Adjusted early estimates of the 2013/14 influenza vaccine effectiveness (VE) in Spain for all age groups was 35% (95% CI: –9 to 62), 33% (95% CI: –33 to 67) and 28% (95% CI: –33 to 61) against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses, respectively. For the population targeted for vaccination, the adjusted VE was 44% (95% CI: –11 to 72), 36% (95% CI: –64 to 75) and 42% (95% CI: –29 to 74), respectively. These preliminary results in Spain suggest a suboptimal protective effect of the vaccine against circulating influenza viruses.

Early assessment of influenza vaccine effectiveness in Spain at national level

In the current influenza season, Spain has experienced a relatively early influenza epidemic compared with other European countries [1]. We present here nationwide early estimates of the effectiveness of the 2013/14 seasonal trivalent influenza vaccine in Spain in preventing medically attended laboratory-confirmed influenza-like illness (ILI) infections, by virus type and subtype in all age groups and in the population targeted for vaccination, during the time when the influenza epidemic in Spain was increasing (9 December 2013 to 26 January 2014). Our early estimates suggest a suboptimal protective effect of the vaccine in preventing medically attended A(H1N1)pdm09 and A(H3N2) laboratory-confirmed influenza.

Background

Since 2008, Spain has been providing interim influenza vaccine effectiveness (VE) results using the cycEVA study – casos y controles para la Efectividad de la Vacuna Antigripal [cases and controls for monitoring influenza vaccine effectiveness], the Spanish component of the I-MOVE (Monitoring Vaccine Effectiveness in Europe) network [2,3]. The agreement between interim and final influenza VE estimates supports the use of interim assessments as a proxy for final VE results [4,5].

In February 2013, the Vaccine Strain Selection Committee of the World Health Organization (WHO) formally received for the first time a compilation of preliminary influenza VE estimates for the 2012/13 season from Europe, Canada and the United States (US) [6]. Interim estimates 2013/14 and final 2013 estimates of influenza VE from countries in the northern and southern hemisphere, respectively, together with results of the characterisation of influenza viruses and vaccine serological studies, have contributed again this year to the decision of the Committee in February on the recommended composition of influenza vaccines for the forthcoming (2014/15) northern hemisphere influenza season [7]. Interim 2013/14 VE estimates have shown substantial protection against laboratory-confirmed A(H1N1)pdm09 illness in Canada and US [8,9] but suboptimal protection against this subtype in the Spanish Navarre region [10].

The results presented here at national level – the first at national level in Europe, in a scenario of multiple Spanish regions with probable differences in some epidemiological features or circulating viruses – might
## Table 1

Reference haemagglutinin sequences obtained from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID) and used in phylogenetic analysis, Spanish Influenza Surveillance System, week 40 2013–week 4 2014 (30 September 2013–26 January 2014)

<table>
<thead>
<tr>
<th>Segment ID</th>
<th>Segment</th>
<th>Country</th>
<th>Collection date</th>
<th>Isolate name</th>
<th>Originating laboratory</th>
<th>Submitting laboratory</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI353304</td>
<td>HA</td>
<td>Australia</td>
<td>2007-02-06</td>
<td>A/Brisbane/10/2007</td>
<td>Queensland Health Scientific Services</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza</td>
<td>Iannello, P; Komadina, N</td>
</tr>
<tr>
<td>EPI182941</td>
<td>HA</td>
<td>Australia</td>
<td>2009-04-07</td>
<td>A/Perth/16/2009</td>
<td>Pathwest QE II Medical Centre</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza</td>
<td>Deng, Y-M; Iannello, P; Erneste, J; Komadina, N</td>
</tr>
<tr>
<td>EPI272062</td>
<td>HA</td>
<td>Australia</td>
<td>2009-06-02</td>
<td>A/Victoria/208/2009</td>
<td>Victorian Infectious Diseases Reference Laboratory</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza</td>
<td>Deng, Y-M; Iannello, P; Caldwell, N; Leang, S-K; Komadina, N</td>
</tr>
<tr>
<td>EPI335923</td>
<td>HA</td>
<td>United States</td>
<td>2010-12-30</td>
<td>A/Iowa/19/2010</td>
<td>Iowa State Hygienic Laboratory</td>
<td>Centers for Disease Control and Prevention</td>
<td>Garten, R</td>
</tr>
<tr>
<td>EPI279881</td>
<td>HA</td>
<td>Hong Kong (SAR)</td>
<td>2010-07-05</td>
<td>A/Hong Kong/2121/2010</td>
<td>Government Virus Unit</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
<tr>
<td>EPI278805</td>
<td>HA</td>
<td>United States</td>
<td>2010-07-13</td>
<td>A/Alabama/05/2010</td>
<td>U.S. Air Force School of Aerospace Medicine</td>
<td>Centers for Disease Control and Prevention</td>
<td>Garten, R</td>
</tr>
<tr>
<td>EPI18272</td>
<td>HA</td>
<td>Sweden</td>
<td>2011-02-21</td>
<td>A/Stockholm/18/2011</td>
<td>Swedish Institute for Infectious Disease Control</td>
<td>Swedish Institute for Infectious Disease Control</td>
<td>Brytting, M</td>
</tr>
<tr>
<td>EPI358885</td>
<td>HA</td>
<td>Greece</td>
<td>2012-02-01</td>
<td>A/Athens/112/2012</td>
<td>Hellenic Pasteur Institute</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
<tr>
<td>EPI450687</td>
<td>HA</td>
<td>Madagascar</td>
<td>2012-06-01</td>
<td>A/Mahajanga/3628/2012</td>
<td>Institut Pasteur de Madagascar</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
<tr>
<td>EPI466963</td>
<td>HA</td>
<td>Madagascar</td>
<td>2013-02-25</td>
<td>A/Maevatanana/563/2013</td>
<td>Institut Pasteur de Madagascar</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
<tr>
<td>EPI349103</td>
<td>HA</td>
<td>Australia</td>
<td>2011-10-24</td>
<td>A/Victoria/361/2011</td>
<td>Melbourne Pathology</td>
<td>WHO Collaborating Centre for Reference and Research on Influenza</td>
<td>Deng, Y-M; Caldwell, N; Iannello, P; Komadina, N</td>
</tr>
<tr>
<td>EPI377999</td>
<td>HA</td>
<td>United States</td>
<td>2012-04-15</td>
<td>A/Texas/50/2012</td>
<td>Texas Department of State Health Services-Laboratory Services</td>
<td>Centers for Disease Control and Prevention</td>
<td>Garten, R</td>
</tr>
<tr>
<td>EPI360950</td>
<td>HA</td>
<td>Germany</td>
<td>2011-07-03</td>
<td>A/Berlin/93/2011</td>
<td>National Institute for Medical Research</td>
<td>Centers for Disease Control and Prevention</td>
<td>Garten, R</td>
</tr>
<tr>
<td>EPI397362</td>
<td>HA</td>
<td>United States</td>
<td>2012-07-09</td>
<td>A/Hawaii/22/2012</td>
<td>State of Hawaii Department of Health</td>
<td>Centers for Disease Control and Prevention</td>
<td>Garten, R</td>
</tr>
<tr>
<td>EPI467994</td>
<td>HA</td>
<td>Ireland</td>
<td>2013-04-02</td>
<td>A/Ireland/28390/2013</td>
<td>National Virus Reference Laboratory of Ireland</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
<tr>
<td>EPI460558</td>
<td>HA</td>
<td>Russian Federation</td>
<td>2013-03-12</td>
<td>A/Samara/73/2013</td>
<td>WHO National Influenza Centre</td>
<td>National Institute for Medical Research</td>
<td>Gregory, V</td>
</tr>
</tbody>
</table>

We gratefully acknowledge the authors, originating and submitting laboratories of the sequences, other than those coming from our surveillance network, retrieved from GISAID’s EpiFlu database.
add substantial value to the previous estimates from Navarre regarding the suboptimal protective effect of the vaccine. By sharing these results with the scientific community, we are providing evidence that will help to fill the current gaps in knowledge of the relationship between antigenic match and the reported effectiveness of the vaccine.

**Estimating vaccine effectiveness and determining virus type**

In the 2013/14 influenza season, six of the 17 regional networks belonging to the Spanish Influenza Sentinel Surveillance System participated in the cycEVA study. The methods used were similar to those carried out in previous seasons in the cycEVA study [11].

Influenza cases were ILI patients who tested positive for influenza virus using real-time reverse-transcription polymerase chain reaction or virus culture. Controls were ILI patients with swabs testing negative for any type of influenza virus.

The WHO National Influenza Centre in Madrid selected a subset of influenza isolates from the entire sentinel surveillance system for genetic characterisation by sequencing the amplified HA1 fragment of the viral haemagglutinin gene. Isolates were selected in order to be as representative as possible of viruses circulating in all Spanish regions. Thus they included viruses collected in every phase of the influenza season (beginning, epidemic peak and end of the season). They were also selected to include all ages, irrespective of the vaccination status of the patients. Phylogenetic analysis and molecular evolutionary analyses of the HA1 sequences was conducted using MEGA version 5 [12] in order to characterise the influenza A strains. Reference haemagglutinin nucleotide sequences were obtained from the Global Initiative on Sharing Avian Influenza Data (GISAID) [13] (Table 1).

We used logistic regression to calculate influenza VE from week 50 (starting 9 December) 2013 to week 4 (starting 26 January) 2014, including in the model potential confounding factors and restricting the analysis to those swabbed within seven days of symptom onset. In a sensitivity analysis, we calculated influenza VE in the population targeted for vaccination (individuals over six months old with chronic conditions, people with risk factors (pregnancy, in women aged 15–44 years, or morbid obesity (body mass index ≥40 kg/m²), people aged over 59 years (over 64 years in some regions), healthcare workers and caregivers).
Table 2
Characteristics of laboratory-confirmed cases with influenza A(H1N1)pdm09 or A(H3N2) viruses and test-negative controls, cycEVA study, Spain, week 50 2013–week 4 2014 (9 December 2013–26 January 2014) (n=601)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Test-negative controls, n=229a</th>
<th>Influenza A(H1N1)pdm09 cases, n=184a</th>
<th>P valueb,c</th>
<th>Influenza A(H3N2) cases, n=188a</th>
<th>P valuec,d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number/total number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>22/229 (9.6)</td>
<td>7/184 (3.8)</td>
<td>0.005</td>
<td></td>
<td>0.617</td>
</tr>
<tr>
<td>5–14</td>
<td>30/229 (13.1)</td>
<td>30/184 (16.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–64</td>
<td>153/229 (66.8)</td>
<td>140/184 (76.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>24/229 (10.5)</td>
<td>7/184 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>36 (0–92)</td>
<td>37 (1–80)</td>
<td>0.868</td>
<td>37 (0–89)</td>
<td>0.778</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>121/229 (52.8)</td>
<td>102/184 (55.4)</td>
<td>0.599</td>
<td>94/188 (50.0)</td>
<td>0.564</td>
</tr>
<tr>
<td>Any chronic condition reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50/228 (21.9)</td>
<td>32/184 (17.4)</td>
<td>0.251</td>
<td>47/187 (25.1)</td>
<td>0.443</td>
</tr>
<tr>
<td>Any risk factor reportedg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/211 (2.8)</td>
<td>5/184 (2.7)</td>
<td>0.947</td>
<td>5/165 (3.0)</td>
<td>0.915</td>
</tr>
<tr>
<td>Any hospitalisation for chronic conditions in previous year</td>
<td>0/229 (0)</td>
<td>3/184 (1.6)</td>
<td>0.052</td>
<td>0/188 (0)</td>
<td>0.100</td>
</tr>
<tr>
<td>Median number of visits to a GP or pediatrician in previous year per patient (range)</td>
<td>3 (0–44)</td>
<td>3 (0–36)</td>
<td>0.450</td>
<td>3 (0–27)</td>
<td>0.775</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38/227 (16.7)</td>
<td>23/184 (12.5)</td>
<td>0.229</td>
<td>24/186 (12.9)</td>
<td>0.277</td>
</tr>
<tr>
<td>Interval between symptom onset and swabbing less than 4 days</td>
<td>223/229 (97.4)</td>
<td>178/184 (96.7)</td>
<td>0.700</td>
<td>184/188 (97.9)</td>
<td>0.744</td>
</tr>
<tr>
<td>Population targeted for vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78/218 (35.8)</td>
<td>43/184 (23.4)</td>
<td>0.027</td>
<td>66/172 (38.4)</td>
<td>0.598</td>
</tr>
</tbody>
</table>

**Vaccination status**

<table>
<thead>
<tr>
<th></th>
<th>Influenza A(H1N1)pdm09 cases, n=184a</th>
<th>Influenza A(H3N2) cases, n=188a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages received seasonal 2013/14 vaccinea</td>
<td>38/229 (16.6)</td>
<td>30/188 (16.0)</td>
</tr>
<tr>
<td>Targeted for vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received seasonal 2013/14 vaccinea</td>
<td>28/78 (35.9)</td>
<td>17/66 (25.8)</td>
</tr>
</tbody>
</table>

**Early national vaccine effectiveness estimates**

**Description of the 2013/14 influenza season in Spain**

The 2013/14 influenza season in Spain started in week 1 (30 December 2013–5 January 2014) and reached the epidemic peak in week 4 (20–26 January 2014) at both the national level and in the six regions participating in the cycEVA study [14]. It was a medium-intensity influenza season, clearly dominated by mixed circulation of influenza A viruses: 61% (571/929) A(H1N1)pdm09 and 39% (358/929) A(H3N2) influenza [14].

**Participants’ characteristics**

Among the 217 participating sentinel physicians in the study, 167 (77%) recruited at least one ILI patient. Of the 687 ILI patients recruited, 202 (29%) belonged to the population targeted for influenza vaccination. After excluding 15 patients swabbed more than seven days...
after symptom onset, 674 ILI patients were included in the study, comprising 445 influenza cases – 188 with influenza A(H3N2) virus, 184 A(H1N1)pdm09, 71 influenza A not subtyped and two with influenza B virus – and 229 test-negative controls (Figure 1).

The percentage of the population targeted for vaccination was higher in the controls (35.8%, 78/218) than in the A(H1N1)pdm09 cases (23.4%, 43/184) (Table 2). Vaccine coverage with the 2013/14 influenza vaccine was not statistically different among controls and A(H1N1)pdm09 or A(H3N2) cases, in all age groups and among the population targeted for vaccination. The majority of cases (96.7–97.9%, 178/184–184/188) and controls (97.4%, 223/229) were swabbed less than four days after symptom onset.

Of the 89 people vaccinated, there were 54 vaccine failures: 30 were positive for influenza A(H3N2) virus, 21 for influenza A(H1N1)pdm09 virus and three with an unknown influenza virus. Of the 54 vaccine failures, 30 were cases belonging to the target population for vaccination.

Vaccine effectiveness estimates

The adjusted influenza VE for all age groups was 35% (95% CI: −9 to 62), 33% (95% CI: −33 to 67) and 28% (95% CI: −33 to 61) against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses, respectively (Table 3).

Among the population targeted for vaccination, the adjusted influenza VE against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses was 44% (95% CI: −11 to 72), 36% (95% CI: −64 to 75) and 42% (95% CI: −29 to 74), respectively (Table 3).

Genetic analysis of selected isolates

Sequence analysis of the amplified HA1 genome fragments showed that all 93 influenza A(H1N1)pdm09 viruses studied clustered into the group 6B [15] represented by A/Norway/2417/2013 and defined by D97N, K163Q, S185T, S203T, A256T and K283E amino acid mutations compared with the vaccine virus A/California/07/2009.

Regarding influenza A(H3N2) virus, all 61 viruses studied clustered into the group 3C [15] which includes the A/Texas/50/2012 vaccine virus strain, but harboured some amino acid changes that make it possible to differentiate them into two subsets (named 3C.2 and 3C.3) (representative isolates are shown in Figure 2, including viruses collected in past seasons for a better understand the genetic drift of influenza A viruses). Six of the 61 viruses clustered within subgroup 3C.2 represented by A/Ireland/M28390/2013, defined by the HA1 amino acid substitution N128T. The remaining 55/61 viruses (90%) clustered within the subgroup 3C.3 represented by A/Samara/73/2013 and defined by N128A and R142G amino acid substitutions. Interestingly, we could differentiate 23 viruses within the 3C.3 subgroup with an additional L157S change, most of them (20 of 23) harbouring a second N122D mutation. Another subset of six viruses harbouring the K160R amino acid substitution could be identified within the 3C.3 subgroup. Changes in influenza A(H3N2) viruses were referred to the A/Texas/50/2012 vaccine virus strain.

| Table 3 |

Crude and adjusted seasonal vaccine effectiveness estimates against laboratory-confirmed influenza by virus type/subtype, overall and among the target population for influenza vaccination, cycEVA study, Spain, week 50 2013–week 4 2014 (9 December 2013–26 January 2014)

<table>
<thead>
<tr>
<th>Population included</th>
<th>All influenza viruses</th>
<th>Influenza A(H1N1)pdm09</th>
<th>Influenza A(H3N2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients for the analysis: cases + controls</td>
<td>674</td>
<td>413</td>
<td>417</td>
</tr>
<tr>
<td>Number of cases/controls</td>
<td>445/229</td>
<td>184/229</td>
<td>188/229</td>
</tr>
<tr>
<td>Number of vaccinated cases/vaccinated controls</td>
<td>53/38</td>
<td>21/38</td>
<td>30/38</td>
</tr>
<tr>
<td>Crude VE % (95% CI)</td>
<td>32 (−7 to 56)</td>
<td>35 (−15 to 63)</td>
<td>5 (−61 to 43)</td>
</tr>
<tr>
<td>Adjusted VE % (95% CI)</td>
<td>35 (−9 to 62)</td>
<td>33 (−33 to 67)</td>
<td>28 (−33 to 61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population targeted for vaccination</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients for the analysis: cases + controls</td>
<td>299</td>
<td>121</td>
<td>144</td>
</tr>
<tr>
<td>Number of cases/controls</td>
<td>121/78</td>
<td>43/78</td>
<td>66/78</td>
</tr>
<tr>
<td>Number of vaccinated cases/vaccinated controls</td>
<td>30/27</td>
<td>12/27</td>
<td>17/27</td>
</tr>
<tr>
<td>Crude VE % (95% CI)</td>
<td>38 (−16 to 67)</td>
<td>27 (−65 to 98)</td>
<td>34 (−35 to 68)</td>
</tr>
<tr>
<td>Adjusted VE % (95% CI)</td>
<td>44 (−11 to 72)</td>
<td>36 (−64 to 75)</td>
<td>42 (−29 to 74)</td>
</tr>
</tbody>
</table>

CI: confidence interval; VE: vaccine effectiveness.

* Adjusted for age (age groups adjusted for: 0–4, 5–14, 15–64 and ≥65 years), sex, severity, number of general practitioner visits, smoking history (had ever smoked), chronic conditions, pregnancy (in women aged 15–44 years), morbid obesity (body mass index ≥40 kg/m²) and week of swabbing.
Figure 2
Phylogenetic tree showing genetic differences in HA1 fragment of the haemagglutinin of influenza A(H3N2) circulating viruses, Spanish Influenza Surveillance System, Spain, week 40 2013–week 4 2014 (30 September 2013–26 January 2014)

Phylogenetic relationships were inferred using the MEGA5 programme applying the neighbor-joining method and the Kimura 2-parameter model [12]. Representative isolates are shown, including viruses collected in past seasons to illustrate genetic drift. Viruses in bold are representative of groups 3C.1, 3C.2 and 3C.3, according to the European Centre for Disease Prevention and Control's Influenza virus characterisation [15].

A / Navarra / 221/ 2014
A / Navarra / 14229/ 2013
A / Navarra / 219/ 2014
A / Navarra / 218/ 2014
A / PaisVasco / 262/ 2014
A / Navarra / 14222/ 2013
A / Navarra / 14228/ 2013
A / Navarra / 14222/ 2013
A / PaisVasco / 261/ 2014
A / Navarra / 14222/ 2013
A / Extremadura / 246/ 2014
A / Navarra / 14224/ 2013

A / Navarra / 14227/ 2013
A / PaisVasco / 14222/ 2013
A / Navarra / 14224/ 2013

A / Navarra / 14228/ 2013
A / Navarra / 14222/ 2013
A / Extremadura / 246/ 2014
A / Navarra / 14224/ 2013

A / Navarra / 850/ 2013
A / Navarra / 14222/ 2013
A / Navarra / 14228/ 2013
A / Navarra / 14222/ 2013
A / Extremadura / 246/ 2014
A / Navarra / 14224/ 2013

A / Balneario / 235/ 2014
A / PaisVasco / 1496/ 2013
A / PaisVasco / 1496/ 2013
A / PaisVasco / 1496/ 2013
A / PaisVasco / 1496/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Castillalamancha / 55/ 2014
A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Casillasalamanca / 55/ 2014
A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Casillasalamanca / 55/ 2014
A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
A / Extremadura / 341/ 2014
A / PaisVasco / 1493/ 2013

A / Navarro / 14224/ 2013
A / Navarro / 14228/ 2013
A / Navarro / 14222/ 2013
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Discussion

Our interim point estimate in preventing A(H1N1)pdm09 infections was 33% in a 2013/14 season with circulating A(H1N1)pdm09 strains antigenically similar and genetically well conserved at the European level, as of week 4/2014 [15,16]. Suboptimal protective effects against well-conserved A(H3N2)pdm09 virus were previously described in Europe during the 2011/12 season by the I-MOVE network [17]. In Spain, during the 2010/11 season, early VE estimates against well-matched A(H1N1)pdm09 virus were also found to be lower than 50% (49%; 95% CI: 3 to 73) [2], which were highly consistent with the final estimates, 46% (95% CI: 0 to 72) [18]. Estimates recently published by Canada and the US for the 2013/14 season [8,9] against A(H1N1)pdm09 were higher than our results. A higher protective effect of the vaccine against A(H1N1)pdm09 in North America compared with Spain could be due to different characteristics of the circulating A(H1N1)pdm09 viruses: most of the viruses analysed were shown to be antigenically similar to the vaccine strain in Canada and the US. In Spain, antigenic tests for A(H1N1)pdm09 virus are unfortunately not yet available. In addition, in light of the positive effect of previous influenza vaccination described in Canada [19] and Spain [18], a higher proportion of the population previously vaccinated with the 2009 monovalent pandemic vaccine in Canada (about 40%) [8] compared with that in Spain (10%) [18,20] could partly explain the higher VE estimates observed in Canada. The use of different types of influenza vaccine could also contribute to the differences between the results of both studies. However, our results were in line (VE below 50%) with those recently published by the Navarre region [10], a Spanish region that also participates in the cycEVA study and I-MOVE network. In the Navarre study, patients recruited in primary healthcare and in hospitals were included, giving similarly low influenza VE estimates in both settings. These observations were in accordance with the evolution of the influenza epidemic in Spain this season: a considerably higher number of severe hospitalised laboratory-confirmed cases were seen than in the two previous seasons. Of these cases, 40% had received the seasonal influenza vaccine [13]. The reasons behind these highly variable estimates of VE are still unclear.

Subtype-specific estimates of VE for influenza A(H3N2) were also in the lower range of VE points described in previous seasons (range: 25–60% [11,21-23]), with adjusted estimates of 28% and 42% for all age groups and population targeted for vaccination, respectively. Reduced protection from influenza A(H3) infection has been described in previous seasons worldwide, including in Spain and the rest of Europe during the 2011/12 season, when A(H3) last circulated as the predominant virus, but was poorly matched to the vaccine [11,23]. The importance of the amino acid changes we describe in the circulating A(H3N2) virus in Spain will be studied at the end of the season once the haemagglutination inhibition assays have been carried out. However, it is important to highlight that the L157S and N122D mutations identified in the HA1 antigenic sites B and A, respectively, of A(H3N2) viruses: this could indicate a suboptimal protective effect of the current vaccine against A(H3N2) virus in Spain.

For the 2014/15 northern hemisphere influenza season, WHO has recommended the inclusion of the same strains included in the current seasonal influenza vaccine [24]. Final estimates in Spain with a larger sample size will allow us to confirm the extent of the protective value of the 2013/14 influenza vaccine in Spain and could give an indication of what could be expected in other countries in the northern hemisphere.

Although VE estimates are subject to change over time, some studies have demonstrated agreement between interim and final influenza VE estimates, with early estimates within five to seven percentage points of final estimates [5,22]. Using the cycEVA study, the early [2,3] and final estimates [11,18] of the influenza VE in the 2010/11 and 2011/12 seasons in Spain have been similar.

The main limitation of our study was the sample size, which makes estimates for virus subtypes imprecise; therefore, final estimates should be obtained at the end of the influenza season.

Early estimates of influenza VE can help to guide health authorities in influenza prevention and provide useful information for the WHO strain selection process. Future influenza VE studies worldwide are necessary to gain more knowledge about which virus amino acid changes could be influencing the protective effect of the current influenza vaccines. Although our results indicate the protection against A(H1N1)pdm09 and A(H3N2) viruses was suboptimal, the VE was higher among those at risk of severe influenza complications, underlying the importance of annual influenza vaccination. The suboptimal protective effect of the vaccine should also lead to a clear public health message underlying the importance of early antiviral treatment for patients at high risk of influenza complications, and the adoption of non-pharmacological preventive measures to avoid influenza infection.

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Conflict of interest

None declared.

Authors’ contributions

Silvia Jiménez-Jorge and Amparo Larrauri designed the study. Silvia Jiménez-Jorge wrote the first draft of the manuscript and undertook the statistical analysis. Silvia Jiménez-Jorge, Salvador de Mateo and Amparo Larrauri participated in data analysis, writing and interpretation of the results. Francisco Pozo and Inmaculada Casas were responsible for the virus characterisation and contributed with the interpretation of the virological data. All authors participated in the interpretation of the data, contributed to the revision of the draft manuscript and approved the final version.

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