Simple models to include influenza vaccination history when evaluating the effect of influenza vaccination

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Background: Most reports of influenza vaccine effectiveness consider current-season vaccination only.

Aim: We evaluated a method to estimate the effect of influenza vaccinations (EIV) considering vaccination history.

Methods: We used a test-negative design with well-documented vaccination history to evaluate the average EIV over eight influenza seasons (2011/12–2018/19; n = 10,356). Modifying effect was considered as difference in effects of vaccination in current and previous seasons and current-season vaccination only. We also explored differences between current-season estimates excluding from the reference category people vaccinated in any of the five previous seasons and estimates without this exclusion or only for one or three previous seasons.

Results: The EIV was 50%, 45% and 38% in people vaccinated in the current season who had previously received none, one to two and three to five doses, respectively, and it was 30% and 43% for one to two and three to five prior doses only. Vaccination in at least three previous seasons reduced the effect of current-season vaccination by 12 percentage points overall, 31 among outpatients, 22 in 9–65 year-olds, and 23 against influenza B. Including people vaccinated in previous seasons only in the unvaccinated category underestimated EIV by 9 percentage points on average (31% vs 40%). Estimates considering vaccination of three or five previous seasons were similar.

Conclusions: Vaccine effectiveness studies should consider influenza vaccination in previous seasons, as it can retain effect and is often an effect modifier. Vaccination status in three categories (current season, previous seasons only, unvaccinated) reflects the whole EIV.

Introduction
The World Health Organization recommends annual influenza vaccination in the target population [1]. People vaccinated against influenza in one season are more likely to be vaccinated in the next one [2]; therefore those in the target population frequently accumulate influenza vaccines over the years.

Influenza vaccines received in previous seasons may retain a notable protective effect [3-5]. In contrast with that, frequent prior vaccination has been related with a reduced effect (i.e. effect modifier) of the current-season vaccine in some studies [6-8]. Since influenza vaccination history is associated with a higher probability of current season vaccination and a lower risk of influenza, it is also a potential confounding factor of the current-season influenza vaccine effectiveness (IVE) [9-11].

IVE studies usually aim at assessing how each seasonal vaccine composition has worked against the circulating influenza viruses in real-life conditions, when frequently repeated vaccination is the most common scenario. However, most of these studies consider only the current-season vaccination [12], and those that consider previous vaccines usually do so as a secondary analysis [3,13].

The estimates from IVE studies are also used to inform population and health professionals about how much influenza vaccination reduces the risk of influenza outcomes; they are also used to estimate the impact of influenza vaccination in the population. For these objectives, it seems more adequate to estimate the effect of influenza vaccinations (EIV) considering both the current-season vaccination and the vaccination history. The inclusion of people only vaccinated in prior seasons in the reference category of unvaccinated may underestimate the EIV.

Influenza epidemics and IVE show important variability among seasons because vaccine composition and circulating virus strains change. The pooled analysis of multiple seasons provides average patterns that can guide public health recommendations.
Table 1  
Participant profile, by influenza case status and current vaccination status, Navarre, Spain, pooled analysis of 2011/12–2018/19 seasons (n = 10,356)

|                          | Laboratory-confirmed cases | Negative controls | p value | Vaccinated in current season | Unvaccinated in current season | p value |
|--------------------------|---------------------------|-------------------|---------|-------------------------------|-------------------------------|---------|
|                          | n  | %   | n    | %   | n   | %   | n   | %   | n   | %   | n   | %   | n   | %   | n   | %   | p value |
| **Total**                | 4,941  | 100 | 5,415  | 100 | NA | 3,952  | 100 | 6,404  | 100 | NA |
| **Age groups (years)**   |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| 9–44                     | 1,798  | 36  | 1,279  | 24  | <0.001 | 265  | 7   | 2,812  | 44  | <0.001 |
| 45–64                    | 1,328  | 27  | 1,194  | 22  | <0.001 | 516  | 13  | 2,006  | 31  | <0.001 |
| 65–84                    | 1,342  | 27  | 2,076  | 38  | <0.001 | 2,189 | 55  | 1,229  | 19  | <0.001 |
| ≥85                      | 473  | 10  | 866  | 16  | <0.001 | 982  | 25  | 357  | 6  | <0.001 |
| **Sex**                  |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| Male                     | 2,510  | 51  | 2,837  | 52  | 0.105 | 2,089 | 53  | 3,258  | 51  | 0.050 |
| Female                   | 2,431  | 49  | 2,578  | 48  | <0.001 | 1,863 | 47  | 3,146  | 49  | <0.001 |
| **Major chronic conditions** |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| No                       | 2,437  | 49  | 1,794  | 33  | <0.001 | 636  | 16  | 3,595  | 56  | <0.001 |
| Yes                      | 2,504  | 51  | 3,621  | 67  | <0.001 | 3,316 | 84  | 2,809  | 44  | <0.001 |
| **Healthcare setting**   |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| Primary care             | 2,872  | 58  | 1,540  | 28  | <0.001 | 693  | 18  | 3,719  | 58  | <0.001 |
| Hospital                 | 2,069  | 42  | 3,875  | 72  | <0.001 | 3,259 | 82  | 2,685  | 42  | <0.001 |
| **Influenza-like illness diagnosis in the immediately preceding season** |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| No                       | 4,806  | 97  | 5,248  | 97  | 0.288 | 3,887 | 98  | 6,167  | 96  | <0.001 |
| Yes                      | 135  | 3  | 167  | 3  | 0.288 | 65  | 2  | 237  | 4  | <0.001 |
| **Vaccination in the current season** |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| No                       | 3,500  | 71  | 2,904  | 54  | <0.001 | NA |     |       |     |     |
| Yes                      | 1,441  | 29  | 2,511  | 46  | <0.001 |     |     |       |     |     |
| **Vaccination in the previous season** |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| No                       | 3,561  | 72  | 2,974  | 55  | <0.001 | 627  | 16  | 5,908  | 92  | <0.001 |
| Yes                      | 1,380  | 28  | 2,441  | 45  | <0.001 | 3,325 | 84  | 496  | 8  | <0.001 |
| **Vaccines in the five previous seasons** |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| 0                        | 3,191  | 65  | 2,410  | 45  | <0.001 | 283  | 7  | 5,318  | 83  | <0.001 |
| 1–2                      | 402  | 8  | 625  | 12  | <0.001 | 454  | 11  | 573  | 9  | <0.001 |
| 3–5                      | 1,348  | 27  | 2,380  | 44  | <0.001 | 3,215 | 81  | 513  | 8  | <0.001 |
| **Influenza season**     |     |     |       |     |     |       |     |       |     |     |     |     |     |     |     |     |
| 2011/12                  | 351  | 7  | 235  | 4  | <0.001 | 96  | 2  | 490  | 8  | <0.001 |
| 2012/13                  | 315  | 6  | 258  | 5  | <0.001 | 92  | 2  | 481  | 8  | <0.001 |
| 2013/14                  | 527  | 11  | 476  | 9  | <0.001 | 331  | 8  | 672  | 10  | <0.001 |
| 2014/15                  | 573  | 12  | 482  | 9  | <0.001 | 325  | 8  | 730  | 11  | <0.001 |
| 2015/16                  | 734  | 15  | 703  | 13  | <0.001 | 457  | 12  | 980  | 15  | <0.001 |
| 2016/17                  | 662  | 13  | 878  | 16  | <0.001 | 711  | 18  | 829  | 13  | <0.001 |
| 2017/18                  | 1,044  | 21  | 1,167  | 22  | <0.001 | 1,029 | 26  | 1,182  | 18  | <0.001 |
| 2018/19                  | 735  | 15  | 1,216  | 22  | <0.001 | 911  | 23  | 1,040  | 16  | <0.001 |

NA: not applicable.
Given the annual recommendation for influenza vaccination, this study’s aim was to evaluate how vaccination history affects the estimates of current-season IVE and to determine the simplest method to obtain valid estimates of the EIV for people according to their influenza vaccination status in the current and previous seasons.

Methods

Design and setting
This methodological proposal is illustrated with data from patients attended in primary healthcare centres and hospitals in the region of Navarre, Spain, during influenza seasons 2011/12 to 2018/19. Annual IVE studies have been conducted since 2009 using the test-negative case–control study design [14], nested in the cohort of the population covered by the Regional Health Service [8,15-21]. This Health Service provides healthcare, free at point of service, to 97% of the population. The trivalent inactivated influenza vaccine was recommended annually and offered free of charge to people 60 years or older (although the uptake was higher from age 65 years upwards) and to those with risk factors or major chronic conditions. Other people could also be vaccinated if they paid for the vaccine.

Case definition and information sources
Influenza surveillance was based on automatic reporting of cases of medically attended influenza-like illness (ILI) from all primary healthcare centres and hospitals [18]. ILI was defined as the sudden onset of any general symptom (fever, malaise, headache or myalgia) in addition to any respiratory symptom (cough, sore throat or dyspnoea). A sentinel network composed of a representative sample of primary healthcare physicians took double swabs, nasopharyngeal and pharyngeal, after obtaining verbal informed consent, from all their patients diagnosed with ILI whose symptoms had begun fewer than 5 days before the patient consultation. The protocol for influenza cases in hospitals establishes early detection and nasopharyngeal and pharyngeal swabbing at admission of all hospitalised patients with ILI. Swabs were tested for influenza viruses by reverse transcription PCR (RT-PCR).

For the present study, we used the test-negative case–control design over eight influenza seasons, from 2011/12 to 2018/19. We included only patients with continued residence in the region during the previous 5 years. Children younger than 9 years, healthcare workers and nursing home residents were excluded. Cases were ILI patients of primary healthcare centres or hospitals, who were confirmed positive for influenza virus by RT-PCR, and controls were similar patients who tested negative for any influenza virus. The influenza vaccination status in the current season and vaccination history were obtained from the regional vaccination register, and only registered doses were considered [2]. Patients who had received an influenza vaccine fewer than 14 days before symptom onset were excluded.

Statistical analysis
Characteristics of study participants by confirmed influenza status and current-season influenza vaccination were compared by chi-squared test. Logistic regression was used to calculate the odds ratios (OR) with their 95% confidence intervals (CI). All models were adjusted for age group (0–44, 45–64, 65–84 and ≥ 85 years), major chronic conditions, calendar month and season of sample collection, and for healthcare setting (primary healthcare or hospital). The IVE and EIV were estimated as \( (1 - \text{adjusted OR}) \times 100\% \).

We evaluated different categorisations of the vaccination status. We considered the reference values to be the EIV estimates obtained from the ‘full model’ with the vaccination status in six categories: current-season vaccination and three to five prior doses, current-season vaccination and one to two prior doses, current-season vaccination and no prior doses, three to five prior doses and no current-season vaccination, one to two prior doses and no current-season vaccination, and unvaccinated in the current and five previous seasons as the reference category [6-8].

The modifying effect of previous seasons’ vaccines on current-season IVE was evaluated in the full model by the absolute difference in effectiveness of each vaccination status in comparison with the category of current-season vaccination and no prior doses as reference. When this difference was statistically significant \( (p < 0.05) \), modifying effect of vaccination history on the current-season vaccine effectiveness was concluded, and the final results were those from combining vaccination categories of the current and previous seasons. Interaction terms between current-season vaccination and prior doses received were tested and these results are presented in the Supplement.

As the full model requires high sample size, estimates from alternate models were compared with those from the full model to determine the analysis with the fewest requirements of vaccination history data and successful management of the remaining and modifying effects of prior vaccines. We also tested models combining vaccination status in the current and either one or three immediately preceding seasons, as well as the model considering only the current-season influenza vaccination (only-current-season model). When the three estimates of the current-season IVE provided by the full model were not statistically different, the analysis was summarised in a ‘summarised model’ with only three categories: current-season vaccination regardless of prior doses, no current-season vaccination but any prior doses, and neither current-season vaccination nor any prior doses as the reference category [22].

The inclusion in the reference category of individuals vaccinated only in previous seasons may bias the EIV estimates. This bias was evaluated as the absolute difference in estimates as \( \Delta \text{IVE} = \text{IVE}_1 - \text{IVE}_0 \); where \( \text{IVE}_0 \) was the current-season EIV estimate in the...
Table 2
Effect of influenza vaccination in the current and previous seasons for all patients and by healthcare setting, Navarre, Spain, pooled analysis of the 2011/12–2018/19 seasons (n = 10,356)

|                              | All patients | Primary healthcare patients | Hospital patients |
|------------------------------|--------------|-----------------------------|-------------------|
|                              | Cases | Controls | Vaccination effect % | 95% CI | Cases | Controls | Vaccination effect % | 95% CI | Cases | Controls | Vaccination effect % | 95% CI |
| Only-current-season model     |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Unvaccinated                 | 3,500  | 2,904    | 0 (ref)               |        | 2,474 | 1,245    | 0 (ref)               |        | 1,026 | 1,659    | 0 (ref)               |        |
| Vaccinated                   | 1,441  | 2,511    | 31 23–38              |        | 398   | 295      | 35 21–47              |        | 1,043 | 2,216    | 29 19–37              |        |
| Summarised model with one previous season |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,333  | 2,575    | 0 (ref)               |        | 2,433 | 1,210    | 0 (ref)               |        | 900   | 1,365    | 0 (ref)               |        |
| Prior and no current         | 167    | 329      | 41 27–52              |        | 41    | 35       | 42 7–64               |        | 126   | 294      | 40 24–53              |        |
| Current regardless prior     | 1,441  | 2,511    | 36 29–43              |        | 398   | 295      | 37 23–48              |        | 1,043 | 2,216    | 36 27–44              |        |
| Full model with one previous season |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,333  | 2,575    | 0 (ref)               |        | 2,433 | 1,210    | 0 (ref)               |        | 900   | 1,365    | 0 (ref)               |        |
| Prior and no current         | 167    | 329      | 41 27–52              |        | 41    | 35       | 42 7–64               |        | 126   | 294      | 40 24–53              |        |
| Current regardless prior     | 1,441  | 2,511    | 39 32–45              |        | 398   | 295      | 39 25–50              |        | 1,043 | 2,216    | 38 29–46              |        |
| Summarised model with three previous seasons |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,179  | 2,351    | 0 (ref)               |        | 2,385 | 1,168    | 0 (ref)               |        | 794   | 1,183    | 0 (ref)               |        |
| Any prior and no current     | 321    | 553      | 37 26–47              |        | 89    | 77       | 46 25–61              |        | 232   | 476      | 35 21–46              |        |
| Current regardless prior     | 1,441  | 2,511    | 39 32–45              |        | 398   | 295      | 39 25–50              |        | 1,043 | 2,216    | 38 29–46              |        |
| Full model with three previous seasons |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,179  | 2,351    | 0 (ref)               |        | 2,385 | 1,168    | 0 (ref)               |        | 794   | 1,183    | 0 (ref)               |        |
| 1–2 prior and no current     | 235    | 362      | 30 16–42              |        | 79    | 61       | 40 14–58              |        | 156   | 301      | 27 9–42               |        |
| 3 prior and no current       | 86     | 191      | 49 33–62              |        | 10    | 16       | 69 29–86              |        | 76    | 175      | 47 28–61              |        |
| Current and no prior         | 118    | 215      | 50 36–61              |        | 58    | 65       | 59 41–72              |        | 60    | 150      | 41 18–57              |        |
| 1–2 prior and current        | 352    | 631      | 40 29–49              |        | 108   | 82       | 38 14–55              |        | 244   | 549      | 41 28–51              |        |
| 3 prior and current          | 971    | 1,665    | 36 28–44              |        | 232   | 148      | 27 4–44               |        | 739   | 1,517    | 37 27–46              |        |
| Summarised model with five previous seasons |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,089  | 2,229    | 0 (ref)               |        | 2,345 | 1,135    | 0 (ref)               |        | 744   | 1,094    | 0 (ref)               |        |
| Any prior and no current     | 411    | 675      | 37 26–46              |        | 129   | 110      | 46 28–59              |        | 282   | 565      | 33 20–4               |        |
| Current regardless prior     | 1,441  | 2,511    | 39 33–47              |        | 398   | 295      | 40 27–51              |        | 1,043 | 2,216    | 39 30–47              |        |
| Full model with five previous seasons |       |          |                       |        |       |          |                       |        |       |          |                       |        |
| Never vaccinated             | 3,089  | 2,229    | 0 (ref)               |        | 2,345 | 1,135    | 0 (ref)               |        | 744   | 1,094    | 0 (ref)               |        |
| 1–2 prior and no current     | 237    | 336      | 30 16–42              |        | 103   | 79       | 37 14–54              |        | 134   | 257      | 25 5–41               |        |
| 3–5 prior and no current     | 174    | 339      | 43 29–53              |        | 26    | 31       | 63 36–79              |        | 148   | 308      | 39 23–52              |        |
| Current and no prior         | 102    | 181      | 50 35–62              |        | 53    | 59       | 59 39–72              |        | 49    | 122      | 40 14–58              |        |
| 1–2 prior and current        | 165    | 289      | 45 31–56              |        | 67    | 58       | 47 23–64              |        | 98    | 231      | 42 24–56              |        |
| 3–5 prior and current        | 1,174  | 2,041    | 38 30–45              |        | 278   | 178      | 28 7–44               |        | 896   | 1,863    | 39 29–47              |        |

CI: confidence interval; ref: reference.

*Vaccination effect adjusted by age groups (9–44, 45–64, 65–84 and ≥ 85 years), major chronic conditions and month and season of sample collection.

* p value < 0.05 for comparison with the category of current season vaccination and no prior doses.
Summary

Influenza vaccination was associated with a statistically significant reduction in the odds of being admitted to hospital for ILI in the current season compared to the previous seasons. The protective effect was greater in patients vaccinated in the current season compared to those vaccinated in the past. The protective effect was also greater in patients with three or more doses of vaccine compared to those with one or two doses. The protective effect was greater in patients vaccinated in the current season compared to those vaccinated in the previous season, with a Protective Effect (PE) of 30% (95% CI: 16–42). The protective effect was also greater in patients vaccinated in the current season compared to those vaccinated in the previous season, with a Protective Effect (PE) of 30% (95% CI: 16–42).

Methods

The study was approved by the Navarra Ethical Committee for Medical Research (Pyto 85/11, Pyto 2015/95 and Pyto 2017/88). We tested the proposal in separated analyses by healthcare setting, age group, virus (sub)-type and influenza season. Seasons with minimal circulation of a given (sub-)type were excluded from the pooled analysis for that outcome. In sensitivity analyses, we included the diagnoses of ILI in the immediately preceding season as a covariable.

Ethical statement

The Navarra Ethical Committee for Medical Research approved the study protocol (Pyto 85/11, Pyto 2015/95 and Pyto 2017/88).

Results

Characteristics of participants

During the eight influenza seasons studied, 10,356 swabbed patients were enrolled: 4,412 patients attended in primary healthcare and 5,944 were hospitalised patients, of whom respectively 2,872 (65%) and 2,069 (35%) were confirmed for influenza virus infection.

Table 1 describes the participants’ characteristics by influenza case status and current vaccination status. Among the total number of patients, 46% were 65 years or older and 38% had received the influenza vaccine in the current season. Current season vaccination was less frequent in cases than in controls (29% vs 44%; p < 0.001). Influenza A(H3N2) accounted for almost half of the cases (47%), while influenza A(H1N1) and B were equally frequent (26% and 27%, respectively) (Supplementary Table S1).

Influenza vaccination in previous seasons met the conditions for being a potential confounding factor in the analysis of IVE, since it was more frequent among controls than in cases (55% vs 35%; p < 0.001) and among those patients vaccinated in the current season than in the rest (93% vs 17%; p < 0.001).

Effect of vaccination in the current and previous seasons

Compared with persons unvaccinated in the current and the five previous seasons, those vaccinated in the current season had an average protective effect of 50% (95% CI: 35–62), 45% (95% CI: 31–56) and 38% (95% CI: 30–45) if they had received none, one to two and three to five prior doses of vaccine, respectively. Persons unvaccinated in the current season also experienced a protective effect of 30% (95% CI: 16–42) and...
Table 3
Comparison of the effect estimates of influenza vaccination from different models with the estimate that compares people vaccinated in the current season with those unvaccinated in the current and five previous seasons, Navarre, Spain, pooled analysis of 2011/12–2018/19 influenza seasons (n = 10,356)

| Vaccination effect | Absolute difference of vaccination effect in % |
|--------------------|-----------------------------------------------|
|                    | % | 95% CI |                           |                               |
| All patients       |               |       |                           |                               |
| Summarised model with five previous seasons | 40 | 33–47 | Reference |
| Summarised model with three previous seasons | 39 | 32–45 | −1 |
| Summarised model with one previous season | 36 | 29–43 | −4 |
| Only-current-season model | 31 | 23–38 | −9b |
| Primary healthcare patientsa |               |       |                           |                               |
| Summarised model with five previous seasons | 40 | 27–51 | Reference |
| Summarised model with three previous seasons | 39 | 25–50 | −1 |
| Summarised model with one previous season | 37 | 23–48 | −3 |
| Only-current-season model | 35 | 21–47 | −5b |
| Hospitalised patients |               |       |                           |                               |
| Summarised model with five previous seasons | 39 | 30–47 | Reference |
| Summarised model with three previous seasons | 38 | 29–46 | −1 |
| Summarised model with one previous season | 36 | 27–44 | −3 |
| Only-current-season model | 29 | 19–37 | −10b,d |
| Age 9–64 years | |               |                           |                               |
| Summarised model with five previous seasons | 45 | 35–54 | Reference |
| Summarised model with three previous seasons | 46 | 34–53 | 1 |
| Summarised model with one previous season | 43 | 32–52 | −2 |
| Only-current-season model | 42 | 31–51 | −3 |
| Age ≥ 65 years | |               |                           |                               |
| Summarised model with five previous seasons | 35 | 24–44 | Reference |
| Summarised model with three previous seasons | 34 | 23–44 | −1 |
| Summarised model with one previous season | 32 | 21–41 | −3 |
| Only-current-season model | 24 | 13–33 | −10b,e |
| Influenza A(H1N1) | |               |                           |                               |
| Summarised model with five previous seasons | 53 | 42–61 | Reference |
| Summarised model with three previous seasons | 50 | 39–60 | −3 |
| Summarised model with one previous season | 51 | 40–59 | −2 |
| Only-current-season model | 47 | 36–56 | −6b |
| Influenza A(H3N2) | |               |                           |                               |
| Summarised model with five previous seasons | 24 | 11–34 | Reference |
| Summarised model with three previous seasons | 24 | 13–35 | 0 |
| Summarised model with one previous season | 21 | 9–32 | −3 |
| Only-current-season model | 14 | 2–25 | −10b,d |
| Influenza B | |               |                           |                               |
| Summarised model with five previous seasons | 53 | 42–61 | Reference |
| Summarised model with three previous seasons | 50 | 39–59 | −3 |
| Summarised model with one previous season | 47 | 35–56 | −6b |
| Only-current-season model | 44 | 32–53 | −9b |

CI: confidence interval.

a Vaccination effect adjusted by age groups (9–44, 45–64, 65–84 and ≥ 85 years), major chronic conditions, healthcare setting (primary healthcare and hospital) and month and season of sample collection.
b Absolute difference of vaccine effect of at least ± 5% was considered as a bias.
c The results of this model should be considered with caution since there was a negative interference between vaccination in the current and previous seasons.
d Absolute difference of vaccine effect of at least ± 10% was considered as a relevant bias.
43% (95% CI: 29–53) if they had received one to two or three to five prior doses, respectively. The EIV estimates from the full models considering combination of vaccination status in the current and previous seasons did not show relevant differences when three or five previous seasons were considered, but the differences increased when only one previous season was considered (Table 2).

In the sensitivity analysis including the ILI diagnosis during the immediately previous season, the EIV estimates were not subject to relevant changes (Supplementary Table S2).

### Modifying effect of prior doses on the current-season influenza vaccine effectiveness

In the overall analysis, the absolute difference of IVE of patients vaccinated in the current and in three or more previous seasons minus IVE of patients vaccinated in the current season and unvaccinated in the five previous seasons was −12 percentage points (38% vs 50%; \( p = 0.118 \)). This difference reached −31 percentage points in primary healthcare patients (28% vs 59%; \( p = 0.014 \)), −22 points among patients aged 9–64 years (36% vs 58%; \( p = 0.046 \)), and −23 points in the analysis of influenza B cases (49% vs 72%; \( p = 0.037 \)) (Figures 1 and 2).

Therefore, all these analyses should maintain separate estimates by vaccination history. Such negative interference was not observed in hospitalised patients, in patients 65 years or older, or in analyses of influenza A(H1N1) and A(H3N2); therefore, the vaccination categories might be simplified in those analyses. The full models considering the vaccination history in three or five previous seasons provided similar results, supporting the use of the first option (Table 2 and Supplementary Tables S3–S8).

In separate analyses by influenza season, the absolute difference in IVE ranged from −3 to +14 percentage points, but the sample sizes were limited and none of these differences had \( p < 0.05 \) (Supplementary Table S9).

### Estimating the bias from prior vaccinations in the reference category

We reduced the number of vaccination categories by combining all individuals vaccinated in the current season regardless of their vaccination history, and these were compared with subjects unvaccinated in the current and five previous seasons. Compared with this summarised model, the only-current-season model underestimated the EIV by an average of 9 percentage points (IVE = 31% vs EIV = 40%; absolute difference −9%), as did the summarised model considering vaccination in only one previous season (−6%) (Table 3). The only-current-season model was affected by a bias of at least 5 percentage points in the analysis of primary healthcare patients (−5%), hospitalised patients (−10%), patients 65 years and older (−11%), and in the analyses of influenza A(H1N1) (−6%), A(H3N2) (−10%) and influenza B (−9%). The bias also reached at least 5 percentage points in the summarised model with vaccination history in only one previous season (−6%) (Table 3). No bias was observed in the summarised models including vaccination history in three previous seasons. The bias in the only-current-season model ranged from −1 to −19 percentage points among influenza seasons, and was at least 5 percentage points in five of the eight seasons studied (Supplementary Table S10).

### Table 4

**Simplest recommended model for estimating the influenza vaccination effect according to the modifying effect and bias from influenza vaccination history**

|                          | Modifying effect | Bias ± 5% or more | Relevant bias ± 10% or more | Simplest model recommended               |
|--------------------------|------------------|-------------------|-----------------------------|-----------------------------------------|
| All patients             | No               | Yes               | No                          | Summarised model with one previous season\(^a\,b\) |
| Primary healthcare patients | Yes             | Yes               | No                          | Full model with three previous seasons\(^c\) |
| Hospitalised patients    | No               | Yes               | Yes                         | Summarised model with one previous season\(^*\) |
| Age 9–64 years           | Yes             | No                | No                          | Full model with three previous seasons\(^*\) |
| Age ≥ 65 years           | No               | Yes               | Yes                         | Summarised model with one previous season\(^*\) |
| Influenza A(H1N1)        | No               | Yes               | No                          | Summarised model with one previous season\(^*\) |
| Influenza A(H3N2)        | No               | Yes               | Yes                         | Summarised model with one previous season\(^*\) |
| Influenza B              | Yes             | Yes               | No                          | Full model with three previous seasons\(^c\) |

\(^a\) Summarised model categories: current-season vaccination regardless of prior doses, no current-season vaccination or prior doses as reference category.

\(^b\) If only relevant bias is considered (± 10% or more), the only-current-season model would be sufficient.

\(^c\) Full model categories: current-season vaccination and three prior doses, current-season vaccination and one to two prior doses, current-season vaccination and no prior doses, no current-season vaccination and three prior doses, no current-season vaccination and one to two prior doses, and no current-season vaccination and no prior doses as reference category.
Selection of the simplest valid model to estimate the effect of influenza vaccinations

The EIV estimates in primary healthcare patients, in patients younger than 65 years and against influenza B were modified by the vaccination history; therefore, the analysis recommended in these situations is the full model which considers the vaccination history in at least three previous seasons. EIV estimates in the overall analysis and the specific analyses of hospitalised patients, of patients 65 years and older and against influenza A(H3N1) and A(H3N2) were not affected by a modifying effect, but were biased (±5% or more) when at least one previous season vaccination was not considered; therefore the summarised model considering one prior dose may be sufficient (Table 4). When only relevant bias was considered (±10% or more), the only-current-season model may be sufficient in the overall and in the specific analysis of influenza A(H1N1), but the summarised model would be the recommended analysis for hospitalised patients, patients 65 years and older and influenza A(H3N2).

Discussion

Influenza vaccination in previous seasons retained a considerable protective effect and in some cases modified the effect of current-season vaccination. Most analyses that did not consider vaccination in the previous seasons underestimated the EIV. Thus, evaluations of EIV should incorporate previous vaccination history. In the analyses of patients in primary healthcare, of persons younger than 65 years, and of influenza B, people who were first vaccinated in the current season had an IVE more than 20 percentage points higher than those who had received the vaccine in the current season and in three or more previous seasons. A new dose of influenza vaccine in a person vaccinated in previous seasons could act by adding its effect to the remaining effect, or by maintaining the greater effect of both. On average over eight influenza seasons, the results observed do not support the sum of effects; some were consistent with maintaining the greater effect; and in various situations, persons with repeated vaccinations had lower protection than those vaccinated for the first time, suggesting there is negative interference (modification of the effect) between influenza vaccines, as described in other studies [7,19,25-29]. In these situations, the final analysis should estimate the effect separately for different combinations of vaccination in the current and previous seasons (full model).

Regardless of the presence of an effect modification, the analyses that did not remove from the reference category individuals vaccinated in only previous seasons underestimated by an average of 9 percentage points (IVE=31% vs EIV=40%) the preventive effect enjoyed by people vaccinated in the current season. This was a relevant bias (±10% or more) in hospitalised patients, in those 65 years and older, and in cases of A(H3N2) influenza. Incorporating vaccination in the immediately previous season into the model largely reduced the bias, and the estimate was even improved by incorporating information from the three previous seasons. Although vaccines received 4–5 years ago may retain some residual effect [5], they did not substantially modify the current-season vaccine effectiveness [10].

Once the existence of an effect modification had been ruled out, the summarised model was a good option for evaluation of EIV, since it controlled the bias, estimated the protective effect in persons vaccinated in the current season, provided information about the remaining effect of previous vaccinations and did not cause excessive fragmentation of the results. While the analysis that considers only vaccination in the current season attempted unsuccessfully to isolate the effect of this vaccine, the summarised model assumed the reality of repeated vaccination and estimated the average protective effect in vaccinated individuals.

Although this study aimed to manage the bias and modifying effect in IVE estimates that inform population and health professionals about the risk reduction of influenza outcomes, similar modifying effect and bias may also affect studies that evaluate the effectiveness of a specific vaccine composition against the circulating influenza virus. Most studies published to date have not taken into account the history of previous vaccination [12], which suggests that the actual protection in vaccinated persons would have been higher than reported in the literature. Since the level of IVE is often low or moderate [12], it is essential to correct for this bias to strengthen the confidence of health professionals and the general population in vaccination, and thus improve vaccination coverage [30]. For many studies, it may be challenging to obtain reliable data on prior vaccination.

Natural immunity due to prior influenza exposure could introduce a bias in IVE and EIV studies [31]. The sensitivity analysis including the diagnoses of ILI during the immediately preceding season showed that the IVE estimates did not suffer relevant changes; therefore, this adjustment in the analysis does not seem necessary, as had been reported [10,18].

Among the strengths of this study is that it analysed an average of eight seasons with circulation of different (sub-)types of influenza virus. Including general practice and hospital settings provides complementary views of the EIV in the same population [20]. Cases were compared with controls recruited in the same healthcare settings before either patient or physician knew the laboratory result, a fact that reduced selection bias [14,32]. The vaccination history was obtained from the regional vaccination registry [2], and the study was limited to the population with stable residence in the region to avoid biases due to vaccination information [33]. The full model has been used in other studies and allows analysis of the effect modification and control for bias due to vaccination in previous seasons [6-8].
This study may also be subject to limitations. It was carried out in a single place where vaccination is indicated in persons 60 years and older and in those with risk factors, and only using the inactivated trivalent vaccine. Consequently, care must be taken when generalising the EIV results to other places with different indications for vaccination, different vaccination coverage, or where other types of vaccines are used. This study included individuals with different chances for repeated vaccination based on their age and influenza vaccination recommendation; therefore, all analyses were adjusted by age, comorbidities and season to control for potential confounding. The test-negative design in inpatient settings may be affected by bias, but the adjustment for cardiorespiratory conditions, as we have done, prevents this bias [34]. As the statistical power in the analysis of a single season was reduced, caution should be exercised when explaining its results. The results should be understood as an average of eight influenza seasons.

Conclusions

This study showed that influenza vaccination in previous seasons may retain an important protective effect and is often a relevant effect modifier of the current-season IVE estimates. Moreover, most analyses that did not consider vaccination in previous seasons underestimated the EIV. Combinations of influenza vaccinations in the current and at least three previous seasons should be analysed to evaluate the existence of a modifying effect. When this is ruled out, a summarised analysis including vaccination status in three categories (current season, previous seasons only and unvaccinated) is a simple option to obtain adjusted estimates and to detect the effect of previous season vaccination. As most previous reports of IVE have not considered vaccination history, the benefit of influenza vaccination may be higher than reported in the literature.

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Conflict of interest

None declared.

Authors' contributions

IMB, IC and JC designed the study. IMB, IC and JC participated in the literature search. IMB, AN, AA, CE and JC participated in the data collection and interpreted the results. IMB and JC were responsible for the data analysis. IMB and JC wrote the manuscript, with editorial contributions from AN, IC, AA and CE. All authors reviewed the manuscript for accuracy and scientific content.

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