MINISTERIO
DE CIENCIA, INNOVACIÓN
Y UNIVERSIDADES

Centro Nacional de Epidemiología

# Test-negative case control design to estimate the Influenza Vaccine Effectiveness (IVE) against mild forms of influenza, confirmed in primary care in Spain

## (the cycEVA study, season 2018-19)

Final report – June 2019

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# 1 Background

For the 2018-19 influenza season in Spain was used almost exclusively the trivalent influenza vaccine (TIV), containing the strains A/Michigan/45/2015 (H1N1)pdm09, A/Singapore/INFIMH-16-0019/2016 (H3N2) and B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage (Victoria lineage). The following TIV brands were available on the market in Spain: Chiroflu-Agripal, Chiromas-Fluad, Influvac, Vaxigrip, Mutagrip and Afluria. Additionally, two quadrivalent vaccine brands (including an additional B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)), were also available: Vaxigrip Tetra and Fluarix Tetra (5,7% and 1% of the total influenza vaccines in Spain, respectively).

The influenza epidemic began in the first week of 2019, when the Influenza-like illness (ILI) incidence crossed the pre-established threshold for the 2018-19 season (56 ILI/100.000 population). The epidemic peak was reached in the fourth week of 2019 (241 ILI cases/100.000 pop.) and the epidemic ended when the ILI incidence decreased to pre-epidemic levels in the week 10/2019. The cycEVA cases and controls recruitment began in the week 45/2018.

The season was characterized by the co-circulation of influenza A(H3N2) and A(H1N1)pdm09. There was a balanced contribution of the two subtypes from the beginning until the end of the 2018-19 season. For the entire season, between weeks 40/2018 and 20/2019, within the Spanish Influenza Sentinel Surveillance System (SISSS), 2562 sentinel influenza detections were notified, of which 99,7% were type A. Among these, 1355 were subtype A(H3N2) (55,3%) and 1096 subtype A(H1N1)pdm09 (44,7%).

Based on the genetic and antigenic studies, the National Centre of Microbiology, characterized 756 influenza virus of which 586 A(H3N2) and 203 A(H1N1)pdm09. Among the A(H3N2) viruses, 256 belonged to the 3C.2a1b clade, represented by A/Alsace/1746/2018, 320 belonged to the 3C.3a clade, represented by A/England/538/2018, three to the 3C.2a2 clade represented by A/Switzerland/8060/2017 and six to the 3C.2a3 clade represented by A/Cote d'Ivoire/544/2016). All the 203 A(H1N1)pdm09 strains characterized were similar to the 2018-19 vaccine strain A/Michigan/45/2015 (H1N1)pdm09.

The susceptibility analysis to the neuraminidase inhibiting antivirals, none of the 27 A(H3N2) strains, nor the 43 A(H1N1)pdm09 were found resistant to Oseltamivir or Zanamivir.

# 2 Objectives

The 2018-19 cycEVA study objectives were:

- To estimate the IVE against confirmed A(H3N2) and A(H1N1)pdm09 influenza in the cycEVA study, for all ages patients, by age-groups and in target population for influenza vaccination
- To estimate the IVE against specific A(H3N2) clades

# 3 Methods

We used a test-negative case-control design, considering as cases, ILI patients attending a general practitioners (GP) within the cycEVA sentinel network and having a PCR/culture positive test for Influenza A(H3N2) or A(H1N1)pdm09. The controls were negative for any influenza virus. ILI patients were systematically select to be swabbed for influenza virus presence: the first two patients below 65 years of age attending the GP each week and all the

elderly patients (aged above 64); recruitment period spanned from week 45/2018 to 15/2019. The last confirmed case was notified in the week 13/2019, thus this week was considered as the final week of the study and the controls recruited in the weeks 14 and 15/2019 were not included in the final analysis. Analysis was restricted to the patients swabbed less than eight days since symptoms onset. Patients were considered as vaccinated if having received the 2018-19 influenza vaccine at least 15 days before the onset of symptoms; those without vaccination date or with less than 15 days until symptom´s onset were eliminated from the analysis.

We calculated the IVE against the confirmed A(H3N2) and A(H1N1)pdm09 influenza as 1-OR of vaccination in cases and controls using a logistic regression model and adjusting for possible confounders such as age (restricted cubic splines – RCS), onset of symptoms (RCS), sex, chronic condition and sentinel network.

We have used a random selection strategy to identify influenza strains to be genetically characterized. For the 2018-19 season, we randomly selected influenza A(H3N2) strains meeting the eligible criteria: swab less than eight days, having a known vaccination status or having received the vaccine at least 15 days before onset of symptoms and meeting the EU-ILI case definition.

# 4 Results

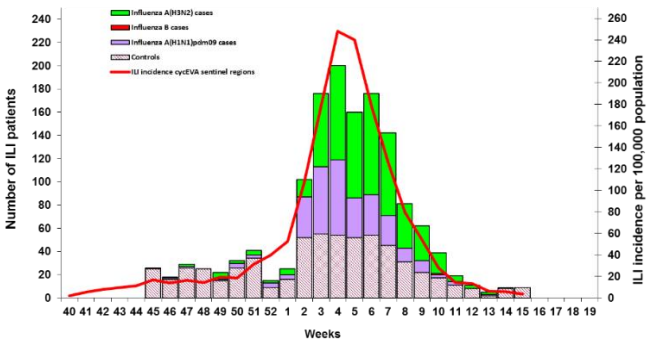
## 4.1 Participating GP's and population under surveillance

For the eleventh edition of the cycEVA study, five sentinel networks participated: Baleares Islands, Madrid, Navarra, La Rioja and Melilla. The study relies on the participation of 236 sentinel GP´s and a catchment population of 330.000 population.

## 4.2 Patients recruitment

Overall, we recruited 1442 ILI patients during the study period (Fig. 1). We excluded 32 patients (12 patients with missing vaccination status, 6 patients with swab interval higher than seven days and 14 controls for being notified in the weeks after the confirmation of the last case) (fig.2). In the final analysis we included 588 controls and 822 cases of which, 509 (62%) were confirmed with influenza A(H3N2) and 298 (36.9%) with A(H1N1)pdm09 (Table1).

*Figure 1. Weekly distribution of cases and controls during the 2018-19 influenza season in Spain (cycEVA study, weeks 45/2018-15/2019)*



Overall, the negative controls were significantly older than A(H3N2) cases and less vaccinated with the 2018-19 influenza vaccine. No other differences were registered between controls and A(H3N2) cases in terms of sex or chronic condition. Compared to the A(H1N1)pdm09 cases, the controls were younger and more vaccinated, however, none of these difference were statistically significant (Table 1).

*Table1. Cases and controls characteristics for the 2018-19 influenza season in Spain (cycEVA study, weeks 45/2018 – 15/2019)*

| | Negative Controls (%) | A(H3N2) Cases (%) | A(H1N1)pdm09 (%) |
|---|---|---|---|
| **Median age (years)** | 37 | 32* | 41 |
| **All patients** | 588 | 509 | 298 |
| 0-14 years | 127/588 (21.6) | 173/509 (33.4) | 61/298 (20.5) |
| 15-64 years | 405/588 (68.9) | 279/509 (54.8) | 211/298 (70.8) |
| >64 years | 56/588 (9.5) | 57/509 (11.2) | 26/298 (8.7) |
| **Sex** | | | |
| Male | 282/588 (48.0) | 226/509 (44.4) | 139/298 (46.6) |
| Female | 306/588 (52.0) | 283/509 (55.6) | 159/298 (53,4) |
| | | | |
| **Any chronic condition** | 107/588 (18.2) | 102/509 (20.0) | 62/298 (20.8) |
| **Interval onset of symptoms - swab ≤ 4 days** | 502/588 (98.6) | 566/509 (96.3) | 291/298 (97,7) |
| | | | |
| **Vaccination in current season 2018/19** | | | |
| All patients | 74/588 (12.6) | 94/59 (18.5) | 25/298 (8.4) |
| 0-14 years | 10/127 (7.9) | 15/173 (8.7) | 4/61 (6.6) |
| 15-64 years | 29/405 (7.1) | 44/279 (15.8) | 11/211 (5.2) |
| >64 years | 35/56 (62,5) | 35/57 (61.4) | 10/26 (38.5) |

*p<0.05

### 4.3 The influenza vaccine effectiveness results

Against A(H3N2) the IVE was -26% (95%IC: -92, 18) for all ages patients. By age groups the IVE was 66% (95%IC: 4, 88), -87% (95%IC: -225; -7) and 17% (95%IC: -157; 73) for children under 15, young adults (15-64) and elderly (>64 years), respectively. For the target group for vaccination the IVE was -4% (95%IC:-83; 41) (Table 1).

Against mild influenza A(H1N1)pdm09, the overall IVE was 50% (95%IC: 11; 71); by age-groups the IVE was 69% (95%IC: -46; 83), 33% (95%IC: -38; 67) y 56% (95%IC: -106; 90) for children under 15, young adults and elderly. For the target group for vaccination, the IVE was 62% (95%IC: 20; 82) (Table 2).

*Table 2. IVE against mild confirmed for all ages, by ages groups and population targeted for vaccination, 2018-19 influenza season, Spain (cycEVA study, weeks 45/2018-15/2019)*

| | A(H3N2) | A(H1N1)pdm09[1] |
|---|---|---|
| **All ages** | | |
| Total patients | 1089 | 886 |
| Vaccinated/Total cases (%) | 94/509 (18,5) | 25/298 (8,4) |
| Vaccinated /Total controls (%) | 74/580 (12,8) | 73/557 (13,1) |
| IVE crude (% (95%CI)) | -55 (-115; -11) | 39 (2, 62) |
| **IVE adjusted % (95% CI) [1]** | **-26 (-92; 18)** | **50 (11; 71)** |
| **0-14 years** | | |
| Total patients | 298 | 181 |
| Vaccinated/Total cases (%) | 15/173 (8,7) | 4/61 (6,6) |
| Vaccinated /Total controls (%) | 10/125 (8,0) | 10/110 (8,3) |
| IVE crude (% (95%CI)) | -9 (-152; 52) | 23 (-157, 77) |
| **IVE adjusted % (95% CI) [1]** | **66 (4; 88)** | **69 (-45, 93)** |
| **15-64 years** | | |
| Total patients | 679 | 596 |
| Vaccinated/Total cases (%) | 44/279 (15,8) | 11/211 (5,2) |
| Vaccinated /Total controls (%) | 29/400 (7,3) | 29/385 (7,5) |
| IVE crude (% (95%CI)) | -140 (-293; -46) | 33 (-38, 67) |
| **IVE adjusted % (95% CI) [1]** | **-86 (-225; -7)** | **38 (-32, 71)** |
| **> 64 years** | | |
| Total patients | 112 | 78 |
| Vaccinated/Total cases (%) | 35/57 (61,4) | 10/26 (38,5) |
| Vaccinated /Total controls (%) | 35/55 (63,6) | 34/52 (65,4) |
| IVE crude % (95%CI)) | 9 (-96, 58) | 67 (12; 88) |
| **IVE adjusted % (95% CI) [3]** | **17 (-158; 73)** | **60 (-94, 92)[2]** |
| **Targeted for vaccination** | | |
| Total patients | 312 | 240 |
| Vaccinated/Total cases (%) | 68/155 (44,9) | 17/87 (19,5) |
| Vaccinated /Total controls (%) | 58/158 (36,9) | 57/153 (37,3) |
| IVE crude (% (95%CI)) | -33 (-110; 15) | 59 (24; 78) |
| **IVE adjusted (% (95% CI) [4]** | **-4 (-82; 41)** | **62 (20; 82)** |

1 an additional 31 controls were eliminated for being notified during week before the first and after the last confirmed A(H1N1)pdm09 case
2 adjusted for age (RCS), week of onset of symptoms, sex, chronic condition, sentinel network
3 adjusted for age (RCS), onset of symptoms (RCS), sex, chronic condition, sentinel network
4 adjusted for age (RCS), onset of symptoms (RCS), sex, sentinel network

### 4.4 A(H3N2) clade specific IVE

Of the total 510 A(H3N2) confirmed cases, 509 fulfilled the inclusion criteria and 447 were randomly selected to be genetically characterized. Finally, 175/447 were characterized. Of these, 109 (62,3%) were similar to A/England/538/2018(H3N2) (clade 3C.3a), 60 (34,1%) to

A/Alsace/1746/2018(H3N2) (clade 3c.2a1b), six to A/Coted'Ivoire/544/2016(H3N2) (clade 3C.2a3) and one was similar to A/Switzerland/8060/2017(H3N2) (clade 3C.2a2). Thirty-nine and 18 strains similar to A/Alsace/1746/2018(H3N2) (clade 3c.2a1b) harboured the T131K and the T135K mutation, respectively.

The clade specific IVE was -25% (95%CI: -202; 49) against the 3c.2a1b clade and -59% (95%CI: -260; 30) against the 3C.3a clade. Similar results were registered when estimating the VE against the strains including one of the two above-mentioned mutations.

# 5 Discussion

The 2018-19 season was characterized by a mixed circulation of A(H3N2) and A(H1N1)pdm09. The A(H3N2) circulation was mainly dominated by two clades: clade 3C.3a and 3c.2a1b, both considered antigenically distinct from the egg-propagated 2018-19 A(H3N2) vaccine strain (A/Singapore/INFIMH-16-0019/2016).

Against A(H3N2) infection the IVE was very low, with a negative point estimate for all age patients, for the 15-64 years age-group and for the target groups. The clade specific VE estimates against the two main clades circulation in Spain suggested also the lack of the vaccine´s protective effect. These results are in line with the pattern of VE against A(H3N2) informed at European level, in mid-season (1) and as final results (I-MOVE 12th Annual meeting. - Veyrier du Lac, June 2019). The antigenic difference between the circulating and the vaccine strains might partially explain the very low VE estimates against A(H3N2). Further investigation on influenza VE against A(H3N2) are ongoing that might help to understand the observed VE differences by age group.

Regarding the IVE against mild influenza confirmed with A(H1N1)pdm09, our results suggested a moderate protective effect for all ages patients, rounding 50% and in line with previously presented IVE results against this virus subtype (2). The lowest VE point estimate was registered for the 15-64 yeas age-group, whereas for the elderly and the target groups a good protective effect is suggested.

Our results have several limitations amongst which the most important remains the overall low vaccine coverage in the general population, leading to limited precision in some of the analysis. Despite these sub-optimal results, influenza vaccination continues to be the most effective protective measure available against severe influenza complications and influenza-associated mortality. However, there is a need of sustained efforts towards an improved vaccine against influenza A(H3N2) infection.

Reference List

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