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Original article

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Abstract

Objectives:

In this study we discuss which method between the test-negative design and the screening method could provide more robust real-time and end-of-season vaccine effectiveness estimates, using data collected from routine influenza surveillance in primary care.

Methods:

We used data collected during two influenza seasons (2014/15 and 2015/16).

Screening method: we estimated end-of-season vaccine effectiveness in preventing medically attended influenza-like illness and laboratory-confirmed influenza among the population at risk.

Test-negative design: we estimated end-of-season vaccine effectiveness in preventing influenza among both the general and the at risk population.

We estimated real-time vaccine effectiveness using both methods.

Results:

Screening method: the overall adjusted end-of-season vaccine effectiveness was 24% (95% Confidence Interval (CI): 16 to 32) and 12% (95%CI: -16 to 33) during season 2014/15, and 53% (95%CI: 44 to 60) and 47% (95%CI: 23 to 64) during season 2015/16, in preventing ILI and laboratory-confirmed influenza respectively.

Test-negative design: the overall adjusted end-of-season vaccine effectiveness was -17% (95%CI: -79 to 24) and -38% (95%CI: -199 to 13) in 2014/15, and 10% (95%CI: -31 to 39) and 18% (95%CI: -33 to 50) in 2015/16, among the general and at risk population respectively.

Real-time vaccine effectiveness estimates obtained through the test-negative design showed more variability across each season and lower precision than those estimated with the screening method.

Conclusions: Although the worldwide use of the test-negative design allows for comparison of overall vaccine effectiveness estimates between countries, the screening method performs

better in providing robust real-time vaccine effectiveness estimates among the population at risk.

Introduction

The main objective of influenza vaccination in France is to prevent complicated influenza infections, hospitalization, and mortality in individuals with increased risk for severe influenza disease or complications (1, 2). Knowledge of influenza vaccine effectiveness (VE) is essential to measure the protective effect of vaccination and to evaluate its public health value, especially among these at risk groups (3).

The study design approach mostly used to estimate influenza VE is the test-negative design (TND) (4), which compares the odds of vaccination among influenza test-positive vs. influenza test-negative patients, after adjusting for potential confounding factors. This approach has been validated theoretically and is believed to be valid under a range of scenarios (4, 5).

Another approach used to estimate VE is the screening method (SM), which compares the vaccination coverage between reported cases and a reference group (e.g. the general population from which the reported cases have emerged) (6, 7). This simple method was designed to be used as a rapid preliminary analysis when incidence and attack rate data are not available yet (8). This approach is convenient because of its inexpensiveness and reliance on already available data (7, 9-11), but it does not take into account all confounding factors, which may result in biased estimates (7). Compared to the TND, the SM could be better suited to provide a real-time indication of VE in the field (7, 9-12).

In a related study, important trade-offs in reliability of the SM-VE estimates related to the incompleteness of data collected through the Canadian Public Health Information System have been reported (13). However, these estimates were obtained from data collected by two distinct surveillance systems (passive and active surveillance data for SM and TND respectively) and using two diagnostic methods (PCR for SM and culture for TND), which could lead to variations in observed SM and TND-VE estimates (13).

In this study, we estimated real-time and final influenza VE with the TND and the SM-approach from: i) ILI cases reported by the French practice-based surveillance system and laboratory-confirmed influenza cases*;* ii) two influenza epidemics (2014/15 and 2015/16) with a different epidemiological and virological profile (14, 15). The main objective was to establish which method was the most appropriate to estimate influenza VE from data reported by the French influenza surveillance system in primary care.

Methods

Data collected by the French *Sentinelles* network

The sentinel general practitioners (SGPs) of the French *Sentinelles* network (16) report and describe on a weekly basis ILI cases observed among their patients using the following definition: "sudden onset of fever >39°C (>102°F) with myalgia and respiratory signs" (17).

The sentinel physicians (SGPs and paediatricians) also collect nasopharyngeal swabs in a randomized sample of their patients consulting for ILI. The random sample consisted of the first two ILI patients of the week aged 6 months and older consulting within less than 48 hours since symptoms onset and consenting to provide a nasopharyngeal specimen. At the moment of swabbing, epidemiological data were collected through a standardised paper questionnaire. Periods of specimen collection are illustrated in Supplementary Figure A1.

Virological results were reported by the French National Influenza Reference Center (CNR, Paris and Lyon) and the laboratory of Virology at the University of Corsica. All the laboratories performed real-time reverse transcriptase polymerase chain reaction (RT-PCR) tests for virus detection, (sub)-typing and determination of the influenza B virus lineage (18, 19).

Study population

We estimated VE in two main populations: the general population and the at risk population.

The "general population" concerned all individuals aged ≥6 months who are likely to consult in primary care in case of ILI episodes. Within this general population, an individual was considered "at risk" if he was aged ≥65 years or presented one of the following risk factors for influenza complications: pregnancy (at any trimester), obesity (BMI≥40 kg/m2) or a chronic disease (cardiovascular disease, respiratory disease, immunodeficiency or diabetes) (2).

Estimation of seasonal vaccine effectiveness using the screening method

The SM's principle is to calculate VE using the following equation (6, 20, 21):

$$VE = \frac{PV - PVC}{PV\ (1 - PVC)} \times 100\ \%$$

where PV is the proportion of vaccinated among the population of reference and PVC is the proportion of vaccinated among observed cases.

PV was obtained from robust administrative sources (CNAMTS – Caisse Nationale d'Assurance Maladie des Travailleurs Salaries, the main National Health Insurance System, covering about 85% of the French population) and was available only for the following two at risk groups: <65 years with chronic disease and ≥65 years (2, 9, 22). Therefore, VE could be estimated only in these at risk groups.

PVC was estimated in two ways: the proportion of vaccinated among at risk ILI cases reported by the SGPs during the epidemic period (9, 12) and the proportion of vaccinated among at risk influenza confirmed cases swabbed by the SGPs during the epidemic period (9). The epidemic periods considered are those declared by the *Sentinelles* network (http://www.sentiweb.fr/) (23).

VE was estimated with a logistic regression model stratified by age (two strata: <65 years with chronic diseases; ≥65 years), with the number of vaccinated cases as the response variable, a binomial error structure equal to the total number of cases and the logit of PV as a different offset in each age strata (7).

We also evaluated the ability of the SM based on ILI cases to provide real-time VE estimates during the season. In order to compute the estimates retrospectively, we used the PV reported at the end of the previous influenza season (12).

Estimation of seasonal vaccine effectiveness using the test-negative design

With the TND, VE is estimated as (1 – OR) ×100 % (20, 24). We used multivariate logistic regression with influenza laboratory result as outcome and vaccination status as main effect to compute the OR of vaccination, while adjusting for the following potential confounding factors: age (coded into eight age bands), time of onset of symptoms, presence of a risk factor for influenza complications, other than age (chronic disease, pregnancy or obesity) and gender (25). We conducted a complete case analysis excluding patients with missing values for any of the variables included in the model and those recruited outside the virus circulation period as defined by the ECDC protocol (26) (Figure 1).

VE was estimated for both the general and the at risk population, overall and by virus (sub)type or lineage, for all ages or by age group.

Real-time VE estimations were carried out on a weekly basis starting with the first week of the epidemic until the end of the virus circulation period.

Ethical statement

The protocol was conducted in agreement with the Helsinki declaration. Authorization was obtained from the French Data Protection Agency (CNIL, registration number #471393).

Results

Description of the 2014/15 and 2015/16 influenza seasons in France.

Dynamics of the 2014/15 and 2015/16 influenza seasons in France are reported in Supplementary Figure A1.

In season 2014/15, 11,508 ILI cases were described by the SGPs during the nine-week-epidemic period (from January 12th to March 15th, 2015) (Supplementary: Figure A1 and Table A1). Among the 2,613 virological specimens collected along the entire season (ISO weeks: 2014w40 to 2015w15), 55.6% (n = 1,450) were influenza-positive, of which 54.8% (n = 794) were subtyped A(H3N2).

In season 2015/16, 9,945 ILI cases were described during the eleven-week-epidemic period (from January 25th to April 10th, 2016) (Supplementary Table A1). Among the 4,031 specimens collected during the season (ISO weeks: 2015w40 to 2015w19), 52.7% (n = 2,123) were influenza-positive, of which 69.6% (n = 1,478) were type B viruses of lineage Victoria.

Study population

Screening method

During the 2014/15 influenza epidemic, 1,401 ILI cases and 218 influenza-positive patients belonged to a group at risk (with chronic disease or ≥65 years) and were eligible for inclusion in the SM-VE study. Among these, 533 (38.0%) ILI cases and 86 (39.4%) influenza-positive cases were vaccinated with the seasonal vaccine (Table 1 and Supplementary Table A1). During the 2015/16 influenza epidemic, 700 ILI cases and 137 influenza-positive patients belonged to the at risk groups (with chronic disease or ≥65 years) and were eligible for inclusion in the study. The vaccine coverage was 27.0% (n = 189) in ILI cases and 27.7% (n = 38) in influenza-positive cases (Table 1 and Supplementary Table A1).

Test-negative design

In season 2014/15, 2,397 swabbed patients with informed vaccination status (1,413 cases and 984 controls) were eligible for inclusion in the TND-VE study, of which 8.7% (n = 208) were vaccinated (9.1% of cases (n = 129) and 8% of controls (n = 79)). In season 2015/16, there were 3,676 (2,084 cases and 1,664 controls) swabbed patients with informed vaccination status eligible for the study, of which 5.1% (n = 187) were vaccinated (4.9% of cases (n = 101) and

5.3% of controls (n = 86)). Characteristics of the participants included are reported in Supplementary Table A2.

Estimated vaccine effectiveness by using the screening method

In season 2014/15, the overall estimated VE among at risk groups was 24% (95%CI: 16 to 32) against medically attended ILI and 12% (95%CI: -16 to 33) against any influenza virus infection; in season 2015/16, the overall estimated VE among the population at risk was 53% (95%CI: 44 to 60) in preventing ILI and 47% (95%CI: 23 to 64) against any influenza virus infection (Table 1). Additional details on SM-VE estimates by virus type and subtype are reported in Supplementary Table A3.

Estimated vaccine effectiveness using the test-negative design

In season 2014/15, the overall adjusted VE estimates among the general population were -17% (95%CI: -79 to 24) against all influenza viruses and -46% (95%CI: -140 to 11) against influenza A(H3N2) (Table 2). Among the population at risk, the overall adjusted VE estimate against all influenza viruses was -38% (95%CI: -119 to 13) (Table 1). In season 2015/16, the overall adjusted VE estimates in the general population were 10% (95%CI: -31 to 39) against all influenza viruses and -22% (95%CI: -85 to 20) against influenza B (Table 2). Among the population at risk, the overall adjusted VE point estimate was 18% (95%CI: -33 to 50) (Table 1).

Detailed VE estimates by age subgroups and virus (sub)type and lineage are reported in Supplementary Table A4.

Estimation of vaccine effectiveness in real-time

Screening method

In 2014/15, the SM provided real-time VE estimates that were stable and precise after the third week of epidemic; the intermediate VE point estimate was 13% higher than the final one among

the overall at risk group (0-64 years: +3%; elderly: +14%). In 2015/16, the real-time VE estimates became stable after the fourth week of epidemic when the intermediate VE point estimate overestimated the final value by 2% among the overall at risk group (0-64 years: +2% ; elderly: same value) (Figure 2.a).

Test-negative design

In 2014/15, overall VE could be estimated starting with the second week of epidemic; compared to the first intermediate estimates, the final overall VE point estimates were 5% higher against all influenza viruses (0-64 years: +61%; elderly: +3%) and 51% higher against A(H3N2) viruses (Figure 2). In 2015/16, overall VE intermediate estimates were also available from the second week of epidemic; compared to the first intermediate results, final VE point estimates were 23% lower overall against all influenza viruses (0-64 years: -8%; elderly; -37%) and 30% lower against type B viruses (Figure 2.b).

As it can be observed from Figure 2.b, the start of real-time TND-VE monitoring varied depending on the season and the type of analysis, as it is subject to the availability of a minimum required sample size.

Discussion

This study highlighted for the first time strengths and weaknesses of the SM and the TND methods in estimating influenza VE from active surveillance data collected by French surveillance system in primary care. Overall, the results suggest that the SM seems more suitable to monitor influenza VE at national level among the population at risk for severe or complicated influenza illness, providing precise real-time VE estimates at early stages of the influenza epidemic. Given its worldwide popularity, the TND provides useful VE estimates in the general population, comparable between countries using a similar study design.

Test-negative design – results, strengths and weaknesses

In 2014/15, in agreement with data reported in other European countries (27-32), our all-ages overall TND-VE estimates in the general population indicated no protection of the vaccine against all influenza viruses (-17% (95%CI: -79 to 24)) and against influenza A(H3N2) (-46% (95%CI: -140 to 11)). This result could reflect the antigenic drift between a part of the circulating A(H3N2) viruses and the A(H3N2) virus strain included in the 2014/15 vaccine (15). In 2015/16, all-ages VE estimates among the general population indicated no protection of the vaccine against influenza type B (-22% (95%CI: -85 to 20)). We observed moderate protection against A(H1N1)pdm09 viruses (45% (95%CI: 3 to 68)), similar to VE estimates published in the UK (54.5% (95%CI: -41.6 to 64.5)) and by the I-MOVE consortium (mid-season VE: 44.2% (95%CI: -3.1 to 69.8)) (33, 34).

A large number of patients were excluded from the 2014/15 TND-VE study, due to missing information on the presence of a risk factor for influenza complications (other than age) (Figure 1). However, complementary analyses including all cases and not adjusting for this confounder or using multiple imputation to correct for missing values yielded similar results, with slightly higher VE point estimates compared to the complete case analysis, considering the large CIs (from +8% to +18% compared to the complete case analysis). Although this confounding factor is often not significant, it was kept in the models as suggested in the literature (24), leading to restricted sample size.

Indeed, the main drawback of the TND is the large sample size required to obtain accurate estimations, difficult to reach at national level (35). Considering the vaccine coverage in our control group (9.3% in 2014/15 and 5.41% in 2015/16) and the observed VE point estimates, 3,341 and 3,848 participants would have been required in 2014/15 and 2015/16 respectively (instead of 1,428 and 3,447) in order to achieve a level of precision of 30%, given the observed positivity rates of 59% in 2014/15 and 56% in 2015/16. Thus, in the absence of a sufficient sample size, the results presented above should be interpreted with caution considering the large

95%CI, all the more when VE is estimated by subgroups such as elderly or at risk population when sample size limitations are even stronger, making adjustment on some confounding factors impossible and, thus, altering the precision and accuracy of VE estimates (36). Therefore, although the TND method could be more suitable for VE estimation at a European level (I-MOVE consortium) where large sample sizes can be achieved, it does not always provide precise VE estimates at national level. Moreover, real-time VE through the TND method were highly variable across the season, becoming stable only after the epidemic peak or towards the end of each season.

Screening method - results, strengths and weaknesses

In agreement with findings from other countries (30, 32-34), the SM-VE indicated a lower protection of the vaccine in season 2014/15 compared to season 2015/16. Similar to the TND, in season 2014/15, the SM-VE indicated a low overall protection of the vaccine in preventing both ILI and influenza infection among the at risk population in France (24% (95%CI: 16 to 32) and 12% (95%CI: -16 to 33) respectively).

In season 2015/16, in contrast to the TND-VE results, SM-VE estimates in the elderly population (42% (95%CI: 28 to 54) and 33% (95%CI: -21 to 64)) were slightly lower compared to the group of 0-64 years with chronic condition (64% (95%CI: 54 to 73) and 54% (95%CI: 26 to 72)). However, SM-VE estimates in the elderly by virus (sub)type or lineage indicate a high level of protection of the vaccine against A(H1N1)pdm09 (68% (95%CI: 7 to 91)), but no protection against B viruses (3% (95%CI: -105 to 54)), which is consistent with TND results in UK and in Europe (33, 34). SM–VE estimates by virus (sub)type were obtained from small sample sizes and should be interpreted with caution.

The SM allowed estimating real-time VE for preventing ILI at an early stage of the epidemic period, providing early information on the potential protective effect of the vaccine in the

French at risk population. Given the high number of patients consulting for ILI during the epidemic period, the sample size was easily reached, resulting in narrow confidence intervals and a good level of precision from the first weeks of the epidemic (third, respectively fourth epidemic week for season 2014/15 and 2015/16). According to Farrington (7), 601 participants are required in order to reach a level of precision of results of 15%, given a proportion of vaccinated among the population of reference (PV) of 50% and an expected VE of 50%.

Using a non-specific endpoint such as medically-attended ILI might bias the results by underestimating the VE in seasons with low influenza activity and high incidence of other respiratory viruses (9, 20, 37, 38). This bias was reduced by using a very specific ILI definition in France (17) and by including in the analysis only the ILI cases reported during the epidemic period (20). This ensured a proportion of 70% patients positive for influenza among all ILI patients recruited during each epidemic period. When VE point estimates in preventing ILI are slightly higher than VE point estimates in preventing laboratory-confirmed influenza in the population at risk, the 95%CI are overlapping and the sample size of influenza-positive cases is too small to allow for precise results (218 cases for season 2014/15 and 137 for season 2015/16). Although GP's are instructed to systematically recruit ILI cases for swabbing regardless their vaccination status, the vaccine coverage in the group of swabbed ILI patients was slightly higher compared to the overall ILI cases at risk, which partially explains the higher VE against influenza compared to VE against ILI.

The SM relies on the availability of adequate values of the vaccine coverage in the reference group, that are not available in real-time in France. However, since vaccine coverage in the population at risk was relatively stable across seasons and the studied epidemics occurred late, the value reported at the end of the previous influenza season was a good approximation of the vaccine coverage for the season under study (2). Data regarding the vaccine coverage in France allows estimating VE only in the at risk population. However, robust VE estimates for the at

risk group are more informative than estimates in the general population (37) since this group presents the highest risk for severe complications due to influenza and is of greatest interest for the national health authorities (39). One limitation of our study was the unavailability of more detailed vaccine coverage statistics which would have allowed for stratification of VE by more specific risk factors and age groups and adjustment on other potential confounding factors (7). Additionally, although French vaccine recommendation for at risk people include pregnancy and obesity, these categories were excluded from the screening method study as data on vaccine coverage in the reference population for these groups were not available. This aspect should be taken into account when comparing results yielded by the two methods for the population at risk.

In the absence of a gold standard, interpretation of vaccine effectiveness results is an important limitation of all VE studies. Regardless the methods used, a deeper understanding is needed (previous immunization effects, cross-immunity) in order to take into account all potential biases. Even studies carried out at European level, using data pooled from several countries, struggle to obtain precise results (30, 34). Moreover, interpretation and comparison of results obtained from different studies should be done carefully and should take into account the outcome measured (40).

However, assuming all these potential biases (6, 9, 12) are constant in time, SM-VE estimates can be compared across seasons, which can help national health authorities in evaluating the impact of each seasonal epidemic in at risk groups. Disposing of precise VE estimates at an early stage of the epidemic is informative on how the current seasonal influenza vaccine works compared to previous seasons. This is of higher importance than obtaining unbiased but imprecise estimates. From this perspective, compared to the TND, the SM could be more adequate for estimating VE at national level for countries with French-like data.

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Transparency Declaration

Nothing to disclose.

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Authors' contribution

AMV and CS performed the statistical analysis; AMV, CS and AF wrote the first draft of the manuscript; all co-authors contributed for the epidemiological and/or virological data, contributed to the interpretation of the results, reviewed the early draft and approved the final version of the manuscript.

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Table 1. Adjusted seasonal vaccine effectiveness in preventing influenza-like illness (ILI) and confirmed influenza in the at risk population, estimated by the screening method and the test-negative design, influenza seasons 2014/15 and 2015/16, French *Sentinelles* network, France.

Population group	ILI Cases (% vaccinated)	Influenza-positive Cases (% vaccinated)	Influenza-negative Cases (% vaccinated)	PV[a] (%)	VE in preventing ILI cases (%) (95%CI)	VE in preventing influenza (%) (95%CI)
Season 2014-15						
Screening method[b]						
All ages at risk	1401 (38.0)	218 (39.4)	-	46.1	24 (16 to 32)	12 (-16 to 33)
6m-64 y with chronic disease	480 (19.0)	120 (26.7)	-	37.5	61 (51 to 69)	39 (10 to 60)
>= 65 y	921 (48.0)	98 (55.1)	-	48.5	2 (-11 to 14)	-30 (-95 to 12)
Test-negative design[c]						
All ages at risk	-	263 (35.9)	198 (24.2)	-	-	-38 (-119 to 13)[d]
6m-64 y with chronic disease	-	149 (23.5)	127 (15.0)	-	-	-51 (-198 to 23)[d]
>= 65 y	-	114 (51.8)	71 (40.9)	-	-	-31 (-147 to 31)[e]
Season 2015-16						
Screening method[b]						
All ages at risk	700 (27.0)	137 (27.7)	-	48.7	53 (44 to 60)	47 (23 to 64)
6m-64 y with chronic disease	363 (17.4)	93 (21.5)	-	37.1	64 (54 to 73)	54 (26 to 72)
>= 65 y	337 (37.4)	44 (40.9)	-	50.8	42 (28 to 54)	33 (-21 to 64)
Test-negative design[c]						
All ages at risk	-	221 (28.1)	210 (28.1)	-	-	18 (-33 to 50)[d]
6m-64 y with chronic disease	-	174 (25.9)	155 (18.7)	-	-	-21 (-120 to 33)[d]
>= 65 y	-	52 (36.5)	56 (55.4)	-	-	66 (19 to 86)[e]

[a] PV - Proportion of vaccinated individuals among the population of reference, provided by the CNAMTS – Caisse Nationale d'Assurance Maladie des Travailleurs Salaries, the main National Health Insurance System, covering about 85% of the French population

[b] The at risk population includes individuals ≥65 years or presenting a chronic disease (cardiovascular disease, respiratory disease, immunodeficiency or diabetes)

[c] The at risk population includes individuals ≥65 years or presenting a risk factor for influenza complications: pregnancy (at any trimester), obesity (BMI≥40 kg/m2) or a chronic disease (cardiovascular disease, respiratory disease, immunodeficiency or diabetes)

[d] Adjusted by age, month of onset of symptoms, gender

[e] Adjusted by month of onset of symptoms

Table 2. All-ages crude and adjusted vaccine effectiveness against laboratory-confirmed influenza by influenza (sub)type and lineage, in the general population, estimated by the test-negative design, influenza seasons 2014/15 and 2015/16, French *Sentinelles* Network, France

	Cases (% vaccinated)	Controls (% vaccinated)	Crude VE (%) (95%CI)	Adjusted[a] VE (%) (95% CI)
Season 2014-15				
Influenza A or B[b]	837 (11.8)	591 (9.3)	-30 (-84 to 8)	-17 (-79 to 24)
Influenza A	622 (13.0)	591 (9.3)	-45 (-109 to -1)	-28 (-103 to 19)
Influenza A(H1N1)pdm09	164 (8.5)	591 (9.3)	7 (-71 to 49)	19 (-65 to 60)
Influenza AH3N2	458 (14.6)	572 (9.6)	-61 (-135 to -10)	-46 (-140 to 11)
Influenza B	212 (8.5)	559 (9.8)	14 (-51 to 50)	11 (-73 to 55)
Influenza B Victoria	14 (7.1)	379 (10.3)	-	-
Influenza B Yamagata	188 (9.0)	559 (9.8)	7 (-64 to 47)	9 (-81 to 54)
Season 2015-16				
Influenza A or B[b]	1930 (5.0)	1517 (5.4)	7 (-25 to 32)	10 (-31 to 39)
Influenza A	549 (4.6)	1378 (5.7)	21 (-26 to 50)	48 (10 to 70)
Influenza A(H1N1)pdm09	518 (4.6)	1284 (6.0)	23 (-23 to 52)	45 (3 to 68)
Influenza AH3N2	19 (5.3)	1326 (5.7)	-	-
Influenza B	1364 (5.1)	1516 (5.4)	5 (-31 to 32)	-22 (-85 to 20)
Influenza B Victoria	1322 (4.9)	1510 (5.4)	10 (-26 to 35)	-21 (-87 to 21)
Influenza B Yamagata	12 (0.0)	881 (6.5)	-	-

[a] adjusted for age, gender, presence of a risk factor for influenza complication other than age and week of onset of symptoms

[b] includes co-infections with more than one influenza virus (n2014/15 = 5; n2015/16 = 19)

Figure 1. Flowchart of data exclusion of swabbed ILI patients, test-negative design study, seasons 2014/15 and 2015/16, French *Sentinelles* Network, France.

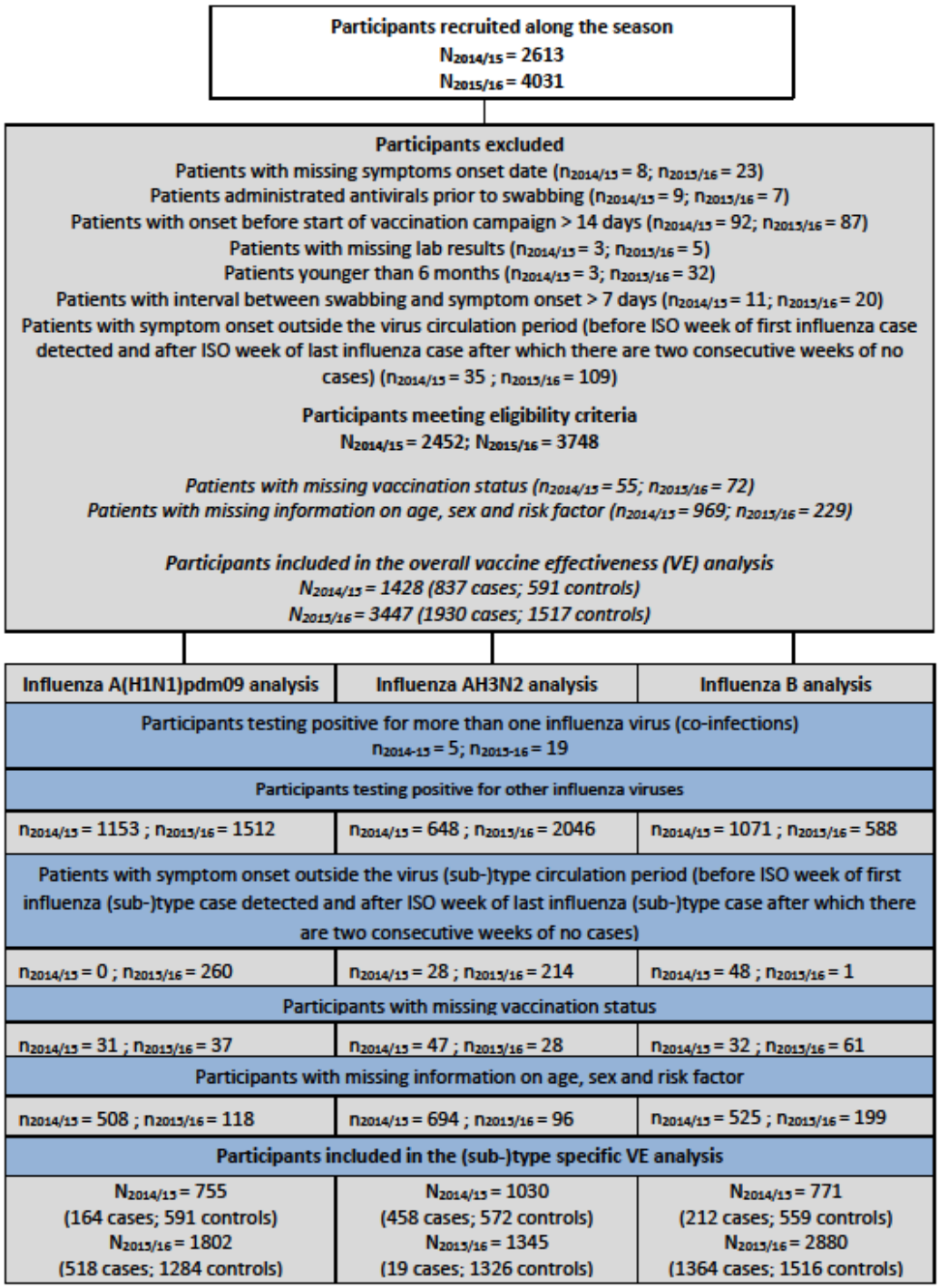

Figure 2.a. Real-time vaccine effectiveness in preventing influenza-like illness (ILI) in at-risk groups (6 months–64 years with chronic disease, ≥65 years, and overall at risk), estimated by the screening method during the 2014/15 and 2015/16 influenza epidemics, French *Sentinelles* network, France.

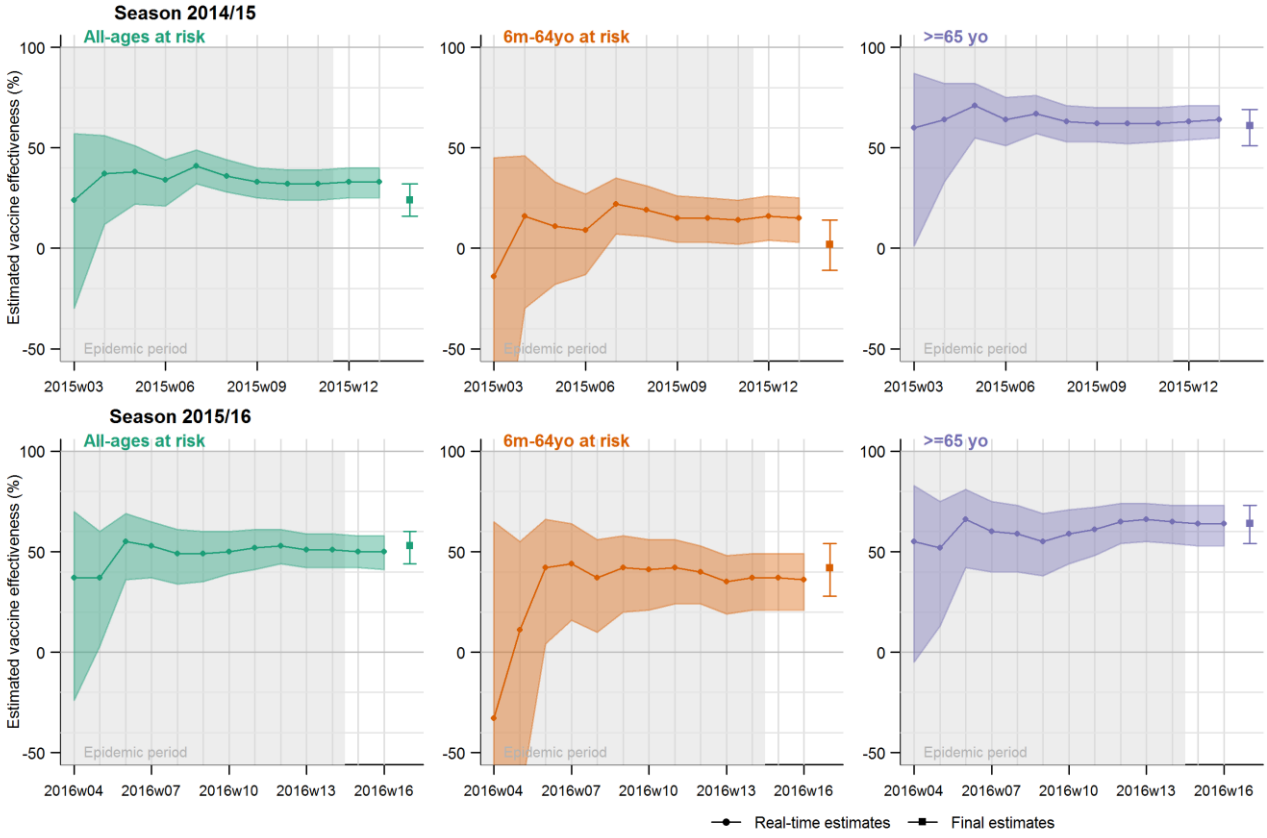

Figure 2.b. Real-time all-ages vaccine effectiveness against laboratory-confirmed influenza virus, by virus (sub)type, in the general population, estimated by the test-negative design during the 2014/15 and 2015/16 seasons, French *Sentinelles* network, France.

Supplementary materials

Figure A1. Number of influenza-like illness patients swabbed by general practitioners who tested positive to at least one influenza virus by types/subtypes and proportion of laboratory-confirmed influenza patients swabbed, by week, French *Sentinelles* surveillance Network; (a) season 2014/2015; (b) season 2015/2016.

Table A1. Description of Influenza-like illness (ILI) cases and swabbed ILI patients positive to at least one influenza virus, reported by the Sentinel General Practitioners (SGPs) during the epidemic period, influenza seasons 2014/15 and 2015/16, French *Sentinelles* network, France.

Table A2. Description of Influenza-like illness (ILI) patients swabbed by the Sentinel physicians (SGPs and paediatricians), with informed vaccination status and eligible for inclusion in the test-negative design study, influenza seasons 2014/15 and 2015/16, French Sentinelles network, France.

Table A3. Estimated vaccine effectiveness in preventing laboratory-confirmed influenza for at risk groups (6 months–64 years with chronic disease, ≥65 years, and overall at risk) by influenza (sub)type, using the screening method, influenza epidemics 2014/15 and 2015/16, French *Sentinelles* Network, France.

Table A4. Estimated crude and adjusted vaccine effectiveness against laboratory-confirmed influenza by influenza (sub)type and by age sub-group, in the general population and in the population at risk, using the test-negative design, seasons 2014/15 and 2015/16, French *Sentinelles* Network, France.