 698 | 50 | 1793 | 45 | 835 | 49 | 2096 | 47 | 1037 | 49 |
| ≥80 | 1837 | 54 | 703 | 50 | 2204 | 55 | 883 | 51 | 2385 | 53 | 1058 | 51 |
| Sex | | | | | | | | | | | | |
| Male | 1736 | 51 | 743 | 53 | 2061 | 52 | 930 | 54 | 2353 | 53 | 1129 | 54 |
| Female | 1669 | 49 | 658 | 47 | 1936 | 48 | 788 | 46 | 2128 | 47 | 966 | 46 |
| Symptom profile | | | | | | | | | | | | |
| Fever AND cough | 1476 | 43 | 1401 | 100 | 1718 | 43 | 1718 | 100 | 2095 | 47 | 2095 | 100 |
| Cough only | 1416 | 42 | 0 | 0 | 1796 | 45 | 0 | 0 | 1742 | 39 | 0 | 0 |
| Fever only | 298 | 9 | 0 | 0 | 352 | 9 | 0 | 0 | 361 | 8 | 0 | 0 |
| Shortness of breath only | 45 | 1 | 0 | 0 | 26 | 1 | 0 | 0 | 57 | 1 | 0 | 0 |
| Sudden loss of taste or smell only | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other combination | 170 | 5 | 0 | 0 | 105 | 3 | 0 | 0 | 226 | 5 | 0 | 0 |
| Chronic conditions[a] | | | | | | | | | | | | |
| No | 373 | 11 | 165 | 12 | 451 | 11 | 231 | 13 | 531 | 12 | 283 | 14 |
| Yes | 3032 | 89 | 1236 | 88 | 3546 | 89 | 1487 | 87 | 3950 | 88 | 1812 | 86 |
| ICU admission | | | | | | | | | | | | |
| No | 3127 | 97 | 1284 | 96 | 3702 | 97 | 1590 | 96 | 4149 | 97 | 1947 | 97 |
| Yes | 102 | 3 | 52 | 4 | 121 | 3 | 64 | 4 | 139 | 3 | 69 | 3 |
| Missing | 176 | | 65 | | 174 | | 64 | | 193 | | 79 | |
| In-hospital death | | | | | | | | | | | | |
| No | 3066 | 94 | 1271 | 94 | 3514 | 93 | 1539 | 94 | 3980 | 94 | 1876 | 94 |
| Yes | 211 | 6 | 76 | 6 | 248 | 7 | 90 | 6 | 276 | 6 | 110 | 6 |
| Missing | 128 | | 54 | | 235 | | 89 | | 225 | | 109 | |
| Influenza result | | | | | | | | | | | | |
| Negative | 3096 | 91 | 1226 | 88 | 3820 | 96 | 1618 | 94 | 3617 | 83 | 1595 | 78 |
| Positive | 309 | 9 | 175 | 12 | 177 | 4 | 100 | 6 | 747 | 17 | 438 | 22 |
| Missing | 0 | | 0 | | 0 | | 0 | | 117 | | 62 | |
| SARS-CoV-2 result | | | | | | | | | | | | |
| Negative | 2512 | 87 | 1070 | 88 | 2999 | 89 | 1339 | 89 | 4090 | 91 | 1899 | 91 |
| Positive | 369 | 13 | 149 | 12 | 367 | 11 | 162 | 11 | 391 | 9 | 196 | 9 |
| Missing | 524 | | 182 | | 631 | | 217 | | 0 | | 0 | |
| Influenza vaccination in 2023/24 season | | | | | | | | | | | | |
| Unvaccinated | 1364 | 40 | 561 | 40 | 1255 | 31 | 550 | 32 | 1365 | 31 | 671 | 32 |
| Vaccinated | 2041 | 60 | 840 | 60 | 2742 | 69 | 1168 | 68 | 3105 | 69 | 1421 | 68 |
| Missing | 0 | | 0 | | 0 | | 0 | | 11 | | 3 | |
| Influenza vaccine type | | | | | | | | | | | | |
| Standard dose | 360 | 21 | 120 | 17 | 388 | 17 | 180 | 18 | 611 | 23 | 270 | 22 |
| High dose | 514 | 29 | 235 | 33 | 651 | 28 | 288 | 29 | 873 | 33 | 415 | 34 |
| Adjuvanted | 663 | 38 | 272 | 38 | 1022 | 43 | 400 | 40 | 812 | 30 | 367 | 30 |
| Cell-propagated | 198 | 11 | 85 | 12 | 288 | 12 | 136 | 14 | 354 | 13 | 161 | 13 |
| Other | 14 | 1 | 7 | 1 | 1 | 0 | 0 | 0 | 28 | 1 | 14 | 1 |
| Missing | 292 | | 121 | | 392 | | 164 | | 427 | | 194 | |
| Time since influenza vaccination | | | | | | | | | | | | |
| 14–59 days | 785 | 38 | 334 | 40 | 644 | 23 | 279 | 24 | 694 | 23 | 328 | 24 |
| 60–119 days | 1114 | 55 | 452 | 54 | 1127 | 41 | 474 | 41 | 1367 | 45 | 618 | 45 |
| ≥ 120 days[b] | 142 | 7 | 54 | 6 | 971 | 35 | 415 | 36 | 967 | 32 | 439 | 32 |
| Missing | 0 | | 0 | | 0 | | 0 | | 77 | | 36 | |
| COVID-19 vaccination in 2023/24 season | | | | | | | | | | | | |
| Unvaccinated | 1497 | 47 | 620 | 48 | 1583 | 42 | 693 | 42 | 1947 | 43 | 935 | 45 |
| Vaccinated | 1663 | 53 | 684 | 52 | 2197 | 58 | 938 | 58 | 2534 | 57 | 1160 | 55 |
| Missing | 245 | | 97 | | 217 | | 87 | | 0 | | 0 | |
| COVID-19 vaccine product | | | | | | | | | | | | |
| Pfizer | 1385 | 85 | 567 | 84 | 1792 | 83 | 776 | 84 | 2062 | 83 | 958 | 84 |
| Other | 238 | 15 | 107 | 16 | 359 | 17 | 148 | 16 | 419 | 17 | 184 | 16 |
| Missing | 40 | | 10 | | 46 | | 14 | | 53 | | 18 | |
| Time since COVID-19 vaccination | | | | | | | | | | | | |
| 14–59 days | 591 | 39 | 255 | 40 | 513 | 23 | 216 | 23 | 579 | 23 | 262 | 23 |
| 60–119 days | 828 | 54 | 339 | 53 | 911 | 42 | 383 | 41 | 1164 | 46 | 537 | 46 |
| ≥ 120 days[c] | 107 | 7 | 42 | 7 | 765 | 35 | 334 | 36 | 791 | 31 | 361 | 31 |
| Missing | 137 | | 48 | | 8 | | 5 | | 0 | | 0 | |

ICU: Intensive care unit; SARI: Severe acute respiratory infection

a: At least one of diabetes, heart disease, immunodeficiency, lung disease, or asthma

b: Maximum days since last influenza vaccination observed — A(H1N1)pdm09 analysis SARI-CD1: 194; A(H1N1)pdm09 analysis SARI-CD2: 153; A(H3N2) analysis SARI-CD1: 220; A(H3N2) analysis SARI-CD2: 218.

c: Maximum days since last COVID-19 vaccination observed — SARI-CD1: 222; SARI-CD2: 222.

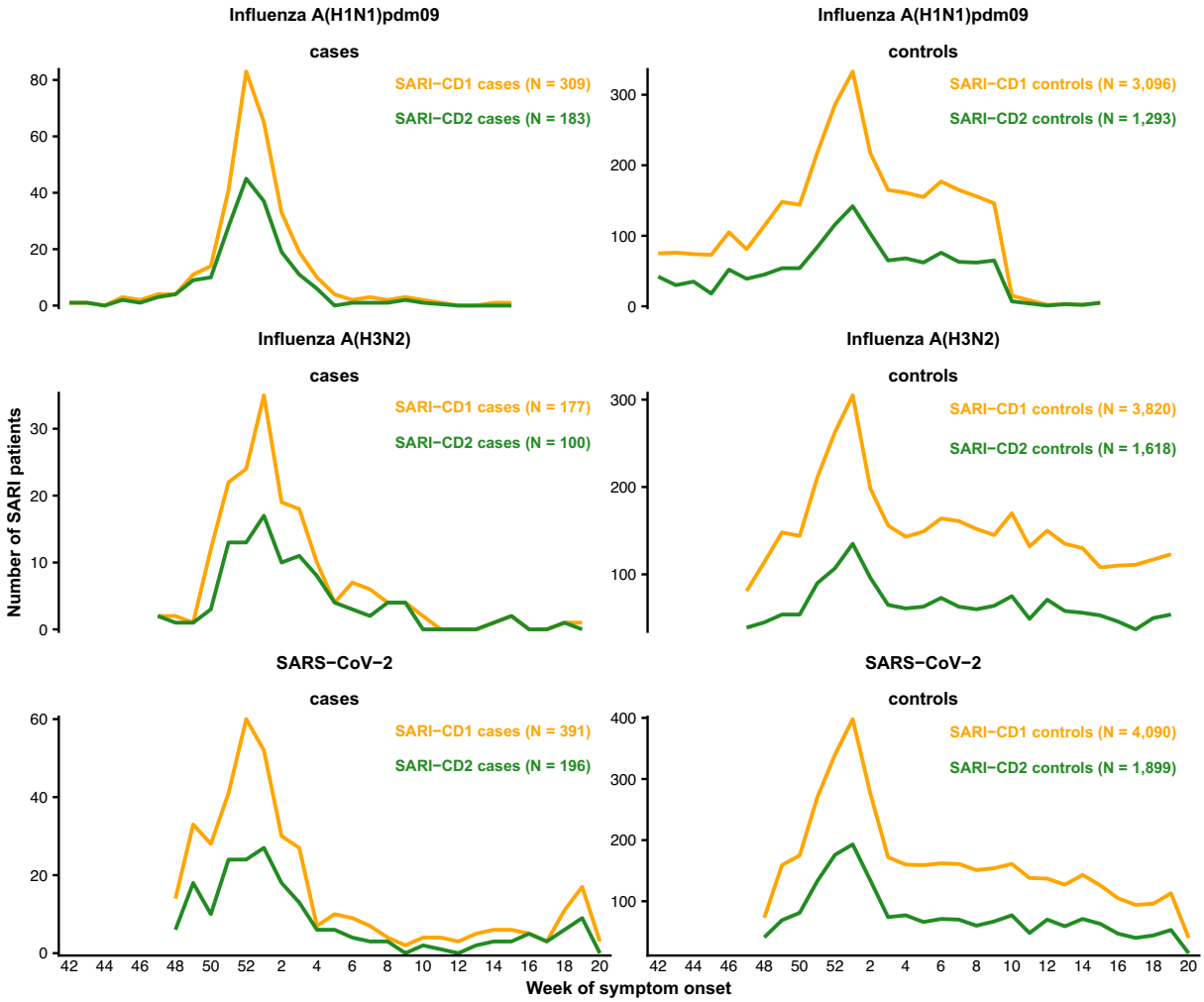



**Fig. 2.** Patients included in the analysis for each pathogen and case status, by case definition and week of symptom onset, VEBIS hospital network, seven European countries, 2023/24. CD: case definition; SARI: Severe acute respiratory infection; SARI-CD1: individual admitted to hospital with at least one of the following symptoms: cough, fever, shortness of breath, anosmia, ageusia, or dysgeusia; SARI-CD2: individual admitted to hospital with cough and fever.

vs 41% for SARS-CoV-2, respectively. Among controls, vaccination ranged between 57 and 69% with minimal differences between CDs. Similar patterns were observed by age group (Supplementary Table S5).

The absolute difference in overall VE against influenza A(H1N1) pdm09 between the two CDs was 10% (SARI-CD1: 34%, 95% CI 14–49%; SARI-CD2: 44%, 95% CI 20–61%). An absolute VE difference of 19% was observed among those aged ≥80 years (SARI-CD1: 21%, 95% CI -16–46%; SARI-CD2: 40%, 95% CI -2–65%), whereas the difference in VE for each CD among those aged 65–79 years was <10%. Against influenza A(H3N2), VE estimates were similar across CDs, with all absolute differences <10%. Against SARS-CoV-2, the absolute difference in overall VE between the two CDs was 11% (SARI-CD1: 29%, 95% CI 11–43%; SARI-CD2: 40%, 95% CI 17–57%). Among those aged ≥80 years, a VE difference of 11% was observed (SARI-CD1: 33%, 95% CI 10–50%; SARI-CD2: 44%, 95% CI 13–64%), while the VE difference among those aged 65–79 years was <10% (Fig. 3 and Supplementary Table S5).

At 14–59 days post-vaccination, VE estimates were nearly identical across SARI-CD1 and SARI-CD2 for all pathogens (differences ≤2%). At 60–119 days, absolute VE differences were 18% for influenza A(H1N1) pdm09 (SARI-CD1: 4%; SARI-CD2: 22%), 29% for A(H3N2) (SARI-CD1: –22%; SARI-CD2: 7%), and 12% for SARS-CoV-2 (SARI-CD1: 34%; SARI-CD2: 46%). At ≥120 days, differences were 13% for A(H3N2) (SARI-CD1: 13%; SARI-CD2: 0%) and 42% for SARS-CoV-2 (SARI-CD1: –10%; SARI-CD2: 32%); VE against A(H1N1)pdm09 could not be estimated at this interval due to small numbers (Fig. 4 and Supplementary Table S6).

In sensitivity analyses excluding SARS-CoV-2-positive controls (Supplementary Table S7), the absolute difference in VE against influenza A(H1N1)pdm09 between the two CDs was 9% (SARI-CD1: 40%; SARI-CD2: 49%), compared with 10% in the main analysis (34% vs 44%). By age group, differences ranged from 5% among those aged 65–79 years to 17% among those ≥80 years. Against influenza A(H3N2), VE estimates were 3–4% for both CD, with absolute differences of 2–5 percentage points by age group, consistent with the main analysis. Excluding influenza-positive controls (see Supplementary Table S7), the absolute difference in VE against SARS-CoV-2 between the two CDs was 10% (SARI-CD1: 32%; SARI-CD2: 42%), similar to the main analysis (29% vs 40%), with age-specific differences of 6–10 percentage points.

## 4. Discussion

We observed <10% difference in VE point estimates across SARI-CD1 and SARI-CD2 for influenza A(H3N2) overall and by age group, and for all three pathogens within 60 days post-vaccination. For influenza A (H1N1)pdm09 and SARS-CoV-2, VE estimates among adults aged 65–79 years were also similar, while overall VE estimates differed by 10–11 percentage points, with higher VE observed using SARI-CD2. Among adults aged ≥80 years, differences were 11% for SARS-CoV-2 and 19% for influenza A(H1N1)pdm09, again with higher estimates for SARI-CD2. At longer intervals of time since vaccination, VE estimates

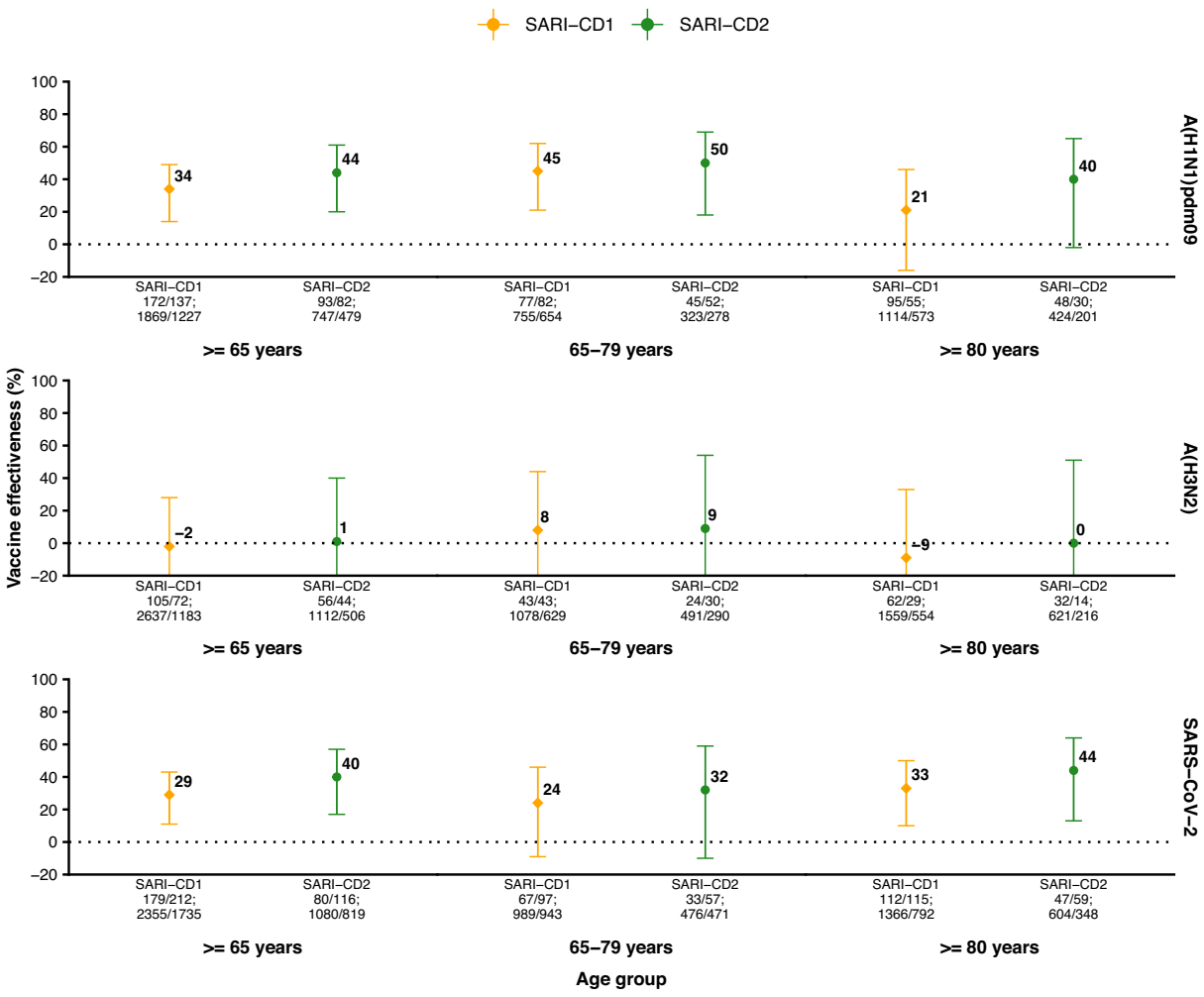



**Fig. 3.** Influenza A(H1N1)pdm09, A(H3N2) and SARS-CoV-2 vaccine effectiveness among adults aged ≥65 years in the target group for vaccination, by case definition and age group, VEBIS hospital network, seven European countries, 2023/24. CD: case definition; SARI: Severe acute respiratory infection; SARI-CD1: individual admitted to hospital with at least one of the following symptoms: cough, fever, shortness of breath, anosmia, ageusia, or dysgeusia; SARI-CD2: individual admitted to hospital with cough and fever. Numbers below each case definition indicate the number of vaccinated/unvaccinated cases (first line) and vaccinated/unvaccinated controls (second line).

were higher with SARI-CD2 across pathogens (12–18% at 60–119 days; 13–42% at ≥120 days). Across all comparisons, the 95% CIs for the two CDs were wide and overlapped with each other's point estimates, reflecting substantial statistical uncertainty due to sample size constraints. The use of SARI-CD2 reduced sample size and the number of contributing countries, resulting in VE estimates with lower precision. Sensitivity analyses excluding influenza- or SARS-CoV-2-positive controls produced similar VE estimates (i.e. within the relevant difference of <10 percentage points), with no meaningful change to the overall pattern.

Although 95% CIs overlapped, the slightly higher VE estimates observed when using SARI-CD2 may be partially reflect: 1) differential inclusion of vaccinated cases, 2) differential inclusion of individuals with more severe clinical presentation, 3) variation in contributing countries and their circulating clades/variants, 4) unmeasured confounding (e.g. differences in prior immunity or frailty not captured in the data), or 5) random variation.

We observed a slightly lower proportion of vaccinated cases included under SARI-CD2, while the proportion of vaccinated controls remained largely unchanged between the two definitions. This pattern suggests potential differential inclusion of vaccinated cases, if the requirement for both fever and cough is associated with both case and vaccination status [9,19]. A possible explanation is that fever, required in SARI-CD2, is less common in older adults [20–22] and may also occur less often among vaccinated individuals [23–26]. Frail or older adults aged ≥80 years, who are more likely to be vaccinated but also more likely to have lower VE [27], may therefore be preferentially included under SARI-CD1, lowering VE estimates in SARI-CD1 and resulting in higher VE for SARI patients included using SARI-CD2.

However, this mechanism of differential inclusion of vaccinated cases does not fully explain the lack of meaningful VE differences observed for influenza A(H3N2) or among those aged 65–79 years, despite similarly lower proportions of vaccinated cases in SARI-CD2. This may reflect intrinsic differences in clinical presentation between influenza subtypes, with A(H3N2) infections in older adults possibly showing less distinct symptom patterns. For influenza A(H3N2), the very low or null effect of vaccination observed overall may also have minimised the impact of case definition on estimates.

Second, it is also plausible that SARI-CD2 (requiring both fever and cough) may preferentially include patients with more severe clinical presentations. Although evidence indicates that more severe outcomes, such as admission to ICU or death, are associated with higher VE estimates [25,28], studies specifically assessing the impact of symptom presentation at hospital admission on VE estimates are lacking. Nevertheless, previous work has suggested that narrower or more stringent case definitions may selectively include patients with more severe

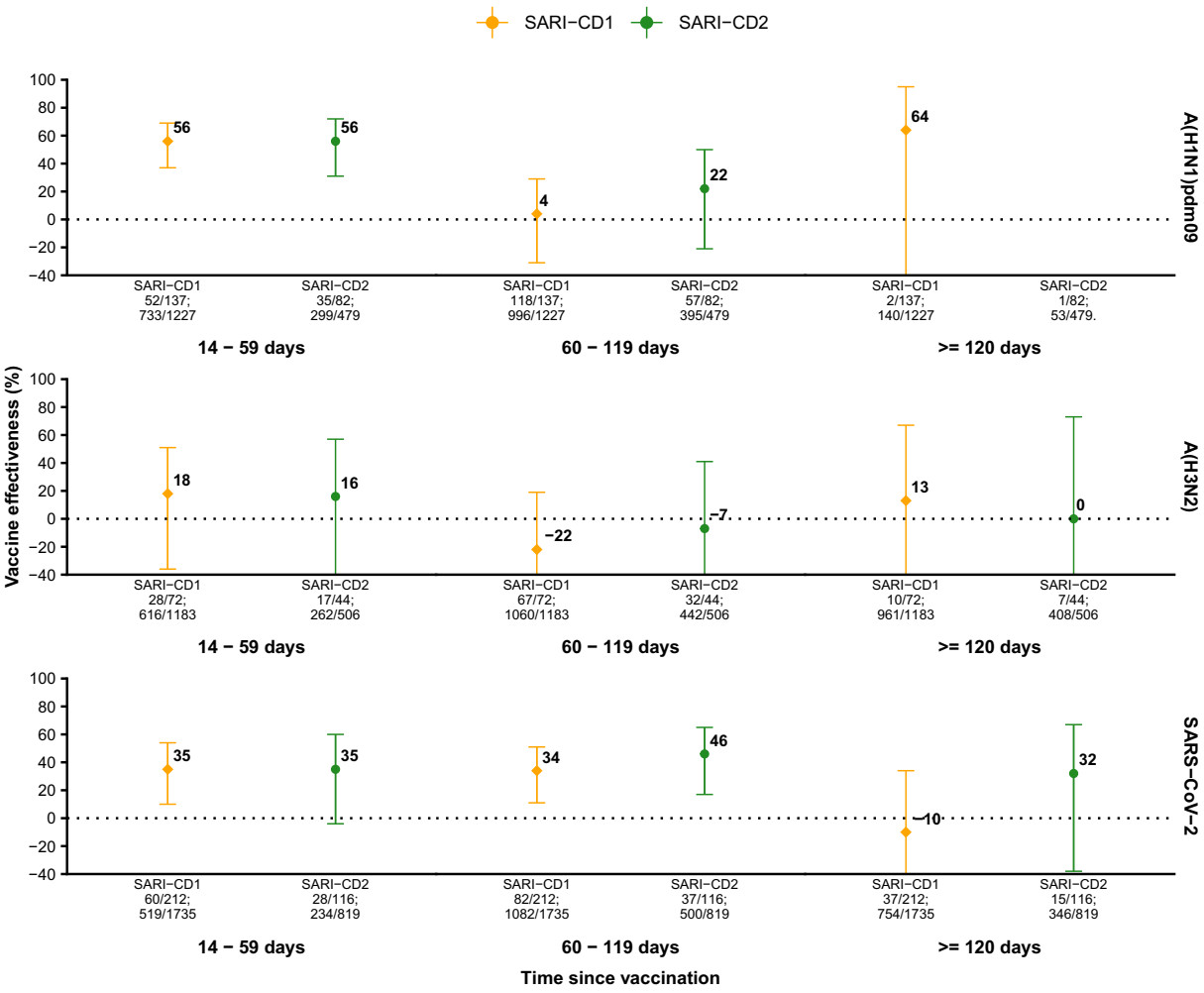



**Fig. 4.** Influenza A(H1N1)pdm09, A(H3N2) and SARS-CoV-2 vaccine effectiveness among adults aged ≥65 years in the target group for vaccination by case definition and time since vaccination, VEBIS hospital network, seven European countries, 2023/24. CD: case definition; SARI: Severe acute respiratory infection; SARI-CD1: individual admitted to hospital with at least one of the following symptoms: cough, fever, shortness of breath, anosmia, ageusia, or dysgeusia; SARI-CD2: individual admitted to hospital with cough and fever. Numbers below each case definition indicate the number of vaccinated/unvaccinated cases (first line) and vaccinated/unvaccinated controls (second line).

presentations, where differential inclusion between vaccinated and unvaccinated individuals is less likely [29,30] and VE is higher [31,32]. In contrast, broader case definitions have been associated with lower VE estimates [31,32].

Despite these possible explanations, our descriptive analyses showed only small differences in age distribution between case definitions, with SARI-CD2 including only 2–4% fewer patients aged ≥80 years than SARI-CD1, and no major differences in co-morbidities, ICU admission or in-hospital death. This suggests that substantial underrepresentation of frailer/older adults or overrepresentation of severe cases was unlikely. It is therefore possible that the modest VE differences with overlapping 95% CIs also reflect variation in contributing countries and their circulating clades/variants, unmeasured confounding (e.g. differences in prior immunity or frailty not captured in the data) or random variation. Nevertheless, the consistent direction of the differences across pathogens, age groups, and TSV bands suggests that random variation alone may not fully explain the observed patterns.

Our aim was not to identify the "correct" CD or VE estimate, but rather to explore how the CD choice may influence VE results. Careful consideration of CDs is essential when designing VE studies and comparing results. In practice, however, applying or modifying CDs may be challenging, particularly when data are collected within systems serving multiple objectives (e.g. SARI surveillance). Collecting individual symptom data within a broader case definition allows for retrospective assessment of alternative inclusion criteria and supports flexibility in aligning surveillance and VE objectives.

Our analysis has several limitations. Firstly, some countries lacked individual symptom data, did not collect all symptoms required for SARI-CD1 classification, or recruited patients using a CD stricter than SARI-CD1. These countries were excluded from the analysis, reducing our sample size which may limit the generalisability of our findings. Compared to the end-of-season 2023/24 VE estimates (based on SARI-CD1 including all countries), our estimates were similar for SARS-CoV-2 (34%) within 60–119 days post vaccination [15], but lower for influenza A(H1N1)pdm09 (34% vs 42%) and A(H3N2) (−2% vs 17%) [33]. These differences may reflect the exclusion of certain countries as well as variation in patient characteristics, circulating clades/variants, vaccination history or random variation. Co-circulation of different clades, such as observed for influenza A(H1N1)pdm09 [34], may also contribute to variability in VE, but we could not estimate clade- or variant-specific VE by CD, due to limited sample size.

Secondly, our analysis focused only on the 2023/24 period, which was marked by a co-circulation of SARS-CoV-2, influenza A(H1N1) pdm09 and influenza A(H3N2). As the distribution of respiratory pathogens varies across seasons, the clinical presentation of test-negative controls may also differ, potentially affecting VE estimates and

limiting generalisability to other periods.

Finally, the limited sample size in some strata may have introduced greater variability in the point estimates and reduced their precision. Consequently, the study lacked sufficient statistical power to confidently detect our a priori relevant absolute difference of 10%. Because the wide, overlapping confidence intervals primarily reflect substantial statistical uncertainty, we cannot confidently rule out chance as a driver for the observed absolute differences >10%, making direct interpretation challenging. Although these differences were not statistically significant, the direction of the effect was consistent. The stricter SARI-CD2 predominantly yielded higher VE point estimates, signalling that the observed differences may not be exclusively due to chance.

Further studies with larger sample sizes and combining multiple seasons, are needed to determine whether the observed signals reflect true differences or are explained by sample size limitations, country variation, unmeasured confounding or other factors such as differences in host immune status or prior immunity that may influence symptom presentation and case definition classification.

## 5. Conclusions

Our comparative pathogen-specific analysis showed no significant differences in VE between the two SARI CDs used in hospital-based TND studies in Europe. VE estimates were similar showing <10% difference for influenza A(H3N2) overall and by age group, and across influenza A (H1N1)pdm09, A(H3N2) and SARS-CoV-2 within 14–60 days since vaccination and among adults aged 65–79 years. Nevertheless, we observed signals of higher VE with SARI-CD2 for influenza A(H1N1) pdm09 and SARS-CoV-2, particularly among the oldest patients and at longer time since vaccination intervals, although 95% CIs overlapped across all comparisons. Such signals suggest that the SARI case definition may contribute to variability in VE estimates alongside other factors such as variation in patient characteristics, circulating clades/variants, vaccination history or random variation. These findings highlight the importance of consistent reporting and application of case definitions in VE studies. This may influence not only how vaccine performance is interpreted and communicated, but also the estimation of the number of cases averted by vaccination in vaccine impact studies.

## Declaration of generative AI in the manuscript preparation process

During the preparation of this manuscript, the author used ChatGPT in order to improve language and readability. After using this tool, all the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

## CRediT authorship contribution statement

**Diogo F.P. Marques:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Formal analysis, Data curation, Conceptualization. **Jennifer Howard:** Writing – review & editing, Visualization, Validation, Software, Methodology, Data curation, Conceptualization. **Marcos Lozano Álvarez:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Ausenda Machado:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Róisín Duffy:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Gergő Túri:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Monika Kuliese:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Odette Popovici:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Goranka Petrović:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Adrien Lajot:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Ralf Dürrwald:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **John Paul Cauchi:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Camino Trobajo-Sanmartín:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Petr Husa:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Francisco Pozo:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Nuno Verdasca:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Eva Rivas Wagner:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Verónica Gómez:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Margaret Fitzgerald:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Beatrix Oroszi:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Ligita Jančorienė:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Mihaela Lazar:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Irena Tabain:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Francesco G. Genderini:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Carolin Hackmann:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Aušra Džiugytė:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Aitziber Echeverria:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Lenka Součková:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Nathalie Nicolay:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **Sabrina Bacci:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **Baltazar Nunes:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Angela M.C. Rose:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

## Ethics declaration

*Informed consent and patient details*

Verbal informed consent to take part in the study was obtained from all participants or their legal representatives, and recorded in the study data collection form. Written informed consent was not required because data collection was largely embedded within routine public health surveillance and standard clinical care for respiratory infections in hospitalised patients. This approach was approved by the respective national and regional ethics committees across participating European countries. The privacy rights of participants have been observed.

*Studies in Human*

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

The planning, conducting and reporting of the studies were in line with the Declaration of Helsinki. Official ethical approval was not required if studies were classified as being part of routine care or SARI surveillance (Ireland, Malta, Spain/National). Other study sites received local ethical approval from a national or regional review board.

Belgium: approved by the central Ethical Committee (CHU Saint-Pierre [AK/12–02- 11/4111] initially in 2011 and UZ VUB [B.U.N. 143,201,215,671] from 2014 on) and each participating hospital's local ethical committees. The most recent amendment was approved on 27/9/2023 (reference 2012/310 Am6). Germany: SARI surveillance was approved by the Charité- Universitätsmedizin Berlin Ethical Board (Reference EA2/218/19). Portugal: Approved by INSA Ethics Committee (07 June 2022). Croatia: approved by the Ethics Committee of the Croatian Institute of Public Health (class: 030–02/24–01/1, 26 November 2024). Hungary: approved by the National Scientific and

Ethical Committee (IV/1885–5/2021/EKU) and (BM/25007–2/2024). Lithuania: approved 03 July 2020 by the Lithuanian Biomedical Research Ethics Committee No.: L-20-3/1–2; and later permission extended for the study period for season 2023–2024. Spain/Navarra: approved by the Navarre Ethics Committee, Ethical Committee for Clinical Research (PI2023/145), which waived the requirement of obtaining informed consent). Romania: approved by the INSP Romania Scientific Council - Ethics Committee (23,468/23 November 2023) and from Ethical Commission Cantacuzino Institute (344/2023).

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.129234.

## Data availability

Authors cannot share the data used for this study, which should be requested to the data owner institutions following their respective procedures.

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