**Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019**

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Citation style for this article:
Kissling Esther, Rose Angela, Emborg Hanne-Dorthe, Gherasim Alin, Pebody Richard, Pozo Francisco, Trebbien Ramona, Mazagatos Clara, Whitaker Heather, Valenciano Marta, European IVE group. Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019. Euro Surveill. 2019;24(8):pii=1900121. https://doi.org/10.2807/1560-7917.ES.2019.24.1900121

Influenza A(H1N1)pdm09 and A(H3N2) viruses both circulated in Europe in October 2018–January 2019. Interim results from six studies indicate that 2018/19 influenza vaccine effectiveness (VE) estimates among all ages in primary care was 32–43% against influenza A; higher against A(H1N1)pdm09 and lower against A(H3N2). Among hospitalised older adults, VE estimates were 34–38% against influenza A and slightly lower against A(H3N1)pdm09. Influenza vaccination is of continued benefit during the ongoing 2018/19 influenza season.

Seasonal influenza vaccine is recommended in all European Union (EU) countries for older people and others at increased risk of severe influenza and its complications, including those with chronic diseases [1]. In the United Kingdom (UK), incremental introduction of a universal childhood influenza vaccination programme began in 2013/14 [2]. The World Health Organization (WHO) recommendations for trivalent influenza vaccine strains for the 2018/19 northern hemisphere influenza season included an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus and a B/Colorado/06/2017-like virus from the B/Victoria lineage [3]. The early 2018/19 influenza season in Europe was characterised by both influenza A virus subtypes circulating widely. There was co-circulation in some countries, with others reporting dominance of either A(H1N1)pdm09 or A(H3N2) viruses. The season started late in most countries compared with previous seasons, with few influenza B viruses detected in the WHO European Region [4]. Since the 2008/09 season, the UK, Denmark, Spain, and several other EU countries conducting multicentre studies, have participated in I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe), a network measuring influenza vaccine effectiveness each season.

We summarise interim 2018/19 season influenza vaccine effectiveness (VE) estimates from four single-country and two multi-country studies, including both outpatient and hospital settings, in order to help guide influenza prevention and control measures for the rest of the 2018/19 season.

**Study setting**

The primary care (PC) setting studies were conducted in Denmark (DK-PC), Spain (ES-PC), the UK (UK-PC) and via the European Union (EU) I-MOVE multi-country network (EU-PC). The hospital setting (H) studies were undertaken in Denmark (DK-H) and via the EU I-MOVE multi-country network (EU-H) (Figure 1).

**Study design and estimation of vaccine effectiveness**

The methods of these six studies are described in detail elsewhere [5-9]. All six studies used a test-negative case control design, with differences between studies in how data were collected and how patients were selected (Table 1) [10]. Briefly, individuals presenting to participating healthcare settings with symptoms of influenza-like illness (ILI) (primary care settings)
or severe acute respiratory infection (hospital settings) were swabbed. These samples were then tested by reverse transcription (RT)-PCR for influenza virus. Patients with positive results were classified as cases (by influenza virus (sub)type), and those with negative results as controls.

Patients were defined as vaccinated with the 2018/19 influenza vaccine if they were vaccinated at least 14 or 15 days (depending on the study) before symptom onset. Patients were excluded if they were vaccinated fewer than 14 or 15 days before symptom onset, or if the date of vaccination was unknown.

In eight EU-PC countries, DK-PC and DK-H, all or a random sample of influenza virus-positive specimens were selected for sequencing (haemagglutinin genome segment and/or whole genome). In ES-PC, in regions not included in EU-PC, an ad hoc sample of influenza viruses was sequenced. In UK-PC, all influenza viruses with sufficient genetic material (Ct value < 31) were sequenced, as well as all viruses derived from vaccinated cases. Sequencing results in Denmark were combined for both studies (DK-PC and DK-H).

We computed VE by comparing the odds of vaccination between cases and controls ($\text{VE} = (1 - \text{odds ratio (OR)}) \times 100\%$). All studies used logistic regression to adjust their VE for measured confounding variables (Table 1). Study-specific VE was estimated overall and where possible, by age group and target population (as defined locally in the various studies and study sites) against influenza A overall, A(H1N1)pdm09 and A(H3N2). If the number of cases (or controls if lower) per parameter was less than 10, a sensitivity analysis was performed using Firth’s method of penalised logistic regression to assess small sample bias [11,12]. Where exposed case numbers were zero, exact logistic regression was used.

**Results**

From 1 October 2018 to 31 January 2019, the total number of patients included in each study for the influenza A analysis in primary care settings was: DK-PC (11,910; 2,807 cases), ES-PC (1,204; 476 cases), UK-PC (936;
### Table 1: Summary characteristics of the included influenza vaccine effectiveness studies, Europe, interim influenza season 2018/19 (n = 23,007)

| Study period | Setting | Location                  | Study design | Data source                                                                 | Age groups of study population | Case definition                                                                 | Selection of patients | Vaccine types used nationally or in the study | Variables of adjustment |
|--------------|---------|---------------------------|--------------|------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------|-----------------------|---------------------------------------------|-------------------------|
| 1 November 2018–31 January 2019 | Primary care | Denmark                    | TND          | Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register | All ages                       | Sudden onset of symptoms with fever, myalgia and respiratory symptoms          | At practitioner’s judgement | In the study among controls: 21% QIV, 79% TIV | Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (Nov-Jan) |
| 5 November 2018–18 January 2019 | Primary care | Spain: Sentinel networks in 16 of 19 regions | TND          | Sentinel physicians and laboratory | ≥ 6 months                     | EU ILI                                                                     | Systematic             | The following vaccine types are available in Spain: TIV, adjuvanted TIV, QIV | For all ages: Age (RCS), onset date (RCS), sex, chronic conditions, region; For target groups: Age (RCS), onset date (RCS), sex, region |
| 21 October 2018–23 January 2019 | Primary care | Croatia, France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain (five regions) and Sweden | TND          | Sentinel physicians and laboratory | All ages                       | EU ILI                                                                     | Systematic             | In the study among controls: 44% QIV, 29% TIV, 23% adjuvanted TIV, 1% LAIV4 | Age (modelled as RCS or age group depending on analysis), sex, presence of any chronic condition associated with influenza vaccination recommendation, onset date (RCS) and study site |
| 1 October 2018–18 January 2019 | Primary care | England, Scotland, Northern Ireland and Wales | TND          | Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register | All ages | ILL: Patient presenting in primary care with an acute respiratory illness, with physician diagnosed fever with onset in previous 7 days | At practitioner’s judgement | In the study among controls: 53% TIV, 35% adjuvanted TIV, 6% QIV and 6% unknown | Age group, sex, onset month, pilot area for child vaccination programme, surveillance scheme, risk group |
| 1 November 2018–31 January 2019 | Hospital | Denmark | TND          | Hospital charts, vaccine registers, interviews with GPs, laboratory | ≥ 65 years | SARI: Sudden onset of symptoms with fever, myalgia and respiratory symptoms among hospitalised patients | Exhaustive | In the study among controls: 18% QIV, 82% TIV | Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (November-January) |
| 5 December 2018–18 January 2019 | Hospital | 11 hospitals in: Croatia, France, Spain and Romania | TND          | TND                                                                          |                                 |                                                                                          |                       | In the study among controls: 53% TIV, 35% adjuvanted TIV, 6% QIV and 6% unknown | Age, sex, presence/number of chronic conditions, onset date (modelled as RCS or categorical depending on analysis) and study site |

DK-H: Denmark hospital study; DK-PC: Denmark primary care study; ES-PC: Spain primary care study; EU: European Union; EU-H: European hospital multicentre I-MOVE study; EU-PC: European primary care multicentre I-MOVE study; GP: general practitioner; ILI: influenza-like illness; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; LAIV4: quadrivalent live attenuated influenza vaccine; LRI: lower respiratory infection; QIV: quadrivalent inactivated influenza vaccines; RCS: restricted cubic spline; SARI: severe acute respiratory infection; TND: test-negative design; UK: United Kingdom; UK-PC: UK primary care study.

*122 of 805 physicians included in ES-PC were also included in EU-PC.

*Vaccines were egg-propagated, non-adjuvanted and administered intramuscularly unless otherwise specified.
In all studies combined, 99.5% (2,252/2,263) of cases were influenza A virus-positive. The proportion of influenza A viruses subtyped in the DK-H/DK-PC, ES-PC, EU-PC and UK-PC was ≥ 95% and in the EU-H it was 75%. Of influenza viruses subtyped, 58–60% were influenza A(H1N1)pdm09 viruses in ES-PC, EU-PC and EU-H; while this proportion was > 80% in DK-PC/DK-H and UK-PC (Figure 2).

### Influenza A overall

#### Primary care settings

In primary care settings among all ages, VE against laboratory-confirmed influenza A ranged between 32% (95% confidence interval (CI): -25 to 63) in ES-PC and 43% in UK-PC and in EU-PC (95% CI: 3 to 67 and 6 to 65, respectively). The VE against influenza A among patients aged 18–64 years ranged from 32% (95% CI: -31 to 65) in the EU-PC to 55% (95% CI: 44 to 64) in the DK-PC study. In children aged 2–17 years in UK-PC, the VE of quadrivalent live attenuated influenza vaccines (LAIV4) was 80% (95% CI: 54 to 97) (Table 2). Among target groups for influenza vaccination, VE was 59% in both ES-PC and EU-PC (95% CI: 1 to 83 and 32 to 78, respectively).

#### Hospital settings

VE against laboratory-confirmed hospitalised influenza A among all ages in DK-H was 38% (95% CI: 24 to 49) and in patients aged 65 years and older, VE was 34% (95% CI: 16 to 48) in DK-H and 38% (95% CI: 12 to 66) in EU-H.

### Influenza A(H1N1)pdm09

#### Primary care settings

In the primary care studies, VE against laboratory-confirmed influenza A(H1N1)pdm09 among all ages ranged from 45% (95% CI: 20 to 75) in ES-PC to 71% (95% CI: 38 to 86) in EU-PC.
**Table 2**

Adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza A, A(H1N1)pdm09 and A(H3N2), by age group, target group for vaccination and study, 11 European countries, interim influenza season 2018/19

| Influenza type/subtype and study site | Setting | Study population | Cases | Controls | Adjusted VE 95% CI |
|---------------------------------------|---------|------------------|-------|----------|-------------------|
| **Influenza A**                       |         |                  |       |          |                   |
|                                       |         |                  | All   | Vacc     | %     | All   | Vacc     | %     |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
| **Influenza type/subtype and study site** |         |                  |       |           |       |       |           |       |                   |
| **Influenza A**                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
| **Influenza A(H3N2)pdm09**            |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
| **Influenza A(H3N2)**                 |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
|                                       |         |                  |       |           |       |       |           |       |                   |
| CI: confidence interval; DK-PC: Denmark primary care study; DK-H: Denmark hospital study; ES-PC: Spain primary care study; EU-H: European hospital multicentre I-MOVE study; EU-PC: European primary care multicentre I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; LAIV4: quadrivalent live attenuated influenza vaccine; NC: Not calculated (percentages not shown where denominators < 60); TIV: trivalent live attenuated vaccines; UK: United Kingdom; UK-PC: UK primary care study; Vacc: vaccinated; VE: vaccine effectiveness.

aGroups targeted by seasonal influenza vaccination as defined locally in the studies and study sites.

bWhile the modal estimate of VE is 100% due to no exposed cases, the point estimates given are from exact logistic regression in Stata with adjustment for month and age where the median estimate is used from the conditional likelihood distribution.

Study sites included in EU-H analysis for influenza A: Croatia, France, Romania and Spain. For analysis against influenza A(H3N2): Romania and Spain only. For analysis against influenza A(H1N1)pdm09: Romania and Spain only.

Study sites included in EU-PC analysis for influenza A: Croatia, France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden. For analysis against influenza A(H1N1)pdm09: France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden are included. For analysis against influenza A(H3N2): France, Germany, the Netherlands, Portugal, Romania, Spain and Sweden are included.
In UK-PC, the VE of LAIV4 among children aged 2–17 years was 87% (95% CI: 4 to 100). Among patients aged 18–64 years, VE was between 39% (95% CI: -23 to 69) and 75% (95% CI: 27 to 91) in UK-PC and EU-PC, respectively. VE among those aged 65 years and older was 0% (95% CI: -61 to 38) in the DK-PC study.

Hospital settings
In hospital-based studies among patients aged 65 years and older, VE was 29% (95% CI: -75 to 71) in EU-H and 37% (95% CI: 3 to 60) in the DK-H study (Table 2). VE among those aged 18–64 years was 49% (95% CI: 13 to 70; DK-H).

Virological results
All 265 A(H1N1)pdm09 viruses sequenced belonged to clade 6B.1 (A/Michigan/45/2015) (Table 3). Among 240 viruses (91%) with information on substitutions in the haemagglutinin gene, all harboured additional substitutions of S74R (except one of the 83 sequenced in DK-H/DK-PC), S164T and I295V, and most of them also included the substitution S183P. The proportion of other substitutions identified (T120A, N129D, E235D and K302T) differed by study (Table 3). None of these substitutions involve a change in potential glycosylation sites.

Influenza A(H3N2)

Primary care and hospital settings
In primary care studies, among all ages, VE against influenza A(H3N2) ranged from -39% (95% CI: -305 to 52) in UK-PC to 24% (95% CI: -22 to 55) in DK-PC. VE among patients aged 65 years and older hospitalised for influenza A(H3N2) was 47% (95% CI: -48 to 81) in EU-H (Table 2).

Virological results
Of 163 influenza A(H3N2) viruses sequenced, 59% (n = 96) belonged to genetic clade 3C.2a1b, 33% (n = 54) to 3C.3a, 7% (n = 11) to 3C.2a3 and 1% (n = 2) to 3C.2a2 (Table 3). Both A(H3N2) viruses sequenced in UK-PC, 29/30 A(H3N2) viruses sequenced in DK-H/DK-PC, 34/52 in EU-PC and 31/79 in ES-PC belonged to clade 3C.2a1b. Of 79 A(H3N2) viruses sequenced in ES-PC, 44 (56%) belonged to clade 3C.3a.

Sensitivity analyses
Sensitivity analyses for small sample size gave similar results (absolute difference range 1–9%).

**Table 3**

| Influenza viruses characterised by clade, amino acid substitutions and study site, 11 European countries, interim influenza season 2018/19 (n = 428) |
|---|---|---|---|---|
| **Clade** | **Total influenza A(H1N1)** | | | |
| | n | % | n | % | n | % | n | % |
| | 820 | - | 272 | - | 272 | - | 152 | - |
| Sequenced | 83 | 100 | 78 | 100 | 79 | 100 | 25 | NC |
| A/Michigan/45/2015 | 6B.1 / Substitutions not available | 0 | 0 | 0 | 0 | 0 | 25 | NC |
| A/Michigan/45/2015 | 6B.1 / None of the below | 2 | 2 | 3 | 4 | 4 | 5 | NA | NA |
| A/Michigan/45/2015 | 6B.1 / T120A | 29 | 35 | 8 | 10 | 2 | 3 | NA | NA |
| A/Michigan/45/2015 | 6B.1 / N129D | 25 | 30 | 31 | 40 | 50 | 63 | NA | NA |
| A/Michigan/45/2015 | 6B.1 / E235D | 0 | 0 | 19 | 24 | 3 | 4 | NA | NA |
| A/Michigan/45/2015 | 6B.1 / K302T | 27 | 33 | 17 | 22 | 15 | 19 | NA | NA |
| A/Michigan/45/2015 | 6B.1 / T120A+K302T | 0 | 0 | 0 | 0 | 1 | 1 | NA | NA |
| **Total influenza A(H3N2)** | n = 187 | n = 186 | n = 179 | n = 34 |
| Sequenced | 30 | NC | 79 | 100 | 52 | NC | 2 | NC |
| A/Alsace/1746/2018 | 3C.2a1b | 29 | NC | 31 | 39 | 34 | NC | 2 | NC |
| A/Switzerland/8060/2017 | 3C.2a2 | 1 | NC | 0 | 0 | 1 | NC | 0 | NC |
| A/Cote d’Ivoire/544/2016 | 3C.2a3 | 0 | NC | 4 | 5 | 7 | NC | 0 | NC |
| A/England/538/2018 | 3C.3a | 0 | NC | 44 | 56 | 10 | NC | 0 | NC |

DK-PC: Denmark primary care study; DK-H: Denmark hospital study; ES-PC: Spain primary care study; EU-PC: European primary care multicentre I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; NA: not available; NC: not calculated (percentages not shown where denominators < 60); UK: United Kingdom; UK-PC: UK primary care study.

*DK-H and DK-PC are combined; sequence information is based on influenza-positive samples received for surveillance at the National Influenza Center Denmark from week 41/2018 and 03/2019.

†Specimens sequenced from Spain originate from the entire National Influenza Surveillance System in weeks 45/2018–03/2019.

‡18 specimens from ES were also included in EU-PC data (12 A/Alsace/1746/2018, 4 A/Cote d’Ivoire/544/2016, two A/Michigan/45/2015).

§At time of publishing, not all specimens from the study period were processed.

¶All include additional substitutions S74R, S164T and I295V, and most also include S183P substitutions.

‖Representative strains for the clades.
**Discussion**

Interim results from six established influenza VE studies across Europe for the 2018/19 season indicate that VE against laboratory-confirmed influenza A ranged between 32% and 43% among all ages in primary care and hospital settings and was 59% in the target groups for vaccination.

Against influenza A(H1N1)pdm09, VE point estimates among all ages ranged from 40% to 71%, and were lower among older adults in DK-PC, DK-H and EU-H, ranging from 0% to 37%. Against influenza A(H3N2), the results of three of four primary care studies suggest that the vaccine was not effective among all ages combined. The VE point estimate against A(H3N2) was higher among older adults in EU-H and among 18–64-year-olds in DK-PC (47% and 48%, respectively). The low number of A(H3N2) cases in all studies resulted in less precise VE estimates against A(H3N2) than against A(H1N1)pdm09.

The influenza A(H3N2)pdm09 VE point estimates among all ages in EU-PC, among adults in DK-PC and EU-PC and among children in the UK-PC were similar to 2018/19 interim VE estimates in Canada [13]. For all ages combined, point estimates for this subtype for ES-PC and DK-H were similar to those recently reported from the United States (US) [14]. In UK-PC, the LAIV4 VE point estimate was high against influenza A(H3N2)pdm09, although sample size was very small. This suggests that the A(H3N2)pdm09 LAIV4 vaccine virus strain change from A/Bolivia/559/2013 to A/Slovenia/2903/2015 that took place after the 2016/17 season may have improved vaccine performance against circulating strains in 2018/19. Compared with 2017/18 interim season estimates in studies where influenza A(H1N1)pdm09 VE results were available, the 2018/19 adjusted VE against influenza A(H1N1)pdm09 was similar in the 18–64 years age group in DK-PC (66% vs 60%, respectively, noting that in 2017/18 the setting in Denmark was primary care and hospital combined) and among all ages in EU-PC (71% vs 68%, respectively). VE was lower among those aged 65 years and older in DK-PC, but similar in the DK-H study.

The genetic diversity observed in the ongoing 2018/19 season did not seem to affect the VE against influenza A(H1N1)pdm09 in most groups and studies. To date, all A(H1N1)pdm09 viruses characterised in Europe were antigenically similar to the vaccine virus [15]. The lower VE among those aged 65 and older in DK-PC may be explained by small sample size, but needs further investigation.

As observed in the 2017/18 season, the 2018/19 interim primary care results suggest that VE against medically attended laboratory-confirmed influenza A(H3N2) was low or non-existent although, due to small sample size, these interim 2018/19 results need to be confirmed by the end-of-season results. End-of-season clade-specific VE results may help us understand whether regional differences in circulating clades of A(H3N2) viruses explain the difference in VE in DK-PC compared with all other primary care studies. Adaptation/alteration of the vaccine seed virus during propagation in eggs, impacting antigenicity, may have been an important explanation for low VE against influenza A(H3N2) in recent and current seasons [16].

The late start of the season resulted in small sample sizes and low precision of many VE estimates, which presents a limitation in this interim analysis. We thus conducted a sensitivity analysis to address potential small sample bias arising from this. Further limitations potentially present in all observational studies include residual confounding and bias.

Vaccination continues to be the most effective preventive measure against influenza and uptake of the 2018/19 influenza vaccines should still be promoted in countries with ongoing influenza virus circulation in line with national guidelines and recommendations. Our results further support the need for effective interventions against influenza A(H3N2) across all age groups. In the UK, the Joint Committee on Vaccination and Immunisation has recently advised the use of cell-grown influenza vaccine that will be licensed for the 2019/20 season for older children and adults in the UK [17]. In addition, given the observed non-effectiveness of the A(H3N2) component of the current vaccine in previous seasons, in settings with influenza A(H3N2) virus circulation, prophylactic and prompt therapeutic use of neuraminidase inhibitors is important to help prevent severe outcomes, irrespective of vaccination status [18].

The Global Influenza VE (GIVE) Collaboration reports on the effectiveness of influenza vaccine in previous and current influenza seasons. Interim VE results presented here were included in the February 2019 GIVE report to help inform the WHO vaccine strain selection committee meeting on 18–21 February 2019 in Beijing. For the 2019/20 northern hemisphere trivalent vaccine, this selection committee recommended to include an A/Brisbane/02/2018 (H1N1)pdm09-like virus and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) [19]. For the quadrivalent vaccine WHO recommended an additional B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). The recommendation for the A(H3N2) component will be postponed until 21 March 2019, due to changes in the proportions of genetically and antigenically diverse A(H3N2), notably an increase in clade 3C.3a in several geographic regions.

End-of-season VE and antigenic studies will provide insight into age- and study-specific variation in VE estimates. In addition, monitoring effectiveness of the 2019 southern hemisphere influenza vaccine against influenza viruses and their genetic diversity will be important to prepare for the next influenza season in the northern hemisphere.
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Acknowledgements

All study teams are very grateful to all patients, general practitioners, paediatricians, hospital teams, laboratory teams, and regional epidemiologists who have contributed to the studies.

Special thanks from the UK team to Nick Andrews and Chris Robertson for statistical advice and Maria Zambon for advice on laboratory aspects.

We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID’s EpiFlu Database used for this study. All submitters of data may be contacted directly via the GISAID website www.gisaid.org.

Conflict of interest

None declared.

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Esther Kissling: coordination I-MOVE network, study design, analysis of primary care data, interpretation of results, manuscript writing. Angela Rose: coordination I-MOVE hospital network, study design, analysis of hospital data, interpretation of results, manuscript writing. Both authors contributed equally to the study and manuscript. Hanne-Dorthe Emborg, Alin Gherasim, Richard Pebody, Ramona Trebbien, Clara Mazagatos and Heather Whitaker: coordination of their respective studies, data analysis and interpretation of results, read, contributed to and approved the final version of the manuscript. Francisco Pozo: coordinated the I-MOVE virological analysis of the primary care study, read, contributed to and approved the final version of the manuscript. European IVE group: Primary care and hospital sites at national/regional level: data collection, data validation, results interpretation, review of manuscript.

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Funding

ECDC has contributed to fund some of the study sites and the coordination of the EU-PC study. WHO-EURO has contributed to fund the EU-H study.

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