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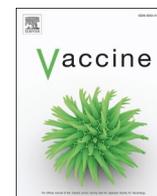
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Short communication

Effectiveness of COVID-19 vaccines administered in the 2023 autumnal campaigns in Europe: Results from the VEBIS primary care test-negative design study, September 2023–January 2024

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ABSTRACT

In autumn 2023, European vaccination campaigns predominantly administered XBB.1.5 vaccine. In a European multicentre study, we estimated 2023 COVID-19 vaccine effectiveness (VE) against laboratory-confirmed symptomatic infection at primary care level between September 2023 and January 2024. Using a test-negative case-control design, we estimated VE in the target group for COVID-19 vaccination overall and by time since vaccination. We included 1057 cases and 4397 controls. Vaccine effectiveness was 40 % (95 % CI: 26–53 %) overall, 48 % (95 % CI: 31–61 %) among those vaccinated < 6 weeks of onset and 29 % (95 % CI: 3–49

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%) at 6–14 weeks. Our results suggest that COVID-19 vaccines administered to target groups during the autumn 2023 campaigns showed clinically significant effectiveness against laboratory-confirmed, medically attended symptomatic SARS-CoV-2 infection in the 3 months following vaccination. A longer study period will allow for further variant-specific COVID-19 VE estimates, better understanding decline in VE and informing booster administration policies.

1. Introduction

Between August and October 2023, the European Medicines Agency (EMA) authorised three adapted XBB.1.5 COVID-19 vaccines: Comirnaty Omicron XBB.1.5, Spikevax XBB.1.5 and Nuvaxovid XBB.1.5 [1]. In the European Union and European Economic Area (EU/EEA) the population groups targeted for COVID-19 vaccination included: older adults, persons with underlying medical conditions, immunocompromised individuals, healthcare workers and pregnant women [2]. The majority of vaccines administered (>98 %) were XBB.1.5 vaccines [3].

At time of the autumn 2023 COVID-19 vaccination campaigns in Europe, Omicron XBB.1.5-like, XBB.1.5-like + F456L and BA.2.86 viruses circulated, with BA.2.86 viruses comprising > 50 % of all variants from mid-December 2023 onwards [4].

Vaccine Effectiveness, Burden, and Impact Studies (VEBIS) of COVID-19 and influenza vaccines is a European Centre for Disease Prevention and Control (ECDC) project using post-marketing observational studies to understand effectiveness of vaccines. The primary care multicentre component of VEBIS is based on a well-established network, the I-MOVE network, estimating influenza VE since 2008 [5,6].

Within VEBIS we aimed to estimate the 2023 autumn vaccination campaign vaccine effectiveness among patients in the COVID-19 vaccination target groups presenting to primary care physicians in the European Union/European Economic Area (EU/EEA), up to January 2024.

2. Methods

The VEBIS primary care study is a test-negative design case-control study conducted at primary care level in 11 European study sites: Croatia (HR); France (FR); Germany (DE); Hungary (HU); Ireland (IE); Portugal (PT); The Netherlands (NL); Romania (RO); Spain, national (ES); Spain, Navarre region (NA); Sweden (SE) (Supplementary Fig. 1).

Detailed methods are available elsewhere [7]. Briefly, in each site, primary care physicians or paediatricians recruit and swab all or a

systematic sample of patients consulting with acute respiratory infection (ARI). Site-specific variations in case definition used for recruitment are available in Table 1. Demographic and clinical information is collected via interview or electronic medical records. COVID-19 vaccination information is obtained from general practitioner records, interviews or national vaccination registries. Biological samples are tested using reverse transcription (RT)-PCR and all (or a random sample of) virus-positive specimens below a specified cycle threshold (Ct) value are sequenced. Patients meeting the EU-ARI case definition (sudden onset of symptoms with at least one of four respiratory symptoms: cough, sore throat, shortness of breath, coryza) testing RT-PCR positive are defined as cases and those testing negative as controls.

The study period for this analysis started 7 days after the start of the autumn 2023 COVID-19 vaccination campaigns in each country (Table 1), with dates ranging between 1 September and 7 November 2023.

We excluded patients who lived in a residential care facility, who were swabbed 10 days after symptom onset, who were vaccinated with a non-EMA approved vaccine for their autumn 2023 dose, who were reported by study sites where there were fewer than 10 cases, and who did not provide information for key covariates.

We included patients in the target groups for vaccination as recommended in each country. The age-specific recommendations varied by country, with the age above which older adults were recommended for vaccination ranging from 50 to 65 years (Table 1). All countries recommended patients with chronic conditions to be vaccinated, among those aged ≥ 6 months. As recommendations for COVID-19 vaccination for those aged under 5 years depended on previous COVID-19 vaccination history, we restricted the study population to those aged 5 years and over [2].

We considered a patient as vaccinated if they had received any dose of COVID-19 vaccine on or after the start date of the autumn 2023 vaccination campaign. Unvaccinated were those not receiving a COVID-19 vaccine as part of the autumn 2023 vaccination campaign, nor in the

Table 1

Autumn 2023 national COVID-19 vaccination campaign, vaccination and recruitment information, by study site, VEBIS primary care study, September 2023–January 2024.

Study sites included in the analysis	Start of autumn 2023 national COVID-19 vaccination campaigns	Age-specific recommendation for COVID-19 vaccination for older adults	Data source for COVID-19 vaccination information	Case definition used for recruitment of patients ^b
Croatia	18 Sep 2023	65	Medical records, vaccination registry, GP interview (self-report)	EU-ILI or EU-ARI
France	2 Oct 2023	65	GP interview (self-report)	Sentinelles ARI
Germany	1 Sep 2023	60	Medical records, patient's certificate of vaccination, GP interview (self-report)	ARI
Hungary	1 Oct 2023	60	National Immunisation Registry (83.5 %), GP records, self-report	EU-ARI
Ireland	2 Oct 2023	50	Data linkage to vaccine registry	EU-ARI
The Netherlands	2 Oct 2023	60	GP interview (self-report)	EU-ILI or EU-ARI
Portugal	29 Sep 2023	60	Vaccine registry look-up by GPs	EU-ARI
Spain, national	25 Sep 2023	60	Data linkage to vaccine registry	EU-ARI
Spain, Navarre region	9 Oct 2023	60	Data linkage to vaccine registry	EU-ILI
Sweden	7 Nov 2023	65	Data linkage to vaccine registry	EU-ARI

ARI: acute respiratory infection; EU: European Union; ILI: influenza-like illness; VEBIS: Vaccine Effectiveness, Burden and Impact Studies.

^a Romania was excluded from the analysis due to too small a sample size (<10 cases).

^b EU-ARI: Sudden onset of symptoms and at least one of four respiratory symptoms (cough, sore throat, shortness of breath, coryza) and a clinician's judgement that the illness is due to an infection; EU-ILI: Sudden onset of symptoms and at least one of four systemic symptoms (fever or feverishness, malaise, headache, or myalgia) and at least one of three respiratory symptoms (cough, sore throat, or shortness of breath); Sentinelles ARI: Sudden onset of fever (or feverishness), and respiratory signs; The ARI case definition in Germany includes patients with at least one of the following four symptoms: fever, cough, coryza or sore throat.

6 months preceding the campaign. Those vaccinated 1–6 days before symptom onset were excluded.

We pooled individual patient data and used logistic regression to estimate the odds ratio (OR) of vaccination among cases and controls, adjusting for study site, age, sex, presence of four commonly collected chronic conditions (diabetes, heart disease, lung disease and immunodeficiency) and onset date. We selected the functional form of continuous variables among categories, linear terms, or restricted cubic splines using the Akaike Information Criterion. We estimated VE as (1-OR), expressed as a percentage.

We estimated VE among the overall target group and then stratified according to country-specific age limits for older adult vaccination (50 to 65 years, depending on the country). We refer to “the younger vaccination target group”, for the group including younger individuals who require medical risk conditions to be part of the target group, and to “the older adult vaccination target group”, for those vaccinated because they meet the age requirement. As recommendations vary by country, those aged 50–64 may be included in the “younger” or the “older” group, depending on the country-specific vaccination recommendations.

We estimated VE by time since vaccination, based on the median days between vaccination and onset, rounded to full weeks (two intervals: <6 weeks; 6–14 weeks). We linked epidemiological and sequencing data to estimate VE against Omicron XBB among all ages within the overall vaccination target group. Here, we restricted to sites providing at least five Omicron XBB cases and excluded any weeks of onset before and after the first and last sequenced case, respectively. Based on sequence data, viruses were classified as Omicron XBB if they belonged to the XBB variant and its descendants, e.g. XBB.1.16, XBB.1.5, XBB.1.9, XBB.2.3, as well as XBB lineages featuring the F456L mutation in Spike protein.

To handle sparse data, we carried out penalised logistic regression if the model violated the 10 events per parameter rule of thumb [8]. If the normal and penalised logistic regression VE point estimates differed by > 10 % we did not report the estimate. Additionally, we did not report any estimate where there were fewer than three patients in any cell of case and exposure status.

We carried out four sensitivity analyses: 1) varying the definition of vaccinated as someone who received vaccine at least 14 days before symptom onset, instead of 7 days as in the main analyses, meaning also that the study period started 14 days after COVID-19 vaccination campaigns; 2) varying the definition of the pre-campaign vaccination exclusion period for the reference group, using 3 months prior to the start of the vaccination campaign (instead of 6 months, as in the main analyses); 3) excluding influenza positive controls to account for potential correlation between influenza and COVID-19 vaccination behaviour [9]; 4) among those aged 65 years and over in order to have a more homogeneously aged older adult group.

3. Results

We included 5,454 patients; 1,057 cases and 4,397 controls aged ≥ 5 years (Fig. 1).

The median age was 64 years (interquartile range [IQR]: 53–73) among cases and 62 years (IQR: 47–72) among controls (Table 2). Sixty-two percent of cases and 60 % of controls were female. Sixty-nine percent of cases and 70 % of controls had one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, immunodeficiency), with 74 % of both cases and controls in the younger vaccination target group with these chronic conditions, compared to 67 % and 68 % of cases and controls in the older vaccination target group. Among cases, 12 % had received COVID-19 vaccination as part of the autumn 2023 vaccination campaign, compared to 16 % of controls. Among vaccinated, 66 % (80/122) of cases and 68 % (482/707) of controls had received their fifth dose. COVID-19 vaccine brand was missing for 39 % (47/122) of vaccinated cases and for 26 % (186/707) of vaccinated controls. All patients but three were vaccinated with

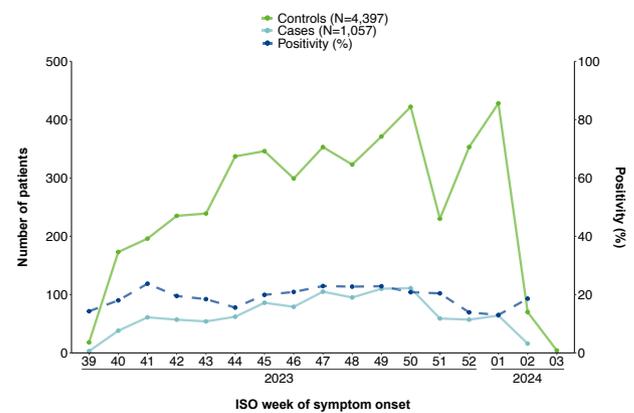


Fig. 1. Patients included in the VEBIS primary care study by COVID-19 case status and ISO week of symptom onset, Europe, September 2023–January 2024 (n = 5,454). ISO: International Organisation for Standardisation; VEBIS: Vaccine Effectiveness, Burden and Impact Studies.

Comirnaty vaccine, where vaccine brand was known.

As of February 2024, 19 % (203/1057) of positive SARS-CoV-2 viruses were sequenced (Table 2). Of these sequenced viruses, 61 % (123/203) belonged to Omicron XBB and its sublineages and 36 % (73/203) belonged to Omicron BA.2.86 and its sublineages. Of the 73 BA.2.86 viruses, 78 % (57/73) belonged to JN.1 and its sublineages. During the study period, Omicron XBB viruses peaked in week 46 with 20 viruses and decreased to 6 viruses or fewer from week 48. In week 48, Omicron BA.2.86 viruses peaked with 15 sequenced viruses (Supplementary Figure 2).

COVID-19 VE was 40 % (95 % CI: 26–53 %) overall (Fig. 2; Supplementary Table 1). The VE was 48 % (95 % CI: 31–61 %) among those vaccinated less than 6 weeks before onset and 29 % (95 % CI: 3–49 %) among those vaccinated 6–14 weeks before onset. The overall VE against Omicron XBB and its sublineages was 50 % (95 % CI: –17–82) and 46 % (95 % CI: –32–82) among those vaccinated less than 6 weeks before onset.

Among younger patients (aged less than 50–65 years, depending on country) VE was 59 % (95 % CI: 18–82 %) overall; 69 % (95 % CI: 28–90 %) if vaccinated less than 6 weeks before onset and 28 % (95 % CI: –128–84 %) if vaccinated 6–14 weeks before onset (Fig. 2; Supplementary Table 1).

Among older patients (aged over 50–65), the VE was 37 % (95 % CI: 19–51 %) overall; 45 % (95 % CI: 26–60 %) if vaccinated less than 6 weeks before onset and 26 % (95 % CI: –3–48 %) if vaccinated 6–14 weeks before onset (Fig. 2; Supplementary Table 1). The overall VE against Omicron XBB and its sublineages was 63 % (95 % CI: 6–88) and 63 % (95 % CI: –2–90) among those vaccinated less than 6 weeks before onset.

When considering participants as vaccinated after 14 days instead of 7 days, the overall VE in the younger target group increased from 59 % (95 % CI: 18–82) to 70 % (95 % CI: 30–90); all other estimates differed by ≤ 7 % (Supplementary Table 2). When excluding unvaccinated patients vaccinated within 3 months of the autumn 2023 vaccination campaign instead of 6 months, VE point estimates differed by ≤ 2 %. When excluding controls positive to influenza virus, all VE point estimates were higher, differing by ≤ 8 %. VE point estimates among those aged 65 years and older were lower, differing by ≤ 6 %.

4. Discussion

Our results suggest that COVID-19 vaccines administered during the autumn 2023 campaigns, mainly Omicron XBB.1.5 vaccines, showed around 40 % effectiveness against laboratory-confirmed, medically attended symptomatic SARS-CoV-2 infection in the 3 months following vaccination among target groups. The COVID-19 VE point estimate was

Table 2

Baseline characteristics of patients included in the VEBIS primary care study by COVID-19 case status, Europe, September 2023–January 2024.

Variables	Number of COVID-19 cases (%) 1057	Number of test-negative controls (%) 4397
Median age (IQR)	64 (53–73)	62 (47–72)
Age groups (years)		
5–19	20/1057 (2 %)	249/4397 (6 %)
20–29	30/1057 (3 %)	186/4397 (4 %)
30–39	53/1057 (5 %)	322/4397 (7 %)
40–49	112/1057 (11 %)	491/4397 (11 %)
50–59	169/1057 (16 %)	700/4397 (16 %)
60–69	299/1057 (28 %)	1096/4397 (25 %)
70–79	243/1057 (23 %)	901/4397 (20 %)
≥80	131/1057 (12 %)	452/4397 (10 %)
Female	651/1057 (62 %)	2631/4397 (60 %)
Presence of four commonly collected chronic conditions^a	733/1057 (69 %)	3093/4397 (70 %)
Pregnant^b	9/116 (8 %)	60/616 (10 %)
Missing	15	65
COVID-19 vaccination in the autumn 2023 campaign		
Received COVID-19 vaccination as part of this campaign	122/1057 (12 %)	713/4397 (16 %)
Detailed COVID-19 vaccination status in the autumn 2023 campaign^c		
First dose	0/122 (0 %)	4/707 (1 %)
Second dose	2/122 (2 %)	2/707 (0 %)
Third dose	3/122 (2 %)	17/707 (2 %)
Fourth dose	19/122 (16 %)	118/707 (17 %)
Fifth dose	80/122 (66 %)	482/707 (68 %)
Sixth dose	12/122 (10 %)	51/707 (7 %)
Seventh dose	6/122 (5 %)	32/707 (5 %)
Eighth dose	0/122 (0 %)	1/707 (0 %)
Missing	0	6
Brand of vaccine received in the autumn 2023 campaign^c		
Comirnaty	74/75 (99 %)	519/521 (100 %)
Spikevax	0/75 (0 %)	1/521 (0 %)
Jcovden	0/75 (0 %)	1/521 (0 %)
Bimervax	1/75 (1 %)	0/521 (0 %)
Missing	47	186
Median number of days since last COVID-19 vaccination received in the autumn 2023 campaign (IQR)^c	40 (22–54)	37 (22–56)
COVID-19 vaccination target group		
Younger target group	374/1057 (35 %)	1858/4397 (42 %)
Older adult target group	683/1057 (65 %)	2539/4397 (58 %)
Influenza virus RT-PCR positive	35/1051 (3 %)	706/4370 (16 %)
Missing	6	27
Study site		
Croatia	22/1057 (2 %)	45/4397 (1 %)
France	83/1057 (8 %)	144/4397 (3 %)
Germany	137/1057 (13 %)	309/4397 (7 %)
Hungary	121/1057 (11 %)	150/4397 (3 %)
Ireland	63/1057 (6 %)	396/4397 (9 %)
Navarra, Spain	15/1057 (1 %)	111/4397 (3 %)
Portugal	29/1057 (3 %)	124/4397 (3 %)
Spain, national	556/1057 (53 %)	2981/4397 (68 %)
The Netherlands	21/1057 (2 %)	95/4397 (2 %)
Sequenced	203/1057 (19 %)	NA
Among sequenced viruses		
Omicron BA.2.75	3/203 (1 %)	NA
Omicron BA.2.86 ^e	73/203 (36 %)	NA
Non-JN.1 sublineages	16 (22 %)	NA
JN.1 sublineages	57 (78 %)	NA
Omicron XBB and sublineages	123/203 (61 %)	NA
Other ^d	4/203 (2 %)	NA

Abbreviations: IQR, Interquartile range; NA: Not applicable; VEBIS: Vaccine Effectiveness, Burden and Impact Studies.

^a The four commonly collected chronic conditions are: diabetes, heart disease, lung disease and immunodeficiency.

^b Among females aged 15–49.

^c Among those vaccinated as part of the 2023 autumn COVID-19 vaccination campaigns.

^d Recombinant strains detected in minimal proportions have been categorized as 'other'. Note that the members of this group (XCH.1, XDD, XDK, and XDL) lack topological congruence.

^e Among Omicron BA.2.86 viruses.

lower among older adults than among younger patients in the target group for vaccination (36 % vs. 59 %, respectively), although confidence intervals overlapped.

Within this approximately 3-month interval, point estimates declined with time since vaccination. However, due to the increase in circulation of BA.2.86 viruses and sublineages over time (Supplement Figure 2), a variant-specific analysis by time since vaccination is needed to disentangle the variant and waning effects of vaccine protection. Omicron BA.2.86 viruses differ by more than 30 additional amino acid substitutions in their spike protein compared to XBB.1.5 and BA.2 viruses [10]. Additionally, JN.1, a descendant of BA.2.86 with the L455S substitution at the receptor binding site, is increasing in Europe and worldwide [11,12]. Neutralisation studies indicate immune escape in JN.1 viruses compared to other recent variants/lineages, including XBB.1.5, although this immune escape is moderate [13]. Further studies in the BA.2.86/JN.1 era are needed to understand the impact on vaccine effectiveness. In our study, VE against Omicron XBB was 46 % and 63 % within 1–5 weeks since vaccination among all ages and among the older target group, respectively. These point estimates were similar or higher than those against any SARS-CoV-2 within the same time since vaccination period in our study, which may indicate that VE against BA.2.86 and its sublineages would be the same or lower, however precision was very low. Sample size was too small to estimate variant-specific VE by time since vaccination against non-XBB lineages in our study, and to estimate VE Omicron XBB by longer time since vaccination intervals.

Our VE results are similar to recently published COVID-19 VE estimates against symptomatic infection at outpatient level [14,15]. In a similar study period, researchers from Canada reported a VE of 45 % among those aged 12 years and over, using similar methods to those in our study [15]. In a US study, younger adult VE was 57 % (compared to our 59 %) and older adult VE was 46 % (compared to our 40 %) [14]. While the US study observed less waning over a period of 4 months than our study did, variant-specific analyses by time since vaccination with more data will help better understand trends over time since vaccination.

Our 2023/24 COVID-19 VE point estimates among older adults within 90 days of vaccination are similar to those reported in the 2022/23 autumn–winter period [16]. In the 2022/23 season, our study suggested no protection against symptomatic infection conferred by the bivalent COVID-19 vaccine after 6 months (data not shown). This rapid waning was coherent with other studies at outpatient level in that season [17,18]. We need a longer study period to understand if the waning of the XBB.1.5 vaccine shows a similar pattern, or if the protection conferred by the vaccine may have longer lasting effects, as indicated in a recent neutralisation study [19].

Our results are subject to limitations. These include unmeasured confounding and potential selection bias. However, the test-negative design aims to reduce potential confounding (mainly access to care) that is difficult to measure [20]. Our sensitivity analyses suggest that selection of influenza positive controls did not result in a selection bias that affected our VE by more than 8 %. We were unable to account for history of SARS-CoV-2 infection, which can potentially be both a confounder and an effect modifier of COVID-19 VE [21,22]. Not all study sites collect information on previous SARS-CoV-2 infection, and this information is most often self-reported as a binary variable (yes/no). The risk of measurement error is then higher than with more objective measurements of previous infection (e.g., serological testing of infection-induced antibodies), and key information such as the date of infection, the variant period, and the number of past infections are not

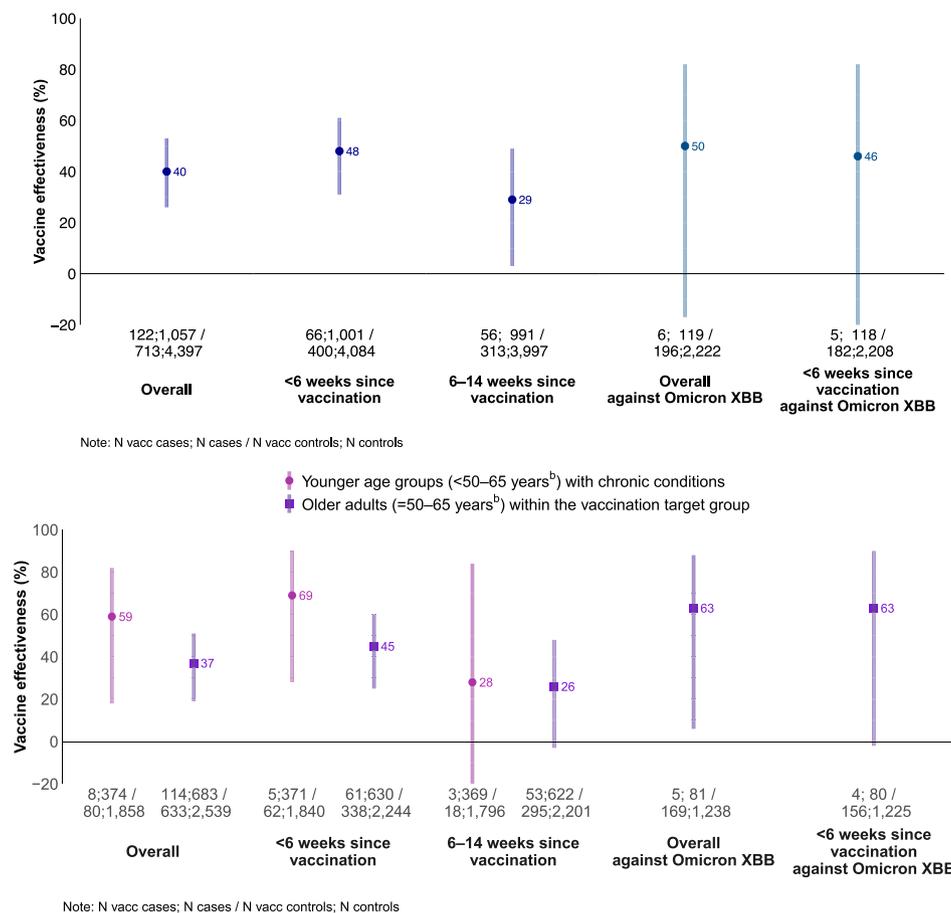


Fig. 2. COVID-19 vaccine effectiveness^a against medically-attended symptomatic SARS-CoV-2 infection among target groups for vaccination, (A) overall against any SARS-CoV-2 and against Omicron XBB and its sublineages and (B) against any SARS-CoV-2 stratified by age-specific vaccination target groups, Europe, VEBIS primary care study, September 2023–January 2024. Abbreviations: VEBIS: Vaccine Effectiveness, Burden and Impact Studies. The series of numbers below the x-axis provides the number of vaccinated cases; number of cases / number of vaccinated controls; number of controls. ^a All VE models included study site, sex and presence of chronic condition as adjustment variables. Using the Akaike information criterion to select the best functional form of onset date and age for each VE model, we included onset date as a restricted cubic spline (RCS) with 3 or 4 knots depending on the analysis, and age as a RCS with 3 or 5 knots, as a continuous variable or as a categorical variable with 5-year age bands depending on the analysis. ^b The target groups for older adults varied by country, see Table 1.

always available. In the context of reduced testing, it is difficult to obtain accurate information on previous mild infection. Sequencing information on SARS-CoV-2 viruses was only available for 19 % of cases. This resulted in low precision for the Omicron XBB-specific analysis, which hindered understanding if decline in VE was related to waning of vaccine protection and/or variant-specific effects. Vaccine coverage among the younger target group was low, limiting the precision of these estimates.

Strengths of the study include a multicentre study design, covering 10 European countries. The study is embedded on well-established platforms sharing a common protocol for robust results.

In conclusion, our study indicated that XBB.1.5 vaccination protected 40 % of vaccinated individuals from symptomatic infection in the short term. Estimating COVID-19 against Omicron BA.2.86 and its sublineages, by time since vaccination, will provide one ingredient to help public health decision-making around scheduling of future COVID-19 vaccination campaigns and vaccine composition.

Ethical statement

The planning, conduct and reporting of the studies was in line with the Declaration of Helsinki. Official ethical approval and patient consent was not required in Spain, as this study was classified as being part of routine care/surveillance. In the Netherlands, as the data are initially collected through surveillance, no formal ethical approval was

necessary. Verbal informed consent from patients for participation in the national respiratory surveillance is required. In addition, patients have the option to opt out for participation in any further research (including influenza vaccine effectiveness studies). Other study sites received local ethical approval from a national or regional review board: Croatia: approved by the Ethics Committee of the Croatian Institute of Public Health (class 030–02/23–01/1); France: 471393; Germany: EA2/126/11; Hungary: IV/1885–5/2021/EKU; Ireland: ICGP2019.4.04; Portugal: approved 14 December 2022 by the Ethics Committee of Instituto Nacional de Saúde Doutor Ricardo Jorge, no registration number given; Romania: CE199/2022; Sweden: 2006/1040–31/2 revised Drn 2021–02791).

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GISAID

Participating laboratories submitted their sequences to GISAID (www.gisaid.org) for easy sharing with the central laboratory in Lisbon.

CRedit authorship contribution statement

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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.

Data availability

Data will be made available on request.

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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.2024.05.067>.

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