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Vaccine effectiveness against influenza A in older adults and the effect of chronic conditions: results from the I-MOVE and VEBIS multicentre European hospital case–control studies, 2015/16–2023/24

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Abstract

Background The Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE/I-MOVE+) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) hospital networks have conducted seasonal multicentre, test-negative, case–control studies in Europe to measure influenza vaccine effectiveness (IVE) since 2015/16. We measured the effect of chronic conditions on VE of influenza A subtypes among older adults (≥ 65 years) using pooled-season data (2015/16–2023/24).

Methods Hospital teams swabbed patients with severe acute respiratory infection (SARI) within 7 days of symptom onset. Cases were RT-PCR positive for influenza A(H1N1)pdm09 or A(H3N2); controls negative for any influenza virus. We calculated overall pooled-season IVE against influenza A(H1N1)pdm09 and A(H3N2), adjusted for study site, sex, age and onset date; and stratified by number of and by each chronic condition (diabetes, heart disease, lung disease/asthma, immunosuppression, kidney disease, liver disease, cancer, obesity). We investigated interaction between vaccination and each condition.

Results We included 1805 A(H1N1)pdm09 cases with 16,329 controls; 2590 A(H3N2) cases with 14,920 controls, from 13 study sites (12 countries). Over all seasons, 63–67% cases and 70% controls had ≥ 2 chronic conditions.

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Against A(H1N1)pdm09, pooled-season IVE was 37% (95%CI: 29–44) overall; 49% (95%CI: 9–72), 30% (95%CI: 12–44) and 38% (95%CI: 29–46) in those with 0, 1, ≥ 2 chronic conditions. Most IVE point estimates were 34–45%, apart from immunosuppression (-7%), kidney disease (17%) and liver disease (54%), but 95% CIs overlapped. Significant interaction was observed for kidney disease ($p = 0.02$) and immunosuppression ($p = 0.01$). Against A(H3N2), pooled-season IVE was 17% (95%CI: 8–25) overall; 15% (95%CI: -26–42), 11% (95%CI: -8–27) and 18% (95%CI: 7–28) in those with 0, 1, ≥ 2 chronic conditions. Here, IVE point estimates ranged 13–25%, apart from immunosuppression (5%), kidney disease (6%) and liver disease (31%), although 95% CIs overlapped. There were no significant interactions.

Conclusions Pooled-season results suggest low–moderate VE against influenza A subtypes among older SARI patients; higher against A(H1N1)pdm09 than A(H3N2), with little evidence of chronic condition modifying effect, apart from kidney disease and immunosuppression. We stress the importance of developing improved influenza vaccines for specific populations, and encourage further research into the effect of chronic conditions on IVE in older adults.

Keywords Vaccine effectiveness, Hospital, Influenza, Chronic conditions, Europe

Background

The World Health Organization (WHO) recommends seasonal vaccination to prevent influenza and influenza-related complications for everyone above 6 months of age, particularly among older ages and including those with chronic conditions such as heart disease, diabetes, and lung disease [1]. The European Commission also recommends influenza vaccination, encouraging European Union (EU) countries to vaccinate high-risk groups (the elderly, immunocompromised individuals of any age or those with chronic conditions) annually [2]. Influenza viruses frequently mutate, resulting in antigenic shift. As a result, vaccines are revised and may be reformulated for each hemisphere annually, and influenza vaccine effectiveness (IVE) needs to be evaluated annually. The IVE can vary depending on vaccine product [3], time since last vaccination [4, 5], and both prior influenza infection [6] and vaccine history [7]. Observed IVE also varies from year to year among population sub-groups (age groups, risk groups) and by influenza type, subtype [8, 9], antigenic group [8, 10] and for each measured outcome (e.g. infection, hospitalisation, death [11, 12]).

European countries target vulnerable populations for vaccination against influenza, e.g. older ages (≥ 60 or 65 years, depending on the country recommendations), pregnant women as well as those with underlying chronic conditions. Influenza vaccination has been shown to reduce hospitalisation and deaths [13] among individuals with cardiovascular disease (CVD) [14, 15] and lung disease [16, 17], particularly among those who are older (≥ 65 years [17]).

The Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE/I-MOVE+) study has estimated IVE annually from 2015/16 among hospitalised patients with severe acute respiratory infection (SARI) [18–24]. From 2021, this became the European Centre for Disease Prevention and Control (ECDC) Vaccine Effectiveness, Burden, and Impact Studies (VEBIS), which currently encompasses most participating study sites from the I-MOVE hospital studies.

Methods

Aim and setting

We pooled data from 19 study sites in 18 European countries participating in either or both the I-MOVE and VEBIS hospital networks [25] from influenza seasons 2015/16 to 2023/24 with sufficient data to estimate IVE against influenza A(H1N1)pdm09 and influenza A(H3N2) (Fig. 1). We estimated IVE against hospitalisation due to RT-PCR-confirmed influenza A subtypes among SARI patients ≥ 65 years old swabbed during any of these seasons, overall, by age group and by presence of specific chronic conditions. This study population of older adults is indicated for influenza vaccination regardless of underlying condition.

Study design

This is a test-negative, case–control study [26] in which participating sites use a common generic protocol [27, 28], adapted for local use. We contacted personnel at each study site since the 2015/16 season for permission to use already-collected data, which has been previously described [18–25]. In brief, for each influenza season, hospital teams swab patients and collect demographic, clinical and influenza vaccination information via electronic medical records or patient interview.

Definitions

Study period and site

Within each influenza season from 2015/16 to 2023/24, we defined the start of the season as ≥ 14 days after the start of that season's vaccination campaign, or the date of the first included influenza case in each participating country, whichever was later. The end of the season was

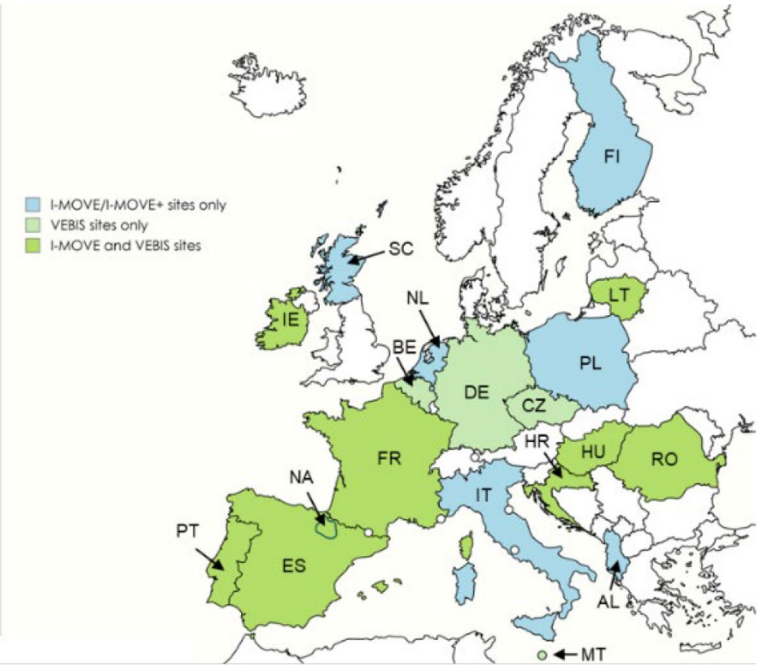

Fig. 1 Participating sites in the I-MOVE/I-MOVE + and VEBIS studies, 2015/16–2023/24. *AL: Albania; BE: Belgium; CZ: Czechia; DE: Germany; ES: Spain (except Navarre Region); FI: Finland; FR: France; HR: Croatia; HU: Hungary; IE: Ireland; I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; IT: Italy; LT: Lithuania; MT: Malta; NA: Navarre Region, Spain; NL: the Netherlands; PL: Poland; PT: Portugal; RO: Romania; SC: Scotland; VEBIS: Vaccine Effectiveness, Burden and Impact Studies*

defined as the week of the last included case, or week 20, whichever was earlier.

We defined a study site as a country or region with at least one participating hospital.

SARI patients, cases and controls

For data collected within the I-MOVE network period (seasons 2015/16–2019/20), we defined a SARI patient as any individual hospitalised for ≥ 24 h with at least one systemic symptom or sign: fever or feverishness, malaise, headache or myalgia or deterioration of general condition (asthenia, loss of weight or anorexia, confusion or dizziness) and at least one respiratory symptom or sign (cough, sore throat or shortness of breath) at admission or within 48 h after admission. For data collected within the VEBIS network period (seasons 2022/23–2023/24), we defined a SARI patient as any individual hospitalised for ≥ 24 h with either: fever, cough, or shortness of breath at admission or within 48 h after admission. SARI patients were excluded from analyses if their symptoms had started (or clearly worsened, if chronic) more than 7 days prior to sample collection.

We defined cases as SARI patients who, within 48 h of admission, were positive by RT-PCR for any influenza A subtype; controls were RT-PCR-negative for any influenza.

Presence of chronic conditions

Study sites collect information on chronic conditions either from the patients' hospital records or by patient or family member interview. Not all sites collect information on all chronic conditions. Commonly collected chronic conditions across all study sites were: heart disease, diabetes, being immunocompromised, and "lung disease or asthma" (one site only collects this information together). We defined the variable "presence of chronic conditions", to be used in adjustment for overall and age-stratified estimates, as at least one of heart these four conditions, as not all study sites collect information on all other conditions. "No chronic conditions" for this adjustment variable was defined as a "no" response for all of these commonly collected conditions. For number of chronic conditions, we included the four commonly collected conditions plus cancer, liver disease, kidney disease and obesity (body mass index > 29).

Vaccination

We defined "vaccinated" as individuals receiving influenza vaccine ≥ 14 days before onset (those vaccinated 1–13 days before onset were excluded; those vaccinated on or after onset were considered unvaccinated). Vaccination status was obtained either

from vaccination registries, patients' medical records, patient self-report, or a combination of these methods (depending on study site and season).

Analysis

We estimated influenza A subtype-specific VE for each individual season, for pooled seasons in which each subtype circulated (1- and 2-stage analyses), and stratified by number of chronic conditions (none, one and at least two). We estimated IVE overall (≥ 65 years), by age group (65–79 and ≥ 80 years), and among those having each of the eight chronic conditions (regardless of the presence of other conditions). We also estimated IVE among those *without* each of these conditions (regardless of the presence of other conditions) for comparison purposes to try to tease out the impact of each specific condition, as overall IVE includes those with and without each condition. As a supplementary analysis, we estimated IVE among those having only one chronic condition, for each of the eight chronic conditions (where sample size allowed).

In sensitivity analyses, we estimated IVE among the VEBIS seasons datasets only (2022/23 and 2023/24), as in these seasons (a) a new case definition was used, and (b) as it was post-pandemic, influenza test-negative controls could be positive for SARS-CoV-2. (1) In the first sensitivity analysis, we selected SARI patients using the older (I-MOVE) vs the newer (VEBIS) case definition, to allow us to observe whether using different case definitions affected the IVE. (2) In the second sensitivity analysis, we excluded SARS-CoV-2 positive controls, as those positive for SARS-CoV-2 were more likely to have been unvaccinated against COVID-19 and therefore potentially also more likely to have been unvaccinated against influenza. If this were true, including the SARS-CoV-2-positive controls would mean that we had been underestimating the IVE.

Statistical analysis

Using logistic regression, we compared the odds of vaccination between cases and controls, adjusting the odds ratio (OR) of vaccination by sex, presence of at least one of the four commonly collected chronic conditions listed above, and by age as a restricted cubic spline or age group as a categorical variable. We calculated IVE as 1 – adjusted OR (expressed as a percentage). We included study site as a fixed effect in the 1-stage analysis. To find the best functional form for calendar time, we created variables for season-month, season-week and season-biweek, including date of onset as a categorical variable, and selected the model with the best functional form designated using the Akaike information criterion. We did not include "any chronic condition" (of the four commonly collected conditions) as an adjustment variable for any of the estimates stratified by chronic condition.

For the 2-stage IVE analysis, firstly, IVE estimates were calculated for each season included in the 1-stage analysis, using time as a restricted cubic spline of onset date or onset month as a categorical variable. Then, season-specific IVE estimates were pooled using a random-effects meta-analysis, and the proportion of inter-season variation due to heterogeneity rather than chance (I^2) estimated.

We excluded sites with < 10 cases or controls for the pooled-season dataset, and excluded seasons with fewer than three sites in total. We did not perform a pooled-season analysis for any (sub)type unless there were at least three seasons of data available after applying the previous two criteria. We estimated interaction terms between vaccination and (1) age group (65–79 and ≥ 80 years); (2) number of chronic conditions (none, one, two or more) and (3) each of the eight individual chronic conditions as described above.

Where the number of cases or controls per IVE model parameter was < 10, we conducted sensitivity analysis using Firth's method of penalised logistic regression (PLR) to assess small sample bias [29, 30]. We do not report estimates having an absolute difference > 10% between the PLR and original VE estimate, as we considered them indicative of small sample bias. Similarly, we do not present estimates for analyses with < 20 vaccinated cases or controls, or where the number of cases divided by 10 was less than the number of included sites.

All analyses were performed using Stata statistical software *Release 19* (College Station, TX: StataCorp LLC.)

Results

Overall, we included SARI patients aged ≥ 65 years from > 80 European hospitals, in 13 of 19 participating study sites (Fig. 1) providing sufficient data for this period.

We included 18,134 SARI patients in the influenza A(H1N1)pdm09 analysis, covering six seasons (2015/16, 2017/18–2019/20, 2022/23, 2023/24); 1805 were cases and 16,329 were controls. We included 17,510 SARI patients in the influenza A(H3N2) analysis, covering six seasons (2016/17–2019/20, 2022/23, 2023/24); 2590 were cases and 14,920 were controls.

Fifty-four percent of influenza A(H3N2) and 41% of influenza A(H1N1)pdm09 cases were aged ≥ 80 years. Each subtype analysis included 54% controls in this age group. Heart disease was the most common chronic condition (present in about 67% of patients with both subtypes and 73% of controls). About 40% of cases of both subtypes were patients with lung disease/asthma vs 46%

controls and about 33% cases of both subtypes were patients with diabetes vs 38% controls. The frequency of all other individual chronic conditions ranged from 5 to 24% among patients with each subtype, and their controls (Table 1).

All seasonal influenza epidemics prior to 2019/20 included slightly more controls than influenza cases, ranging from a ratio of 1.4:1 to 3.4:1 (Table 1; Fig. 2). However, since then, the number of controls has risen each year, with currently a 10:1 ratio of controls to cases (Table 1; Fig. 2).

Three sites did not report vaccine brand/type. For the influenza A(H1N1)pdm09 analysis, 16% vaccinated cases and 27% vaccinated controls were missing this information; 12% cases and 26% controls were missing vaccine brand/type for the influenza A(H3N2) analysis (Table 1). In the influenza A(H1N1)pdm09 analysis, 20% vaccinated cases and 26% vaccinated controls received high dose or adjuvanted vaccine, while in the influenza A(H3N2) analysis, 11% vaccinated cases and 29% vaccinated controls received these enhanced vaccine types (Table 1).

Vaccine effectiveness

The VE against hospitalisation with influenza A(H1N1) pdm09 overall and in both age groups was higher than against influenza A(H3N2) (Table 2).

Against influenza A(H1N1)pdm09, VE was 3–7 percentage points higher among those who received a high-dose or adjuvanted vaccine type, and 10–27 percentage points lower among those who received all other vaccine types, although numbers were small, 95%CIs wide and only three sites were included in the analysis (data not shown). We did not estimate type-specific VE against influenza A(H3N2) as there were only two sites with cases who received neither high-dose nor adjuvanted vaccines, predicating a pooled analysis. Against both subtypes, the overall IVE was similar for 1- and 2-stage analyses (heterogeneity of VE by season, $I^2=0$ for each (Additional file 1: Figures S1a and S1b), and was slightly higher among those aged 65–79 than among those aged ≥ 80 years. Against influenza A(H1N1)pdm09, VE was 49% (95%CI: 9–72) among those with none, 30% (95%CI: 12–44) among those with one, and 38% (95%CI: 29–46) among those with two or more chronic conditions (Table 2). Against influenza A(H3N2), VE was 15% (95%CI: −26–42), 11% (95%CI: −8–27) and 18% (95%CI: 7–28) among those with none, one, or two or more chronic conditions, respectively (Table 2). Interaction terms between vaccination and age group, and vaccination and number of chronic conditions, were not statistically significant ($p > 0.05$; data not shown).

The annual VE against influenza A(H1N1)pdm09 over the seasons ranged from 30% (95% CI 3–50) in 2022/23 to 53% (95% CI 36–65) in 2019/20 (Additional file 1: Figure S1a). Against influenza A(H3N2), the VE ranged from 10% (95% CI −13–28) in 2018/19 to 27% (95% CI 6–44) in 2022/23. (Additional files 1: Figure S1b).

Against influenza A(H1N1)pdm09, we observed the highest IVE among those with liver disease (54%; 95%CI: 24–72), and lowest among those with kidney disease (17%; 95%CI: −7–36) and those who were immunosuppressed (−7%; 95%CI: −61–29) (Table 2). Numbers were particularly small among cases who were immunosuppressed, obese or who had liver disease. Against influenza A(H1N1)pdm09, those with no chronic condition had a higher IVE point estimate (49%; 95%CI: 9–72) than than those with each of the other chronic conditions, except those with liver disease (54%). Statistically significant interaction terms were observed only between vaccination and kidney disease ($p=0.023$), and between vaccination and immunosuppression ($p=0.01$) (data not shown).

We observed very similar VE against influenza A(H3N2) among all those with none, and with each of the eight chronic conditions, with again the highest IVE among those with liver disease (31%; 95%CI: −9–57) and lowest IVE among those with kidney disease (6%; 95%CI: −18–26) and those who were immunosuppressed (5%; 95%CI: −47–38). Here, those with no chronic conditions had VE against influenza A(H3N2) of 15% (95%CI: −26–42). Numbers were particularly small among cases who were immunosuppressed, obese or had liver disease. None of the interaction terms between vaccination and individual chronic condition was statistically significant ($p > 0.05$; data not shown).

In supplementary analyses, VE point estimates against influenza A(H1N1)pdm09 among most of those with and without each specific condition were 2–11 percentage points different, except among those with heart, liver or kidney disease, or immunosuppression. Those with heart disease or liver disease had an IVE respectively 12 or 17 percentage points higher than those without the condition ($p=0.12$ and $p=0.04$, respectively), while those without kidney disease or immunosuppression had an IVE respectively 27 and 47 percentage points higher than among those with the condition ($p=0.07$ for each) (Additional files 1: Figure S2).

Against influenza A(H3N2), we observed point estimate differences among those with and without most conditions ranging from 1 to 9 percentage points. Patients without kidney disease or immunosuppression, however, had IVE point estimates 15 percentage points higher than those with each condition ($p=0.30$ and 0.49, respectively), while those without liver disease had a VE point estimate against influenza A(H3N2) which was 12 percentage points lower than the IVE among those with liver disease ($p=0.34$) (Additional files 1: Figure S3).

Table 1 Patient characteristics of cases and controls, Influenza – Monitoring Vaccine effectiveness in Europe (I-MOVE/I-MOVE+) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) hospital networks, pooled influenza seasons 2015/16–2023/24, Europe

	Influenza A(H1N1)pdm09				**Influenza A(H3N2)**			
Patient characteristic	**Cases (*n* = 1805)**		**Controls (*n* = 16,329)**		**Cases (*n* = 2590)**		**Controls (*n* = 14,920)**	
Median age in years (IQR)	**78 (71–84)**		**80 (73–87)**		**80 (73–86)**		**81 (73–87)**	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Age groups (years)								
65–79	1060	58.7	7586	46.5	1200	46.3	6830	45.8
≥ 80	745	41.3	8743	53.5	1390	53.7	8090	54.2
Sex								
Male	950	52.6	8444	51.7	1274	49.2	7683	51.5
Female	855	47.4	7885	48.3	1316	50.8	7237	48.5
Number of chronic conditions[a]								
None	86	5.0	642	4.1	203	8.0	629	4.3
One	483	28.0	3815	24.1	746	29.4	3473	23.9
Two or more	1159	67.1	11,347	71.8	1590	62.6	10,422	71.8
Missing data	77	4.3	525	3.2	51	2.0	396	2.7
Individual chronic conditions								
Heart disease	1202	66.9	11,926	73.4	1745	67.7	10,907	73.4
Missing data	9	0.5	48	0.3	11	0.4	29	0.2
Lung disease/asthma	721	40.9	7233	45.5	992	38.6	6694	46.0
Missing data	40	2.2	417	2.6	19	0.7	358	2.4
Diabetes	595	34.1	6064	38.4	799	31.2	5614	38.8
Missing data	58	3.2	521	3.2	32	1.2	449	3.0
Kidney disease	349	20.0	3687	23.6	502	19.9	3301	23.5
Missing data[b]	53	3.0	678	4.2	35	1.4	697	4.9
Cancer	302	18.3	2348	15.4	465	18.6	1997	14.2
Missing data[c]	6	0.4	44	0.3	4	0.2	12	0.1
Obesity	181	13.0	1614	13.9	254	10.7	1539	14.1
Missing data[d]	376	21.2	4619	28.5	204	7.9	3996	26.8
Immunosuppression	136	7.9	1283	8.3	127	5.0	1248	8.8
Missing data	73	4.0	860	5.3	34	1.3	804	5.4
Liver disease	87	6.3	841	5.8	115	4.8	850	6.1
Missing data[b]	403	22.7	1842	11.4	147	5.7	921	6.2
Influenza vaccination								
No	940	52.1	5691	34.9	1208	46.6	5309	35.6
Yes	865	47.9	10,638	65.1	1382	53.4	9611	64.4
Influenza vaccine type (among vaccinated)								
High-dose or adjuvanted[e]	145	19.9	1998	25.7	135	11.1	2101	29.4
Other	584	80.1	5776	74.3	1086	88.9	5051	70.6
Missing data	*136*	*15.7*	*2864*	*26.9*	*161*	*12.0*	*2459*	*25.6*
Influenza season								
2015/16	305	16.9	786	4.8	-[f]		-[f]	
2016/17	NA		NA		1042	40.2	1463	9.8
2017/18	112	6.2	1503	9.2	331	12.8	1326	8.9
2018/19	269	14.9	1177	7.2	536	20.7	1292	8.7
2019/20	281	15.6	1141	7.0	65	2.5	578	3.9
2021/22	-[f]		-[f]		-[f]		-[f]	
2022/23	190	10.5	5182	31.7	328	12.7	4006	26.9
2023/24	648	35.9	6540	40.1	288	11.1	6255	41.9

Table 1 (continued)

Patient characteristic	Influenza A(H1N1)pdm09				Influenza A(H3N2)			
	Cases ($n=1805$)		Controls ($n=16,329$)		Cases ($n=2590$)		Controls ($n=14,920$)	
Median age in years (IQR)	78 (71–84)		80 (73–87)		80 (73–86)		81 (73–87)	
	No	%	No	%	No	%	No	%
Site/country[g]								
Belgium	116	6.4	923	5.7	72	2.8	817	5.5
Germany	32	1.8	117	0.7	10	0.4	21	0.1
Spain (except Navarre Region)	615	34.1	7794	47.7	929	35.9	8112	54.4
France	61	3.4	463	2.8	203	7.8	582	3.9
Croatia	89	4.9	158	1.0	60	2.3	59	0.4
Ireland	0		0		19	0.7	127	0.9
Italy	21	1.2	359	2.2	73	2.8	136	1.0
Lithuania	58	3.2	180	1.1	127	4.9	163	1.1
Malta	21	1.2	186	1.1	25	1.0	144	1.0
Navarre Region, Spain	578	32.0	5441	33.3	697	26.9	4114	27.6
Netherlands	22	1.2	36	0.2	84	3.2	192	1.3
Portugal	55	3.1	342	2.1	113	4.4	160	1.1
Romania	137	7.6	330	2.0	178	6.9	293	2.0

IQR interquartile range, *NA* not applicable (in the 2016/17 season, there were no influenza A(H1N1)pdm09 cases submitted to the study)

[a] At least one of eight chronic conditions: diabetes, heart disease, lung disease/asthma, immunosuppression (collected by all sites in all seasons); cancer (not collected by two sites in one season, and one site in another season), liver disease (not collected by two sites in one season), renal disease (not collected by two sites in one season), and obesity (not collected by one site in one season)

[b] Two sites did not collect information on kidney or liver disease for influenza A(H3N2) analysis, and one site for influenza A(H1N1)pdm09 analysis (the other site began collecting these data in 2023/24). Total N for A(H1N1)pdm09 analyses: 1795 cases, 16,308 controls; for influenza A(H3N2) analyses: 2555 cases, 14,755 controls

[c] Two sites do not collect information on cancer. Total N for A(H1N1)pdm09 analysis: 1657 cases, 15,289 controls; for influenza A(H3N2) analysis: 2508 cases, 14,082 controls

[d] One site does not collect information on obesity. Total N for A(H1N1)pdm09 analyses: 1773 cases, 16,212 controls; for influenza A(H3N2) analyses: 2580 cases, 14,899 controls

[e] For influenza A(H1N1)pdm09, the 146 cases of "high dose or adjuvanted" vaccine were reported from a total of three sites, but for influenza A(H3N2), the 135 cases were reported from only two sites

[f] In season 2015/16 there were no submitted influenza A(H3N2) cases, so this season was not included in the influenza A(H3N2) pooled-season analyses; in 2021/22 there were no submitted influenza A(H1N1)pdm09 cases, and only two sites submitted influenza A(H3N2) cases for this season, so this season was not included in any of the pooled-season analyses

[g] Final cleaned and restricted data for Albania, Czechia, Hungary and Scotland included < 10 influenza cases or controls and, for Poland, included no vaccinated controls; so these sites were not included in either subtype vaccine effectiveness (VE) analysis. Final data for Ireland included < 10 influenza A(H1N1)pdm09 cases, so Ireland was not included in A(H1N1)pdm09 VE analyses

In sensitivity analyses comparing the two case definitions, we observed small (≤ 5 percentage points) differences in VE against influenza A(H1N1)pdm09. Against influenza A(H3N2), in those aged ≥ 65 years we observed differences ≤ 10 percentage points in IVE point estimates overall, with larger differences among those with at least two chronic conditions, although numbers were small and 95% CIs were very wide (Additional file 1: Figure S4). Differences in IVE point estimates after excluding controls positive for SARS-CoV-2 ranged from 0 to 7 percentage points against influenza A(H1N1)pdm09 and from 1 to 6 percentage points against influenza A(H3N2) (Additional file 1: Figure S5).

Discussion

Our results from this multi-country European hospital study suggest that the overall pooled-season moderate VE point estimate against influenza A(H1N1)pdm09 among those aged ≥ 65 years in this setting (37%) did not vary much among those with any of the three main chronic conditions (diabetes, heart disease and lung disease/asthma: range 34–41%). We observed a similar pattern, though with lower point estimates, against influenza A(H3N2) (IVE 17% overall; range 16–25%). Against both subtypes, however, comparatively higher IVE point estimates were observed among those with liver disease (54% against influenza A(H1N1)pdm09; 31% against influenza A(H3N2)), and low to no protection among those who had kidney disease (17% and 6%,

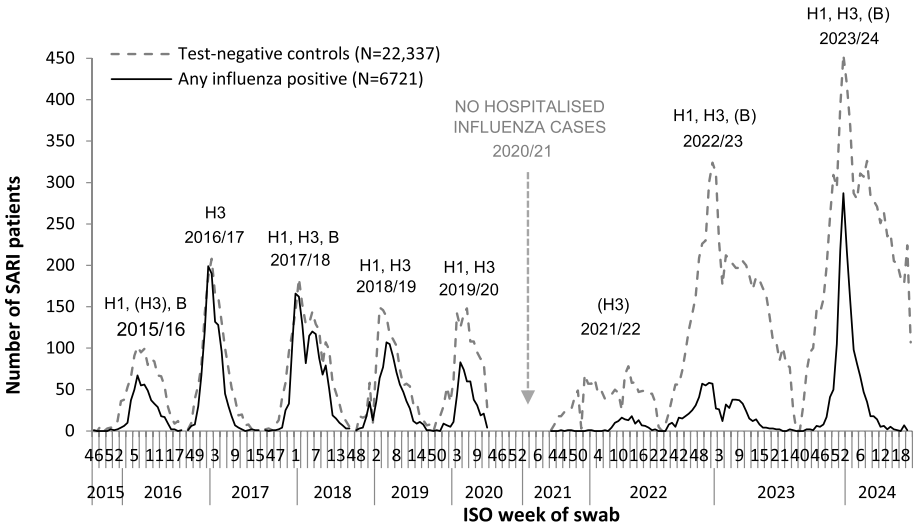

Fig. 2 Number of cases and controls over time, I-MOVE/I-MOVE+ and VEBIS studies, pooled influenza seasons 2015/16–2023/24, Europe[a]. *B: influenza B; H1: influenza A(H1N1)pdm09; H3: influenza A(H3N2); I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine Effectiveness, Burden and Impact Studies.* [a]*Letters in parentheses indicate very small numbers of that type or subtype for that season. In the 2020/21 season there were no hospitalised cases reported from participating sites. As there were only two influenza B seasons with enough data from three or more sites/countries, we could not perform an influenza B pooled-season VE analysis*

respectively) or were immunosuppressed (−7% and 5%, respectively), although numbers were small and most 95% CIs overlapped.

Among individuals with heart disease, there is much supporting literature on the beneficial effect of influenza vaccination in preventing more severe cardiac events [31, 32] and even reduction in all-cause mortality [33–36], although some studies cite low certainty of this evidence [37, 38]. There are some studies providing evidence of a protective effect among this patient group, particularly if aged ≥ 65 years, against influenza-related hospitalisations and deaths [18, 39, 40]. Among individuals with diabetes, although some reviews report little evidence to show the benefit of influenza vaccination [37, 41], other studies show reductions in influenza occurrence [42, 43] and hospital admissions [43, 44] among these patients. Influenza vaccination has been found to reduce hospitalisation from lung diseases [17], and a Cochrane review showed that influenza vaccination limited aggravation of chronic obstructive pulmonary disease among hospitalised patients [45]. Although one study found a benefit among immunocompromised patients with end-stage renal disease (in the early days following kidney transplant [46]), there are many that found little to no effect of influenza vaccination among immunocompromised patients [47–50]. However, due to the high risk of influenza complications and the low vaccine response among those who are immunocompromised, authors of one review highlight the importance of influenza vaccination among family members and healthcare workers caring for this population [50]. There is a study reporting a protective effect against hospitalisation after influenza vaccination among those with liver disease [51]. A systematic review revealed many studies with low quality evidence, reflecting uncertainty in the influenza vaccine's protective effect among patients with chronic liver disease [52], but the authors nonetheless believed that the benefits of the vaccine outweighed the risks among these patients, considering their high risk of severe outcomes.

Among this older population of hospitalised SARI patients, one-third of cases and almost three-quarters of controls had heart disease, between one-third and one-half of SARI patients had lung disease or asthma, and about one-third had diabetes. Two-thirds of all recruited SARI patients had two or more chronic conditions. One of the limitations of this analysis is therefore the inability to disentangle the effects of age (as we only included older adults) as well as the effects of one individual chronic condition from another, particularly among these three most common conditions. Another limitation is the proportion of SARI patients missing some chronic condition information, other than the principal conditions used in analysis adjustments, which all had ≤ 5% missing values (although this varied by site and condition; see Additional file 1: Table S1). The smaller sample sizes among patients with liver disease (6–23% among cases; 6–11% among controls) or obesity (8–21% among cases, 27–29% among controls) could lead to biased IVE estimates among patients with these conditions if

Table 2 Vaccine effectiveness against influenza hospitalisation, Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE/I-MOVE +) and Vaccine Effectiveness, Burden and Impact Studies (VEBIS) in the hospital setting, pooled influenza seasons 2015/16–2023/24, Europe

Main analysis 1: pooled-season influenza A subtype VE overall, by age group and by number of chronic conditions				
Influenza A subtype	**No. sites (N)**	**Vaccinated/unvaccinated cases; vaccinated/unvaccinated controls**	**VE[a]**	**95% CI**
Influenza A(H1N1)pdm09				
All ≥ 65 years (1-stage)	12[b] (18,134)	865/940; 10,638/5691	37	29–44
Age group (years)				
65–79	12[b] (8646)	445/615; 4459/3127	39	29–48
≥ 80	12[b] (9488)	420/325; 6179/2564	32	18–43
Number of chronic conditions[c]				
None	10[d] (728)	24/62; 338/304	49	9–72
One	12[b] (4219)	222/261; 2370/1445	30	12–44
Two or more	12[b] (12,012)	596/563; 7661/3686	38	29–46
Missing chronic condition information	(602)	23/54; 269/256	NA	
Influenza A(H3N2)				
All ≥ 65 years (1-stage)	13[e] (17,510)	1382/1208; 9611/5309	17	8–25
Age group (years)				
65–79	13[e] (8030)	530/670; 3965/2865	20	8–31
≥ 80	13[e] (9480)	852/538; 5646/2444	14	0–25
Number of chronic conditions[c]				
None	10[f] (832)	92/111; 322/307	15	−26–42
One	13[e] (4219)	382/364; 2129/1344	11	−8–27
Two or more	13[e] (12,012)	898/692; 6971/3451	18	7–28
Missing chronic condition information	(447)	10/41; 189/207	NA	
Main analysis 2: pooled-season influenza subtype VE by individual chronic conditions[g]				
Influenza A subtype and individual chronic condition	**No. sites (N)**	**Vaccinated/unvaccinated cases; vaccinated/unvaccinated controls**	**VE[a]**	**95% CI**
Influenza A(H1N1)pdm09				
Heart disease	12[b] (13,128)	585/617; 8024/3902	41	32–48
Lung disease/asthma	12[b] (7954)	419/302; 4903/2330	34	21–44
Diabetes	12[b] (6659)	306/289; 4053/2011	34	20–46
Kidney disease	11[h] (4036)	209/140; 2562/1125	17	−7–36
Cancer	10[d] (2650)	144/158; 1653/695	45	27–59
Obesity	11[h] (1795)	72/109; 964/650	36	7–56
Immunosuppression	12[b] (1419)	78/58; 769/514	−7	−61–29
Liver disease	11[i] (928)	36/51; 553/288	54	24–72
Influenza A(H3N2)				
Heart disease	13[e] (12,652)	959/786; 7304/3603	21	10–30
Lung disease/asthma	13[e] (7686)	565/427; 4488/2206	25	12–36
Diabetes	13[e] (6413)	462/337; 3750/1864	16	−1–30
Kidney disease	11[j] (3803)	308/194; 2260/1041	6	−18–26
Cancer	11[k] (2462)	270/195; 1370/627	16	−7–34
Obesity	11[l] (1793)	99/155; 921/618	13	−24–39
Immunosuppression	13[e] (1375)	66/61; 736/512	5	−47–38
Liver disease	11[j] (3803)	59/56; 546/304	31	−9–57

[a] Odds ratio adjusted (aOR) by country, time (restricted cubic spline of swab date or swab month as categorical variable, depending on model and including season), age (restricted cubic spline or age as linear variable, depending on model), sex, presence/absence of at least one chronic condition (immunocompromised, diabetes, heart disease, lung disease/asthma); VE = 1-aOR

[b] Twelve sites: Belgium, Croatia, France, Germany, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

Table 2 (continued)

[c] In analyses stratified by chronic condition, the adjustment for presence/absence of chronic condition was removed

[d] Ten sites: Croatia, France, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

[e] Thirteen sites: Belgium, Croatia, France, Germany, Ireland, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

[f] Ten sites: Croatia, France, Ireland, Italy, Lithuania, Navarra, the Netherlands, Portugal, Romania and Spain

[g] Regardless of the presence of other chronic conditions. For these analyses, adjustment was made for presence/absence of at least one chronic condition as above, except without including the condition being analysed (for each of the four commonly collected conditions used in adjustment). For example, the OR for estimating VE among those with diabetes was adjusted by country, time, age, sex, and "at least one of immunocompromised, heart disease, lung disease/asthma"

[h] Eleven sites: Belgium, Croatia, France, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

[i] Ten sites: Belgium, Croatia, France, Italy, Lithuania, Malta, Navarra, Portugal, Romania and Spain

[j] Eleven sites: Belgium, Croatia, France, Ireland, Italy, Lithuania, Navarra, the Netherlands, Portugal, Romania and Spain

[k] Eleven sites: Croatia, France, Ireland, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

[l] Eleven sites: Belgium, France, Ireland, Italy, Lithuania, Malta, Navarra, the Netherlands, Portugal, Romania and Spain

the missingness is related to vaccination or case status. In addition to these points, there is also the potential for heterogeneity between sites/countries (and perhaps even between hospitals) in terms of how each chronic condition is defined/ascertained and recorded. While some conditions may have standard definitions (e.g. diabetes), others may vary. For example, we ask sites to provide information on "immunosuppression". In some sites, this includes patients who are HIV + as well as those on chemotherapy for active cancer or who are taking immunosuppressive medication post-transplant. Other sites only include those who are HIV +. However, the number of patients overall who are immunosuppressed is very small (< 10%).

Other limitations include those related to the heterogeneity inherent to pooled multi-country estimates and to pooling data across several seasons. We used a pooled-season approach to increase sample size. Differences in VE by season, along with different chronic condition distribution by season, could introduce bias. However, our analysis of VE by individual season indicates little differences in point estimates (shown in Additional file 1: Figure S1) or in proportion of chronic conditions by season (data not shown).

We observed that IVE estimates among those with and without each of the individual chronic conditions (regardless of the presence of other conditions) were very similar except for three conditions (kidney disease, liver disease, immunosuppression) against both subtypes. Against both subtypes, the IVE point estimate among those with the condition was considerably lower than among those without the condition for kidney disease and immunosuppression, and higher for liver disease. Against influenza A(H1N1)pdm09, although IVE point estimates were 12 percentage points higher among those with than without heart disease, 95% CI overlapped and we did not find evidence of a statistically significant difference ($p = 0.12$). Significant interactions were only observed in the influenza A(H1N1) pdm09 analysis, between vaccination and each of the two chronic conditions with low to no observed protection. Possibly the sample size was too low in influenza A(H3N2) analyses to detect significant interactions, although total analytic sample sizes were not much lower in the A(H3N2) than A(H1N1)pdm09 analyses. (The total number of SARI patients was 4036 and 1419 for influenza A(H1N1)pdm09 kidney disease and immunosuppression analyses, respectively, vs 3803 and 1375 in the influenza A(H3N2) analyses.)

Many IVE estimates among those with a less prevalent chronic condition were very similar to the overall IVE, due in part to some "masking" of any differences among these less prevalent conditions by the high prevalence of the three main conditions. We also investigated IVE with and without each condition alone (i.e. among those with only one condition), but sample sizes were too small to draw conclusions from the results (data not shown).

Sensitivity analyses mostly showed little to no difference in IVE with different case definitions used, nor when excluding those positive for SARS-CoV-2 among controls.

Conclusions

Our multi-country, pooled-season study suggests low–moderate IVE against influenza A subtypes among SARI patients ≥ 65 years for 2015/16–2023/24, higher against A(H1N1)pdm09 than against A(H3N2), with little evidence of a modifying effect for most chronic conditions. We stress the importance of developing improved influenza vaccines for specific populations, in particular, the lower IVE consistently observed against influenza A(H3N2). The much lower VE observed against both influenza subtypes among those with kidney disease and those who were immunosuppressed warrant further investigation, and we encourage further research into the effect of chronic conditions on IVE in older adults.

Abbreviations

aOR Adjusted odds ratio

ECDC	European Centre for Disease Prevention and Control
EU	European Union
I-MOVE	Influenza – Monitoring Vaccine Effectiveness in Europe
IQR	Inter-quartile range
IVE	Influenza vaccine effectiveness
NA	Not applicable
OR	Odds ratio
PLR	Penalised logistic regression
SARI	Severe acute respiratory infection
VE	Vaccine effectiveness
VEBIS	Vaccine Effectiveness, Burden and Impact Studies
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04426-y.

Additional File 1: Figures S1–S5, Table S1. Fig. S1. Vaccine effectiveness among those aged ≥ 65 years against (a) influenza A(H1N1)pdm09 and (b) A(H3N2), by individual season and pooled (1- and 2-stage analysis) over six seasons, 2015/16–2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe[a]. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine effectiveness, Burden and Impact Studies. [a]Note: we adjusted the odds ratios for each individual season using the same variables used in the final pooled-season analysis, to have better comparison between the 1- and 2-stage pooled VE results. Some minor differences between these and previously published data for any individual season may therefore exist, due to differences in adjustment variables and analytic approaches. For each subtype, heterogeneity $I^2 = 0$ for the 2-stage analysis. Fig. S2. Vaccine effectiveness among those aged ≥ 65 years against influenza A(H1N1)pdm09 by presence and absence of (a) heart disease, lung disease/asthma, diabetes, and kidney disease; (b) cancer, obesity, immunosuppression and liver disease, pooled over six seasons, 2015/16–2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine effectiveness, Burden and Impact Studies. Fig. S3. Vaccine effectiveness among those aged ≥ 65 years against influenza A(H3N2) by presence and absence of (a) heart disease, lung disease/asthma, diabetes, and kidney disease; (b) cancer, obesity, immunosuppression and liver disease, pooled over six seasons, 2015/16–2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine effectiveness, Burden and Impact Studies. Fig. S4. Sensitivity analysis 1. Vaccine effectiveness among those aged ≥ 65 years and among those with at least two chronic conditions against (a) influenza A(H1N1) pdm09 and (b) A(H3N2) by SARI case definition, 2022/23 and 2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine effectiveness, Burden and Impact Studies. Fig. S5. Sensitivity analysis 2. Vaccine effectiveness among those aged ≥65 years and among those with at least two chronic conditions against influenza (a) A(H1N1)pdm09 and (b) A(H3N2), overall and excluding SARS-CoV-2-positive controls, 2022/23 and 2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; VEBIS: Vaccine effectiveness, Burden and Impact Studies. Table S1. Proportion of each chronic condition among test-negative controls, by site/country, among hospitalised SARI patients aged ≥ 65 years, pooled seasons 2015/16–2023/24, I-MOVE and VEBIS multicentre hospital studies, Europe. I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe; SARI: Severe acute respiratory infection; VEBIS: Vaccine effectiveness, Burden and Impact Studies. [a] Two sites did not provide information on liver disease. [b] One site did not provide information on renal disease. [c] Two sites did not provide information on cancer.

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Authors' contributions

AMCR, NN, SB2, and EK conceived and designed the study; CM, IM-B, OL, LDM, AB, ML, AM, MK, SA, VVV, RvG-L, SB1, RD1, IP-S, JKH, RD2, PH, JM, FP, ML-M, JC, LBLN, ND, FR, AI, VG, LJ, GX, GP, SM, AV, KT, JB, BO, LD, LS, KM, and the I-MOVE/I-MOVE+ and VEBIS Hospital Network team members supervised local teams, collected, cleaned and prepared local data from their sites; JH prepared the software for the data management and cleaning of pooled data; AMCR analysed the pooled data, prepared the first draft and updated the manuscript with all co-author comments; all authors reviewed and commented on early version(s), and have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

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/surveillance (Ireland, Italy, Malta, later seasons in Spain). In Belgium and Germany, VE is included in SARI surveillance. For Belgium, the study protocol was approved by the central Ethical Committee (CHU ST Pierre, Bruxelles) and each participating hospital's local ethical committees in 2011 (AK/12-02-11/4111), and updated from 2014 (UZ-Brussel en VUB B.U.N. 143201215671). The German SARI surveillance was approved by the Charité-Universitätsmedizin Berlin Ethical Board (Reference EA2/218/19). Other study sites obtained local ethical approval from a national review board (Croatia: approved by the Ethics committee of the Croatian Institute of Public Health on 25 September 2015 (3-year approval), 21 November 2018, 7 November 2019, 26 November 2020, 24 May 2021, 26 January 2022, 20 June 2022 and 3 July 2023, Number 80-2661/1-15; Klasa: 030-02/18-01/1, Ur. broj 381-10-18-2; Klasa: 030-02/18-01/1, Ur.broj 381-15-19-4; Klasa:030-02/20-01/3, Ur.broj 381-15-20-2; Klasa:030-02/21-01/1, Ur.broj:381-15-21-7; Klasa:030-02/21-01/1, Ur.broj:381-15-22-14, Klasa: 030-02/22-01/2, Ur.broj:381-15-22-2, Klasa:030-02/23-01/3, Ur.broj: 117-15-23-3; Hungary: approved by the National Scientific and Ethical Committee (ETT/TUKEB 56025-3/2014/EKU; ETT/TUKEB 44088-3/2015/EKU; IV/1885-5/2021/EKU); Lithuania: approved by Kaunas Regional Biomedical Research Ethics Committee for influenza seasons 2015-2020 (Nos P1-158200-04-476-138/2012, P2-158200-04-476-138/2012, P3-158200-04-476-138/2012, P4-158200-04-476-138/2012, P5-158200-04-476-138/2012, P6-158200-04-476-138/2012, P7-158200-04-476-138/2012), and approved by Lithuanian Bioethics Committee on 03 July 2020, and later permission extended for the study period for seasons 2020-2024, No. L-20-3/1-2; Navarre: approved by the Navarre Ethical Committee for Medical Research, Pyto2015/95 and EO2021/21; The Netherlands: the Dutch Medical Research Involving Human Subjects Act (Dutch acronym: WMO) did not apply, because only fully anonymous data were used and there were no interventions other than routine clinical care. A waiver for full medical ethical review was obtained from the Medical Ethical Committee of the University Medical Center Utrecht, reference No. WAG/om/15/034147; Portugal: approvals and/or amendments 22 May 2015, 28 September 2026, 12 December 2018, 28 April 2020, 19 January 2021, 7 June 2022 by the Ethics Committee of Instituto Nacional de Saúde Dr Ricardo Jorge, no registration number given; Romania: approved by the Ethics Committee of the Ministerul Apărării Naionale Institutul Naional de Cercetare pentru Dezvoltare Medico-Militară "Cantacuzino" for the period 2022–2023, No. CE199/2022; Spanish local sites for the I-MOVE periods (Donostia University Hospital, Virgen de las Nieves University Hospital from Granada, and Miguel Servet University Hospital from Zaragoza) obtained their ethical approvals for each season or protocol, from different ethic committees – Euskadi: PI2015104, 14 September 2015, Aragón: PI15/0123, 15 April 2015, with amendment 28 September 2016, Osakidetza: 20 November 2018, Aragón: PI19/430 01 April 2020, Andalucía: code f12f8377d78c34a25d6935eff535cd26715e2b8c, 15 April 2020).

Consent for publication

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Competing interests

The authors declare no competing interests.

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