Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: multicentre study analysis by age-group, vaccine brand and time since vaccination, I-MOVE-COVID-19 and ECDC networks, July–August 2021

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Abstract

Introduction

In July and August 2021, the SARS-CoV-2 Delta variant dominated in Europe. We measured COVID-19 vaccine effectiveness (VE) against symptomatic infection, using a multicentre test-negative study at primary care/community level in Europe.

Methods

Patients presenting with COVID-19/ARI symptoms at primary care/community level in 10 countries were tested for SARS-CoV-2. We measured complete primary course overall VE among those aged 30–44, 45–59, 60–74 and ≥ 75 years, and among those 30–59 and ≥ 60 years by vaccine brand and by time since vaccination.

Results

Overall VE was 74% (95%CI: 69–79), 76% (95%CI: 71–80), 63% (95%CI: 48–75), 63% (95%CI: 16–83) among those aged 30–44, 45–59, 60–74 and ≥ 75 years, respectively. VE among those aged 30–59 years was 78% (95%CI: 75–81), 66% (95%CI: 58–73), 91% (95%CI: 87–94) and 52% (95%CI: 40–61), for Comirnaty, Vaxzevria, Spikevax and COVID-19 Vaccine Janssen, respectively. VE among those aged ≥ 60 years was 67% (95%CI: 52–77), 65% (95%CI: 48–76), 83% (95%CI: 64–92) for Comirnaty, Vaxzevria and Spikevax, respectively.

Comirnaty VE among those aged 30–59 years was 87% (95%CI: 83–89) and 65% (95%CI: 56–71%) at 14–29 days and ≥ 90 days between vaccination and onset of symptoms, respectively.

Conclusions

VE against the symptomatic SARS-CoV-2 Delta variant infection varied among brands, ranging from 52–91%. While some waning of the vaccine effect may be present (sample size limited this analysis to only Comirnaty), protection was 65% ≥ 90 days between vaccination and onset.

Introduction

COVID-19 has caused considerable morbidity and mortality with over 76.7 million cases and 1.4 million deaths reported in Europe (1). The highly transmissible Delta variant (B.1.617.2 and the AY sublineages in the Pango nomenclature system) dominated over the Alpha variant in Europe from July 2021 onwards and accounted for over 99% of sequenced samples in weeks 35–36 2021 (2–4). From the end of October 2021, four COVID-19 vaccines were authorised in the European Union by the European Medicines Agency: two mRNA vaccines (Comirnaty and Spikevax), and two adenoviral vector vaccines (Vaxzevria and COVID-19 Vaccine Janssen)(5). Prior to the Delta circulation, randomised controlled trials indicated a high efficacy for these vaccines (6–9).

Observational post-authorisation studies in Europe are therefore important to measure the effectiveness of the different COVID-19 vaccines against the currently circulating Delta variant.

Recent discussions around recommendations for booster doses, for various populations, highlight the need to measure vaccine effectiveness (VE) by time since vaccination. Some studies have reported a decrease in VE against infection with increasing time since vaccination, but not all (10–16). It may be difficult to disentangle potential changes in VE by time since vaccination from changes in VE due to circulation of different variants over time.

The I-MOVE-COVID-19 and ECDC networks in Europe carry out COVID-19 VE studies, including a VE study at primary care/community level (17). All studies are based on a common generic protocol (18).

We conducted a study in symptomatic patients swabbed at primary and care/community level in July and August 2021, assuming SARS-CoV-2 cases were of the Delta variant due to its dominance in Europe during this period. We estimated VE against SARS-CoV-2 symptomatic infection, by vaccine brand, age group, and by time since vaccination to understand if there may be waning of protection conferred by vaccines over time.

Methods

Study design

Ten of 14 I-MOVE-COVID-19 primary care/community study sites participated in this analysis: Croatia (HR), France (FR), Ireland (IE), the Netherlands (community testing: NL-CO), Portugal (PT),

Romania (RO), Spain (3 regions: ES; Navarra region: NA), and the UK (England: EN; Scotland: SC) (Figure 1).

Figure 1: Countries and study sites taking part in the I-MOVE-COVID-19 and ECDC VE studies at primary care/community level

BE: Belgium; EN: England; ES: Spain; FR: France; HR: Croatia; HU: Hungary; IE: Ireland; NL-CO: the Netherlands community-based study; NL-PC: the Netherlands primary care; PT: Portugal; RO: Romania; SE: Sweden.

We used the test-negative design to estimate VE against symptomatic infection (19). Cases were patients testing positive and controls patients testing negative for SARS-CoV-2. Study sites adapted a generic study protocol to their country-specific setting (18). In eight of the 10 participating study sites a sentinel physician recruited patients. SC uses a combination of physician-based and community-based swabbing, and NL-CO uses a purely community-based swabbing approach. Sites included all or a systematic sample of acute respiratory infection (ARI) patients or patients presenting with COVID-19 symptoms (at least one of the following symptoms: fever, cough, shortness of breath, sudden onset of anosmia/ageusia) who contacted the sentinel physician/swabbing centre (**Supplementary table 1**). NA included all patients presenting to the Navarra Health Service primary care physicians. SC included a systematic sample of patients

presenting to community-attended COVID-19 centres, where both self- and clinical staff-based swabbing were performed. In NL-CO, participating patients were self-selected.

Demographic, clinical (age, sex and chronic conditions) and COVID-19 vaccination information (number of doses, brand and date for each dose) was collected, via questionnaire, electronic medical records and vaccine registry linkage (Supplementary table S1).

Where technically feasible, the whole or partial genome of viruses confirmed by PCR was sequenced. Results from four study sites (HR, IE, NA, RO) were available at time of writing. Phylogenetic analysis was performed to identify the Phylogenetic Assignment of Named Global Outbreak (Pango) lineage based on the classification v.3.1.16 2021.

Study period

The study period included swab dates in July and August 2021, as this is when the Delta variant was dominant in participating study sites (20,21).

Study inclusion criteria

We included patients aged 30 years and older who belonged to their country's age-specific target group for vaccination at time of swab. Where known, we excluded patients with contraindications for vaccination, living in a residential care facility, controls previously testing positive for SARS-CoV-2 and controls testing positive for seasonal coronaviruses. We further excluded those who were swabbed more than 10 days (PCR tests) or 5 days (rapid antigen tests) after symptom onset. We excluded those with a delay between doses not recommended by the vaccine manufacturer (<21 days for Comirnaty, <28 days for Spikevax/Vaxzevria, <21 days if vaccine brand was unknown) and those with onset within 1–13 days of first (if COVID-19 vaccine Janssen) or second dose (for two-dose vaccines) of COVID-19 vaccine.

Definitions of vaccination

We defined persons as completely vaccinated 14 days after receiving either the second of two recommended doses of a two-dose vaccine or a single dose of COVID-19 Vaccine Janssen. Persons were considered unvaccinated if they did not receive any COVID-19 vaccine or were vaccinated on or after the day of onset of symptoms. Persons partially vaccinated were excluded from the analysis.

For the brand-specific analysis, we restricted to the period in which the brand was available in the country by age group. For two-dose vaccines, we only included persons vaccinated with the same brand for both doses

Statistical analysis

We compared the odds of vaccination between cases and controls. We used logistic regression and calculated VE as 1 minus the odds ratio expressed as a percentage. We included study site as a fixed effect and date of swab (modelled as a restricted cubic spline or as a categorical variable of swab week) in both crude and adjusted VE analyses, as time is an integral part of the test-negative design and study site of a multicentre study.

We further adjusted for age group, sex and presence of at least one of the six commonly collected COVID-19 relevant chronic conditions (diabetes, chronic lung disease, immunodeficiencies, heart disease, renal disease and liver disease). In SC, the question “Did you receive a letter asking you to shield?” was used as a proxy for “presence of chronic condition”, assuming those not answering the question were not shielding.

In one study site where symptom onset date was not available (NA) and in two study sites with $\geq 20\%$ of missing information (IE and PT), we imputed it as 3 days before the swab date, three days being the median between onset and swab date where information was available.

For the age-specific analyses for all vaccines, we stratified the data into the following age groups: 30–44, 45–59, 60–74 and ≥ 75 years.

For the analyses among those with a chronic condition, vaccine brand and by time since vaccination, we stratified the data into the age groups 30–59 and ≥ 60 years.

We modelled VE by time since vaccination using an interaction between vaccination and time since vaccination as a restricted cubic spline with 4 knots at 0 and 20 days and at the 45th and 90th centile, based on a priori knots and adaptations of Harrell’s percentiles (22). We also measured VE by days between vaccination and onset of symptoms with stratified by monthly cut-offs: <30, 30–59, 60–89 days and ≥ 90 days, and superimposed these values on the graph of the model to provide a validation of the modelling. We did not compute VE if one of these strata had less than 100 patients.

We conducted sensitivity analyses excluding the study site without systematic selection of patients for swabbing (NL-CO), excluding the largest study site (NA), varying the imputed onset dates between 2 and 5 days, including only those swabbed within 7 days of symptom onset (PCR tests), and varying the number and position of knots in the time since vaccination analysis.

Ethics

The planning, conduct and reporting of the studies was in line with the Declaration of Helsinki. Official ethical approval was not required if studies were classified as being part of routine care or within surveillance regulations: Spain (three regions) regulated by royal decree 2210/1995 of December 28 provided by the Ministry of Health and Consumer Affairs, England and Scotland (Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002 to collect confidential patient information (www.legislation.gov.uk/ukxi/2002/1438/regulation/3/made.opensinnewtab) under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii), and 3), and Ireland (virological and clinical surveillance of COVID-19 is classified as routine operational public health activities conducted in the public interest can therefore be conducted without informed consent under one of the appropriate Article 6 grounds (like public interest) and Article 9(2)(i) of the General Data Protection Regulations (GDPR) (or HSE can avail of sections 38 and 39)). Other study sites obtained local ethical approval from a national review board: France: approved by the French ethics research committee ('Comité de Protection des Personnes' - CPP), no registration number given; Navarra, Spain, approved by Comité de ética de la investigación con medicamentos(PI2020/45); Portugal: approved 16 March 2021 by the Ethics Committee of Instituto Nacional de Saúde Doutor Ricardo Jorge, no registration number given; Croatia: approved 17 June 2021 by the Ethics Committee of the Croatian Institute of Public Health, no registration number; the Netherlands (NL-CO): a waiver for ethical review was issued by the National Institute for Public Health and the Environment of the Netherlands, online informed consent was provided by all participants; Romania: the study was approved on 12 of April 2021 by the Cantacuzino Institute ethics committee (CE 47/2021).

Results

After applying the exclusion criteria, we included 14,282 patients, of which 2,725 were cases and 11,557 were controls (Supplementary Figure S1).

Among the cases and controls, 11,312 were completely vaccinated. Vaccination rollout continued as cases and controls were selected (Figure 2).

Figure 2: Number of patients by week of swab and case status, as well as number of patients by week of their complete vaccination, I-MOVE-COVID-19 and ECDC primary care and community multicentre networks, July–August 2021

Cases and controls received their second dose (for 2-dose schedules), or first dose (for COVID-19 Vaccine Janssen) of COVID-19 vaccination up to 213 days before symptom onset (Figure 3).

Figure 3: Completely vaccinated patients by case status and days between complete vaccination and symptom onset, I-MOVE-COVID-19 and ECDC primary care and community multicentre networks, July–August 2021

Among controls, 35% were aged 60 and older compared to 24% of cases, 59% were female (vs 54% of cases), and 31% (vs 23% of cases) presented with at least one chronic condition (diabetes, heart disease, chronic lung disease, immunodeficiency, renal disease, or liver disease) (Supplementary Table S2).

A total of 84% of controls had received complete COVID-19 vaccination at time of swab, compared to 59% of cases. Comirnaty was the most commonly used vaccine, with 66% of vaccinated controls and 60% of vaccinated cases receiving two doses.

Of the 2190 cases presenting in the four study sites with sequencing results available, 130 (6%) were sequenced and 118 (91%) of these belonged to the SARS-CoV-2 Delta variant and its sublineages.

The overall complete dose VE against symptomatic SARS-CoV-2 infection was 74% (95% CI: 70–77) among persons aged 30 years and older, adjusting for swab date, study site, age group, sex and chronic condition. The adjusted VE was 74% (95% CI: 69–79), 76% (95% CI: 71–80), 64% (95% CI: 48–75) and 63% (95% CI: 16–83) for those aged 30–44, 45–59, 60–74 and 75 years and older, respectively (**Table 2**). The VE for two doses of Comirnaty was 78% (95% CI: 75–81) and 67% (95% CI: 52–77) among 30–59-year-olds and those aged 60 and older, respectively. The VE for two doses of Vaxzevria was 66% (95% CI: 58–73) and 65% (95% CI: 48–76) among 30–59-year-olds and those

aged 60 years and older, respectively. The VE for two doses of Spikevax was 91% (95% CI: 87–94) and 83% (85% CI: 64–92) among 30–59-year-olds and those aged 60 years and older, respectively. The VE of COVID-19 Vaccine Janssen was 52% (95% CI: 40–61) among 30–59-year-olds. VE was not computed for COVID-19 Vaccine Janssen among those aged 60 years and older, as all countries but one dropped out of the analysis.

The overall VE for those aged 30–59 years with presence of chronic condition was 63% (95% CI: 50–73) and without 77% (95% CI: 73–80) (p-value for interaction term 0.007). The VE for those aged 60 years and older with presence of chronic condition was 58% (95% CI: 27–76) and without 66% (95% CI: 49–78). Among those aged 30–59 years the VE was 69% (95% CI: 56–78) and 80% (95% CI: 77–83), 50% (95% CI: 11–72) and 68% (95% CI: 60–75), 94% (95% CI: 83–98) and 90% (95% CI: 86–94), and 24% (95% CI: -25–53) and 57% (95% CI: 45–66), for those with and without presence of chronic condition for Comirnaty, Vaxzevria, Spikevax and COVID-19 Vaccine Janssen, respectively (Table 1). Sample size was too small to measure brand-specific VE stratified by presence of chronic condition among those aged 60 years and older.

Table 2: Effectiveness of complete COVID-19 vaccination among participants in the primary care and community I-MOVE-COVID-19 and ECDC VE study, by age group and vaccine product, Europe, July–August 2021

Vaccine brand	Analysis type	Cases; vaccinated/ controls; vaccinated	Crude VE (95% CI) ^a	Adjusted VE (95% CI) ^b
Age group-specific analysis				
All vaccines^c	Ages 30 years and older	2725;1606/11557;9706	74 (72–77)	74 (70–77)
	30–44 years	1066;291/3268;1938	75 (71–79)	74 (69–79)
	45–59 years	992;722/4229;3875	76 (71–80)	76 (71–80)
	60–74 years	410;346/2412;2277	64 (48–75)	63 (48–75)
	75 years and older	255;245/1639;1613	62 (16–83)	63 (16–83)
Comirnaty^d	30–59 years	1640;595/5546;3856	78 (75–80)	78 (75–81)
	60 years and older	449;375/2735;2574	67 (54–76)	67 (52–77)

Vaxzevria^d	30–59 years	1141;151/2294;639	66 (58–73)	66 (58–73)
	60 years and older	220;150/1073;915	62 (45–74)	65 (48–76)
Spikevax^d	30–59 years	1071;38/2268;596	91 (87–93)	91 (87–94)
	60 years and older	86;20/387;243	81 (66–90)	83 (64–92)
COVID-19 Vaccine Janssen^e	30–59 years	1136;217/2199;621	46 (35–56)	52 (40–61)
	60 years and older ^e	99;42/235;101		
Chronic condition-specific analysis				
All vaccines^f	Presence of chronic condition, 30–59 years	331;199/1604;1305	68 (58–76)	63 (50–73)
	Absence of chronic condition, 30–59 years	1709;807/5778;4424	75 (72–78)	77 (73–80)
	Presence of chronic condition, 60 years and older	289;266/1976;1908	55 (24–74)	58 (27–76)
	Absence of chronic condition, 60 years and older	367;320/2049;1960	67 (51–78)	66 (49–78)
Comirnaty	Presence of chronic condition, 30–59 years	257;125/1190;891	72 (62–80)	69 (56–78)
	Absence of chronic condition, 30–59 years	1383;470/4329;2946	79 (75–81)	80 (77–83)
Vaxzevria	Presence of chronic condition, 30–59 years	143;20/381;89	54 (20–74)	50 (11–72)
	Absence of chronic condition, 30–59 years	997;131/1904;543	67 (59–74)	68 (60–75)
Spikevax	Presence of chronic condition, 30–59 years	136;5/464;167	94 (85–98)	94 (83–98)
	Absence of chronic condition, 30–59 years	935;33/1802;429	89 (85–93)	90 (86–94)

COVID-19 Vaccine Janssen	Presence of chronic condition, 30–59 years	168;46/423;132	25 (-15–50)	24 (-25–53)
	Absence of chronic condition, 30–59 years	968;171/1774;489	50 (39–60)	57 (45–66)

^a Adjusted by study site, swab date.

^b Adjusted by study site, swab date, 10-year age group, presence of chronic condition, sex.

^c Six controls dropped from the 30–44 years (RO), four controls dropped from the 45–59 years (RO), and two cases dropped from the 75 years and older analysis (RO).

^d Only countries included where at least one study participant in the age group for analysis had received the vaccine under study. Comirnaty: NL-CO, EN, ES, FR, HR, IE, NA, PT, RO, SC; Vaxzevria: NL-CO, EN, ES, FR, HR (30–59-year-olds only), IE, NA, PT, SC; Spikevax: NL-CO, ES, FR, HR (30–59-year-olds only), IE (30–59-year-olds only), NA, PT, RO (60 years and older only), SC (30–59-year-olds only); COVID-19 Vaccine Janssen: NL-CO, ES, FR, HR, IE, NA, PT

^e VE was not computed for COVID-19 Vaccine Janssen among those aged 60 and older, as all countries but one dropped out of the analysis.

^f Countries included in the 30–59 years old analysis: NL-CO, ES, FR, HR, NA, PT, SC; countries included in the 60 years and over analysis: NL-CO, EN, ES, FR, IE, NA, RO, SC

Comirnaty VE among those aged 30–59 by days between vaccination and onset of symptoms was 87% (95% CI: 83–89) at 14–29 days and 65% (95% CI: 56–71%) at ≥90 days (p-value test for trend <0.001) (Table 3). Using our modelling approach, the VE declined from 90% (95% CI: 84–94) at 14 days to 61% (95% CI: 43–73) at 213 days (Figure 4).

Comirnaty VE among those aged 60 years and older by days between vaccination and onset of symptoms was 65% (95% CI: 37–80) at 30–59 days and 64% (95% CI: 44–77%) at ≥90 days (Table 3). Sample size was too small to measure VE at 14–29 days (2 vaccinated cases and 30 controls, respectively). Using the modelling approach the VE declined from 89% (95% CI: -22–99) at 16 days to 50% (95% CI: 2–75) at 203 days (Figure 4).

Vaxzevria VE among those aged 30–59 years by days between vaccination and onset of symptoms was 72% (95% CI 52–83) at 14–29 days and 65% (95% CI: 48–76) at 60–89 days (Table 3). Spikevax VE among those aged 30–59 years by days between vaccination and onset of symptoms was 98% (95% CI 93–100) at 14–29 days and 90% (95% CI: 76–96) at 60–89 days (Table 3). COVID-19 Vaccine Janssen VE among those aged 30–59 years by days between vaccination and onset of symptoms was 50% (95% CI: 36–62) at 30–59 days and 52% (95% CI: 33–66) at 60–89 days. Sample size was too small to measure COVID-19 Vaccine Janssen VE for 14–29 days and to measure VE among those vaccinated ≥90 days for all vaccines except Comirnaty, and modelling was not

attempted. Sample size was also too small to measure VE by time since vaccination among those aged 60 years and older for these vaccine brands.

Table 3: Effectiveness of complete COVID-19 vaccination among participants in the primary care and community I-MOVE-COVID-19 and ECDC VE study, by time since vaccination and vaccine product, Europe, July–August 2021

Analysis by time since vaccination			
Brand, age group and time since vaccination	Cases / controls	Crude VE (95% CI) ^a	Adjusted VE (95% CI) ^b
Comirnaty, age 30–59 years^c			
Unvaccinated	1045/1684		
Vaccinated 14–29 days	123/1287	87 (84–89)	87 (83–89)
Vaccinated 30–59 days	261/1584	75 (71–79)	76 (72–81)
Vaccinated 60–89 days	60/335	70 (59–78)	72 (61–80)
Vaccinated ≥90 days	151/647	66 (58–72)	65 (56–71)
Comirnaty, age 60+ years^c			
Unvaccinated	74/161		
Vaccinated 14–29 days	2/30	-	-
Vaccinated 30–59 days	32/425	67 (42–81)	65 (37–80)
Vaccinated 60–89 days	146/951	65 (49–76)	66 (48–78)
Vaccinated ≥90 days	192/1159	66 (51–76)	64 (44–77)
Vaxzevria, age 30–59 years^d			
Unvaccinated	990/1655		
Vaccinated 14–29 days	21/107	71 (52–83)	72 (52–83)
Vaccinated 30–59 days	79/320	67 (56–75)	67 (57–75)
Vaccinated 60–89 days	42/162	64 (47–76)	65 (48–76)
Vaccinated ≥90 days	9/50	-	-
Spikevax, age 30–59 years^e			
Unvaccinated	1033/1672		
Vaccinated 14–29 days	2/180	98 (92–100)	98 (93–100)
Vaccinated 30–59 days	19/285	91 (85–94)	91 (85–95)

Vaccinated 60–89 days	6/98	89 (75–96)	90 (76–96)
Vaccinated ≥90 days	11/33	-	-
Janssen, age 30–59 years^f			
Unvaccinated	919/1578		
Vaccinated 14–29 days	19/61	-	-
Vaccinated 30–59 days	123/338	46 (32–57)	50 (36–62)
Vaccinated 60–89 days	70/205	45 (26–60)	52 (33–66)
Vaccinated ≥90 days	5/17	-	-

^a Adjusted by study site, swab date.

^b Adjusted by study site, swab date, 10-year age group, presence of chronic condition, sex.

^c Comirnaty: NL-CO, EN (30–59-year-old analysis only), ES, FR, HR, IE, NA, PT, RO (60 years and older analysis only), SC

^d Vaxzevria: NL-CO, EN, ES, FR, HR, IE, NA, PT, SC

^e Spikevax: NL-CO, ES, FR, IE, NA, PT, SC

^f Janssen: NL-CO, ES, FR, HR, IE, NA, PT

Figure 4: Effectiveness of Comirnaty vaccination among participants in the primary care/community I-MOVE-COVID-19 and ECDC VE study by days between dose of complete vaccine and onset of symptoms, and by age group, Europe, July–August 2021

^aAdjusted by study site, age group, sex, date of swab and presence of chronic condition.

^b Sample size was too small to measure VE for 14–29 days for Comirnaty among those aged 60 years and older

Sensitivity analysis

Excluding the study site with self-selected participants (NL-CO), varying the imputed onset dates by 2 and 5 days, and restricting to those swabbed within 7 days of symptom onset, changed the VE point estimates by less than 3%. Excluding the study site providing the most cases and controls (NA) resulted in lower sample size and not all stratified VE could be estimated, particularly for older age groups. VE point estimates among those aged 30–59 years old differed by $\leq 8\%$ for all estimates. For those aged 60 years and older, only VE for Comirnaty could be estimated, where the VE differed by 12%, although confidence intervals overlapped (67% (95% CI: 52–77) and 79% (95% CI: 54–91), including and excluding NA, respectively).

Varying the position of knots in time since vaccination analysis (equal intervals, different percentiles) changed the Akaike Information Criterion (AIC) by <3 points among those aged 30–59 years and <4 points among those aged 60 and older, and the functional forms remained the same.

Discussion

In this multicentre test-negative design study, including 14,282 patients, we measured VE for Comirnaty, Vaxzevria, Spikevax and Janssen vaccines against symptomatic SARS-CoV-2 infection in July and August 2021, thus restricting to a period where Delta variant circulation dominated.

VE was greater for mRNA vaccines than for the other vaccines among those aged 30–59 years, with Spikevax at 91%, Comirnaty at 78%, and Vaxzevria and COVID-19 Vaccine Janssen VE at 66% and 52%, respectively.

Among those aged 60 years and older, VE was 67% (Comirnaty), 83% (Spikevax) and 65% (Vaxzevria). Sample size was too small to measure VE in this age group for COVID-19 Vaccine Janssen. Confidence intervals overlapped due to small sample size in this age group, and no comparison by vaccine brand was possible.

For the two mRNA vaccines, the point estimates were higher for Spikevax compared to Comirnaty in for the 30–59 and 60 years and older age groups, confidence intervals overlapped in the older age group.

Due to the observational nature of this study, comparison between vaccine brands should be made with caution, as different population groups (with varying levels of risk and exposure) may

have been offered different vaccines at different times. Nevertheless, our results suggest a reduction greater than 50% in symptomatic SARS-CoV-2 infection by all vaccine brands across all adults aged 30 years upwards in July and August 2021 during Delta circulation dominance.

The Comirnaty VE among those aged 60 years and older was lower than in our previous publication among those aged 65 and older for the study period December 2020 to May 2021 (67% vs. 87%, respectively)(17). The differences in VE may be explained by the difference in predominant circulating variants between these periods (alpha variant vs. delta variant) and potential waning of the effect of the vaccine over time.

Our estimates are also similar to the VE against symptomatic infection in other observational studies during Delta circulation. In the UK, while the VE point estimate of Comirnaty was higher (88% compared to our VE of 67–78%), the VE for Vaxzevria was similar (67% to 65–66%)(23). In Qatar, the VE of Comirnaty was lower (54% compared to our 67–78%) and the VE for Spikevax was similar (85% compared to our 83–91%), although the study design differed to ours (24).

We observed a lower VE point estimate among those presenting at least one chronic condition, compared to those without both for 30–59-year-olds and those aged 60 years and older. Precision was low in the older age group and the difference (14%) was only statistically significant among those aged 30–59 years. Brand-specific VE by chronic conditions among those aged 30–69 suggest that for most brands, VE is higher among those without chronic conditions as observed in the overall study population. Brand-specific VE by presence of chronic condition was not available for other age groups due to limited sample size. Small differences between VE against infection among those with and without underlying chronic conditions has been suggested in a Danish study(25), and specifically for those immunocompromised, but not for any chronic condition in a UK study(26). Other studies did not observe differences in VE against infection among those with and without presence of chronic conditions(27,28). Further studies presenting brand-specific VE by age group, including also estimates among those without chronic conditions as a comparator group are needed to add to the evidence of how the vaccines perform in different risk groups.

There was some evidence of decline in VE by time since vaccination among those aged 30–59 for Comirnaty (ranging from 87% at 14–29 days to 65% at 90+ days). Modelling suggested the VE declined to 61% after 200 days. Among those aged 60 years and older, VE point estimates differed minimally between 30–59 days and 90+ days (63–66%), using an approach of measuring VE by time since vaccination by cutoffs, but precision was low. Modelling VE by time since vaccination as

a continuous variable indicated some potential decline over time, but confidence intervals are also compatible with no decline. Sample size in this age group was too low to measure VE by time since vaccination for Spikevax and Vaxzevria. It is worth noting that this study does not include the frail elderly, e.g., those who present directly to hospital or are care facility residents.

Using a modelling approach to measuring VE by days since vaccination provides added value compared to the stratified approach, as we do not lose information by transforming a continuous variable into a categorical one. However, the modelling approach may not be adequate in the tails of the model, due to sparse data, as can be seen by the very wide confidence intervals around the model among those aged 60 years and older. This may explain why the stratified estimates do not match the ones in the model well up to 60 days between vaccination and symptom onset.

In the UK, a smaller decline of Comirnaty VE against infection for younger adults and of both mRNA vaccines for adults in Canada was observed (both 12% compared to our 22% over a similar time since vaccination period)(14,16). A larger decline in Comirnaty VE against Delta infection was observed among healthcare workers in the US (93% to 53% over 5 months) (29). Similar to our study, no decline was observed for Vaxzevria among this age group in the UK and at most a 12% decline among adults in Canada. No decline was observed in the UK for Spikevax, however a 14% decline was observed in the US (30).

To disentangle the decline in VE by time since vaccination from variant-related reduction in VE over time, effects of vaccine brands given at different times and differences in age-specific VE, it is important to examine the data and measure VE by time since vaccination by age group, and vaccine brand within a period of stable variant circulation. While this is possible to a certain extent in our study, sample size becomes limited and some results may be spurious. We will endeavour to repeat these analyses going forward with larger sample size.

Study design-specific issues and mechanism of protection of the vaccine can hide or exacerbate changes in VE by time since vaccination (31). A spurious waning in the vaccine effect can be observed if the vaccine provides only partial protection, due to differential depletion of susceptibles in unvaccinated and vaccinated groups (32). In the context of a high baseline VE, which is what we observe here, the bias may be minimal (33).

Those vaccinated earlier may belong to specific groups with different risks of exposure and susceptibility to the virus than those vaccinated late. Adjusting for presence of chronic condition, time and age in our analyses may not be sufficient. Measuring age group and brand-specific VE by

time since vaccination by vaccine cohort (vaccinated early, middle or late) may provide additional information.

Our study is subject to several limitations. While many study sites sequence the whole or partial genome of viruses, the proportion sequenced overall did not allow a variant-specific VE analysis. To overcome this limitation, we restricted the study period to July–August 2021, a period in which we know the Delta variant dominated in the European sites participating in our study. Among the 130 viruses sequenced, 91% belonged to the SARS-CoV-2 Delta variant, indicating that the vast majority of viruses in the study were likely to belong to the Delta variant. The proportion of viruses sequenced is low in our study, the main reason for this is the difficulty of being able to match the clinical-epidemiological data with the virological data.

The vaccine coverage was high in July and August in many European countries, particularly among older age groups. Apart from affecting our results in terms of precision, patients who are unvaccinated may be different from vaccinated patients in terms of exposure to the virus, thus violating a key precondition of VE studies (34). Inclusion of confounders in the VE model can help adjust for different exposures. Including measures of clinical extremely vulnerable people may help overcome confounding (35). Confounding factors relating to behaviour are difficult to collect, although ongoing prospective cohort studies in special populations (e.g., healthcare workers) may help us understand what confounding to expect.

We use a multicentre study design, and aim to reduce heterogeneity with study sites adapting the same generic protocol. The study site in Navarra, Spain, dominates in terms of sample size, as it provides data from all symptomatic patients tested using their comprehensive surveillance using electronic medical records/registries. Excluding Navarra from the analysis reduces precision, however the point estimates for all analyses remain <10% different in terms of absolute VE, with the exception of Comirnaty VE among those aged ≥ 60 years, where excluding Navarra resulted in a point estimate greater by 12%, but due to sample size confidence intervals overlapped.

Our study has several strengths. Selection bias can be a problem with observational studies, particularly in analyses involving electronic medical records. In our study, in all study sites, but one, all or a systematic sample of patients are selected for inclusion. The swabbing procedure is known, reducing the risk of selection bias. Additionally, the test-negative design aims to minimise selection bias by adjusting for healthcare-seeking behaviour. Omitting the one study with self-selected patients changes the VE by <2% overall, by age group and vaccine brand.

Conclusions

Our study provides evidence of 52–91% protection of complete dose vaccination against the Delta variant among those aged 30 years and older for four vaccine brands. The results also indicate a lower VE among those with presence of chronic condition among those aged 30–59 for some vaccine brands. While our study suggests some waning of the vaccine effect with increased time since vaccination, we observed sustained protection above 60% up to 200 days post vaccination for Comirnaty. Further studies are needed to better analyse this observed decline in VE. We will continue the analysis of VE by days since vaccination and onset within the I-MOVE-COVID-19 and ECDC network study as more data come in.

High complete vaccine coverage in the primary series of vaccination is important as it provides good direct protection of individuals against symptomatic SARS-CoV-2 infection as illustrated by this and other studies, as well as providing protection against severe disease (16,36).

References

1. European Centre for Disease Prevention and Control. COVID-19 situation update worldwide, as of week 44, updated 11 November 2021 [Internet]. 2021 [cited 2021 Nov 15]. Available from: <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>
2. European Centre for Disease Prevention and Control (ECDC), World Health Organization Regional Office for Europe (WHO/Europe). Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update [Internet]. European Centre for Disease Prevention and Control; 2021 Sep [cited 2021 Oct 28]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-16th-update-september-2021.pdf>
3. Nextstrain. Genomic epidemiology of novel coronavirus - Europe-focused subsampling [Internet]. [cited 2021 Oct 30]. Available from: <https://nextstrain.org/ncov/gisaid/europe>
4. Shu Y, McCauley J. GISAID: Global initiative on sharing all influenza data – from vision to reality. *Euro Surveill*. 2017 Mar 30;22(13):30494.
5. European Medicines Agency. COVID-19 vaccines [Internet]. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines>
6. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021 Feb 4;384(5):403–16.
7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020 Dec 31;383(27):2603–15.
8. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021 Jun 10;384(23):2187–201.
9. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*. 2021 Jan;397(10269):99–111.
10. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. COVID-19 Vaccine Effectiveness by Product and Timing in New York State [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2021 Oct [cited 2021 Oct 28]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.10.08.21264595>
11. Istituto Superiore di Sanita. Impact of COVID-19 vaccination on the risk of SARS-CoV-2 infection and hospitalization and death in Italy [Internet]. Rome, Italy: Istituto Superiore di Sanita; [cited 2021 Oct 28]. Available from: https://www.iss.it/documents/20126/0/report_on_vaccine_effectiveness_Italy+%281%29.pdf/53d71dc2-c8c5-24c1-3467-705a8587a339?t=1633529045681

12. de Gier B, Andeweg S, Backer JA, RIVM COVID-19 surveillance and epidemiology team, Hahné SJM, van den Hof S, et al. Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), August-September 2021, the Netherlands [Internet]. *Epidemiology*; 2021 Oct [cited 2021 Oct 28]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.10.14.21264959>
13. Martínez-Baz I, Miqueleiz A, Casado I, Navascués A, Trobajo-Sanmartín C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. *Eurosurveillance* [Internet]. 2021 May 27 [cited 2021 Jun 21];26(21). Available from: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.21.2100438>
14. N Andrews, E Tessier, J Stowe, C Gower, F Kirsebom, R Simmons, et al. Preprint: Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. [cited 2021 Oct 30]; Available from: <https://khub.net/documents/135939561/338928724/Vaccine+effectiveness+and+duration+of+protection+of+covid+vaccines+against+mild+and+severe+COVID-19+in+the+UK.pdf/10dcd99c-0441-0403-dfd8-11ba2c6f5801>
15. Poukka E, Baum U, Palmu AA, Lehtonen TO, Salo H, Nohynek H, et al. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020 - October 2021 [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2021 Nov [cited 2021 Nov 24]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.11.03.21265791>
16. Skowronski DM, Setayeshgar S, Febriani Y, Ouakki M, Zou M, Talbot D, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2021 Oct [cited 2021 Oct 30]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.10.26.21265397>
17. Kissling E, Hooiveld M, Sandonis Martín V, Martínez-Baz I, William N, Vilcu A-M, et al. Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021. *Eurosurveillance* [Internet]. 2021 Jul 22 [cited 2021 Oct 28];26(29). Available from: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.29.2100670>
18. Epiconcept. COVID-19 vaccine effectiveness at primary care level in Europe: I-MOVE-COVID-19 generic protocol [Internet]. [cited 2021 Jun 22]. Available from: <https://www.imoveflu.org/wp-content/uploads/2021/05/I-MOVE-COVID-19-primary-care-COVID-19-vaccine-effectiveness-protocol-v2.3.pdf>
19. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine*. 2013 Apr 19;31(17):2165–8.
20. Wellcome Sanger Institute. COVID–19 Genomic Surveillance [Internet]. COVID–19 Genomic Surveillance. [cited 2021 Oct 28]. Available from: <https://covid19.sanger.ac.uk>
21. European Centre for Disease Prevention and Control. Data on SARS-CoV-2 variants in the EU/EEA [Internet]. [cited 2021 Oct 28]. Available from: <https://www.ecdc.europa.eu/en/publications-data/data-virus-variants-covid-19-eueea>

22. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001. 568 p. (Springer series in statistics).
23. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med*. 2021 Aug 12;385(7):585–94.
24. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Khatib HAA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar [Internet]. *Epidemiology*; 2021 Aug [cited 2021 Oct 30]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.08.11.21261885>
25. Emborg H-D, Valentiner-Branth P, Schelde AB, Nielsen KF, Gram MA, Moustsen-Helms IR, et al. Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV-2 infections, hospitalisations and mortality in prioritised risk groups [Internet]. *Public and Global Health*; 2021 Jun [cited 2021 Nov 25]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.05.27.21257583>
26. Whitaker HJ, Tsang RS, Byford R, Andrews NJ, Sherlock J, Pillai PS, et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups. [cited 2021 Nov 25]; Available from: <https://khub.net/documents/135939561/430986542/RCGP+VE+riskgroups+paper.pdf/a6b54cd9-419d-9b63-e2bf-5dc796f5a91f>
27. Thompson MG, Stenehjem E, Grannis S, Ball SW, Naleway AL, Ong TC, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. *N Engl J Med*. 2021 Oct 7;385(15):1355–71.
28. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021 Apr 15;384(15):1412–23.
29. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *The Lancet*. 2021 Oct;398(10309):1407–16.
30. Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against Delta, Mu, and other emerging variants [Internet]. *Infectious Diseases (except HIV/AIDS)*; 2021 Oct [cited 2021 Oct 30]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.09.29.21264199>
31. Halloran ME, Longini IM, Struchiner CJ. Design and analysis of vaccine studies. New York: Springer; 2010. 387 p. (Statistics for biology and health).
32. World Health Organisation. Evaluation of COVID-19 vaccine effectiveness - Interim guidance [Internet]. World Health Organization; 2021 [cited 2021 Oct 31]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1

33. Kahn R, Schrag SJ, Verani JR, Lipsitch M. Identifying and alleviating bias due to differential depletion of susceptible people in post-marketing evaluations of COVID-19 vaccines [Internet]. *Epidemiology*; 2021 Jul [cited 2021 Oct 31]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2021.07.15.21260595>
34. Greenwood M, Yule GU. The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general. *Proc R Soc Med*. 1915;8(Sect Epidemiol State Med):113–94.
35. Andrews N. High vaccine coverage: Are unvaccinated at the same risk of exposure to SARS-CoV-2 as the vaccinated? How can we measure this and implications for studies? ECDC VE study workshop; 2021 Oct 15.
36. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Guevara M, Fernández-Huerta M, Burgui C, et al. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. *Eurosurveillance* [Internet]. 2021 Sep 30 [cited 2021 Oct 28];26(39). Available from: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.39.2100894>

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