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

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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 (VE = \(1 – \text{odds ratio (OR)}\) x 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; 211 cases), EU-PC (11,910; 2,807 cases), EU/H and ES-PC (11,910; 2,807 cases), DK-PC/DK-H (11,910; 2,807 cases), and UK-PC (936; 211 cases).
<table>
<thead>
<tr>
<th>Study period</th>
<th>DK-PC</th>
<th>ES-PC</th>
<th>EU-PC</th>
<th>UK-PC</th>
<th>DK-H</th>
<th>EU-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 November 2018–</td>
<td>1 November 2018–</td>
<td>21 October 2018–</td>
<td>1 October 2018–</td>
<td>1 November 2018–</td>
<td>5 December 2018–</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>Primary care</td>
<td>Primary care</td>
<td>Primary care</td>
<td>Primary care</td>
<td>Hospital</td>
<td>Hospital</td>
</tr>
<tr>
<td>Location</td>
<td>Denmark</td>
<td>Spain: Sentinel networks in 16 of 19 regions</td>
<td>Croatia, France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain (five regions) and Sweden</td>
<td>England, Scotland, Northern Ireland and Wales</td>
<td>Denmark</td>
<td>11 hospitals in: Croatia, France, Spain and Romania</td>
</tr>
<tr>
<td>Study design</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
</tr>
<tr>
<td>Data source</td>
<td>Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register</td>
<td>Sentinel physicians and laboratory</td>
<td>Sentinel physicians and laboratory</td>
<td>Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register</td>
<td>Hospital charts, vaccine registers, interviews with GPs, laboratory</td>
<td></td>
</tr>
<tr>
<td>Age groups of study population</td>
<td>All ages</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
<td>All ages</td>
<td>All ages</td>
<td>≥ 65 years</td>
</tr>
<tr>
<td>Case definition</td>
<td>Sudden onset of symptoms with fever, myalgia and respiratory symptoms</td>
<td>EU ILI</td>
<td>EU ILI</td>
<td>ILL: Patient presenting in primary care with an acute respiratory illness, with physician diagnosed fever with onset in previous 7 days</td>
<td>EU SARI</td>
<td></td>
</tr>
<tr>
<td>Selection of patients</td>
<td>At practitioner’s judgement</td>
<td>Systematic</td>
<td>Systematic</td>
<td>At practitioner’s judgement</td>
<td>Exhaustive</td>
<td></td>
</tr>
<tr>
<td>Vaccine types used nationally or in the study</td>
<td>In the study among controls: 21% QIV, 79% TIV</td>
<td>The following vaccine types are available in Spain: TIV, adjuvanted TIV, QIV</td>
<td>In the study among controls: 44% QIV, 29% TIV, 23% adjuvanted TIV, 1% LAIV4</td>
<td>Healthy children 2–11 years of age: LAIV4; At risk children &lt;18 years of age: QIV; Adults 18–64 years of age: QIV; Adults ≥ 65 years: mainly adjuvanted TIV with some differences across UK countries.</td>
<td>In the study among controls: 18% QIV, 82% TIV</td>
<td>In the study among controls: 53% TIV, 35% adjuvanted TIV, 6% QIV and 6% unknown</td>
</tr>
<tr>
<td>Variables of adjustment</td>
<td>Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (Nov-Jan)</td>
<td>For all ages: Age (RCS), onset date (RCS), sex, chronic conditions, region; For target groups: Age (RCS), onset date (RCS), sex, region</td>
<td>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</td>
<td>Age group, sex, onset month, pilot area for child vaccination programme, surveillance scheme, risk group</td>
<td>Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (November–January)</td>
<td>Age, sex, presence/number of chronic conditions, onset date (modelled as RCS or categorical depending on analysis) and study site</td>
</tr>
</tbody>
</table>


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).

**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**

In 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

<table>
<thead>
<tr>
<th>Influenza type/subtype and study site</th>
<th>Setting</th>
<th>Study population</th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>Vacc</td>
<td>%</td>
<td>All</td>
</tr>
<tr>
<td><strong>Influenza A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>2,807</td>
<td>342</td>
<td>12</td>
<td>9,103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>1,509</td>
<td>112</td>
<td>7</td>
<td>4,298</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 65 years</td>
<td>398</td>
<td>218</td>
<td>55</td>
<td>2,115</td>
</tr>
<tr>
<td>ES-PC</td>
<td>PC</td>
<td>All ages</td>
<td>476</td>
<td>32</td>
<td>7</td>
<td>728</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target group</td>
<td>85</td>
<td>19</td>
<td>22</td>
<td>145</td>
</tr>
<tr>
<td>EU-PC</td>
<td>PC</td>
<td>All ages</td>
<td>478</td>
<td>35</td>
<td>7</td>
<td>1,601</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–17 years</td>
<td>142</td>
<td>4</td>
<td>3</td>
<td>570</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>296</td>
<td>19</td>
<td>6</td>
<td>846</td>
</tr>
<tr>
<td>UK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>177</td>
<td>31</td>
<td>18</td>
<td>819</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–17 years (LAIV4)</td>
<td>27</td>
<td>2</td>
<td>2</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–17 years (LAIV4 or TIV)</td>
<td>28</td>
<td>3</td>
<td>NC</td>
<td>123</td>
</tr>
<tr>
<td>DK-H</td>
<td>Hospital</td>
<td>All ages</td>
<td>653</td>
<td>187</td>
<td>29</td>
<td>5,867</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>272</td>
<td>46</td>
<td>17</td>
<td>1,894</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 65 years</td>
<td>297</td>
<td>138</td>
<td>46</td>
<td>3,174</td>
</tr>
<tr>
<td>EU-H</td>
<td>Hospital</td>
<td>All ages</td>
<td>67</td>
<td>30</td>
<td>45</td>
<td>231</td>
</tr>
<tr>
<td><strong>Influenza A(H1N1)pdm09</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>980</td>
<td>72</td>
<td>7</td>
<td>9,103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>573</td>
<td>32</td>
<td>6</td>
<td>4,298</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 65 years</td>
<td>72</td>
<td>38</td>
<td>53</td>
<td>2,115</td>
</tr>
<tr>
<td>ES-PC</td>
<td>PC</td>
<td>All ages</td>
<td>272</td>
<td>14</td>
<td>5</td>
<td>728</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target group</td>
<td>49</td>
<td>8</td>
<td>NC</td>
<td>145</td>
</tr>
<tr>
<td>EU-PC</td>
<td>PC</td>
<td>All ages</td>
<td>272</td>
<td>10</td>
<td>4</td>
<td>1,381</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>178</td>
<td>5</td>
<td>3</td>
<td>736</td>
</tr>
<tr>
<td>UK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>143</td>
<td>20</td>
<td>14</td>
<td>819</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–17 years (LAIV4)</td>
<td>23</td>
<td>0</td>
<td>NC</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–17 years (LAIV4 or TIV)</td>
<td>23</td>
<td>0</td>
<td>NC</td>
<td>123</td>
</tr>
<tr>
<td>DK-H</td>
<td>Hospital</td>
<td>All ages</td>
<td>111</td>
<td>16</td>
<td>14</td>
<td>440</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>110</td>
<td>17</td>
<td>15</td>
<td>1,894</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 65 years</td>
<td>85</td>
<td>38</td>
<td>45</td>
<td>3,174</td>
</tr>
<tr>
<td>EU-H</td>
<td>Hospital</td>
<td>All ages</td>
<td>28</td>
<td>13</td>
<td>NC</td>
<td>177</td>
</tr>
<tr>
<td><strong>Influenza A(H3N2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>136</td>
<td>24</td>
<td>18</td>
<td>9,103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18–64 years</td>
<td>76</td>
<td>6</td>
<td>8</td>
<td>4,298</td>
</tr>
<tr>
<td>ES-PC</td>
<td>PC</td>
<td>All ages</td>
<td>186</td>
<td>17</td>
<td>9</td>
<td>728</td>
</tr>
<tr>
<td>EU-PC</td>
<td>PC</td>
<td>All ages</td>
<td>179</td>
<td>21</td>
<td>12</td>
<td>1,437</td>
</tr>
<tr>
<td>UK-PC</td>
<td>PC</td>
<td>All ages</td>
<td>25</td>
<td>9</td>
<td>NC</td>
<td>819</td>
</tr>
<tr>
<td>EU-H</td>
<td>Hospital</td>
<td>All ages</td>
<td>20</td>
<td>9</td>
<td>NC</td>
<td>198</td>
</tr>
</tbody>
</table>

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.

groups 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 Statas 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(H1N1)pdm09: Romania and Spain only. For analysis against influenza A(H3N2): 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.

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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.

In 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).

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.2a, 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)

<table>
<thead>
<tr>
<th>Clade</th>
<th>DK-H/DK-PC</th>
<th>ES-PC</th>
<th>EU-PC</th>
<th>UK-PC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Total influenza A(H1N1)</td>
<td>n = 820</td>
<td>n = 272</td>
<td>n = 272</td>
<td>n = 152</td>
</tr>
<tr>
<td>Sequenced</td>
<td>83</td>
<td>100</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / Substitutions not available</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / None of the below</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / T120A</td>
<td>29</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / N129D</td>
<td>25</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / E235D</td>
<td>0</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / K302T</td>
<td>27</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>A/Michigan/45/2015</td>
<td>68.1 / T120A+K302T</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total influenza A(H3N2)</td>
<td>n = 187</td>
<td>n = 186</td>
<td>n = 179</td>
<td>n = 34</td>
</tr>
<tr>
<td>Sequenced</td>
<td>30</td>
<td>NC</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td>A/Alsace/1746/2018</td>
<td>3C.2a1b</td>
<td>29</td>
<td>NC</td>
<td>31</td>
</tr>
<tr>
<td>A/Switzerland/8060/2017</td>
<td>3C.2a2</td>
<td>1</td>
<td>NC</td>
<td>0</td>
</tr>
<tr>
<td>A/Cote d’Ivoire/554/2016</td>
<td>3C.2a3</td>
<td>0</td>
<td>NC</td>
<td>4</td>
</tr>
<tr>
<td>A/England/538/2018</td>
<td>3C.3a</td>
<td>0</td>
<td>NC</td>
<td>44</td>
</tr>
</tbody>
</table>

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.


18 specimens from ES were also included in EU-PC data (12 A/Alsace/1746/2018, 4 A/Cote d’Ivoire/554/2016, two A/Michigan/45/2015).

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

Include additional substitutions S74R, S164T and L295V, 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(H1N1)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), and 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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Conflict of interest

None declared.

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