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Complexities in assessing the effectiveness of inactivated influenza vaccines

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For many years it has been generally accepted that well-matched vaccines are the most effective single measure to protect people who are predisposed to a more severe outcome following infection with the influenza virus [1]. This group includes those aged at least 65 years, pregnant women and those who suffer from specific chronic conditions and/or are immunocompromised.

There is nonetheless widespread professional and public interest in, and some debate about, the level of protection afforded by annual influenza vaccination [2,3]. The level of such protection is assessed in two main ways: as estimates of efficacy from randomised controlled trials and as estimates of effectiveness from observational studies. Both are estimates of the proportion of vaccinated people, compared to the proportion of unvaccinated people, who are protected from a specified influenza outcome. Efficacy estimates (from trials) may be higher than effectiveness estimates (from observational studies) because trials are conducted in a controlled environment. A recent meta-analysis of trials using laboratory-confirmed influenza based on culture or PCR testing as the study endpoint estimated influenza vaccine efficacy for healthy adults at 59% (95% confidence interval (CI): 51 to 67) for vaccines licensed in the United States (US) [4]. The majority of those included in the studies were younger than 40 years. Unfortunately there were too few methodologically acceptable observational studies for a pooled analysis of vaccine effectiveness (VE).

A number of observational studies published recently in Eurosurveillance [5-10] have reported estimates of influenza VE less than 60%, and thus below that from the meta-analysis. Possible reasons for this may include (i) the study design, (ii) different age or risk groups being studied, (iii) waning immunity, within a season or between seasons, (iv) the match between circulating viruses and vaccine strains, and (v) the effect of repeated annual vaccination.

In the following each of these factors is considered separately to determine whether they may explain VE estimates below 60% reported recently in this journal.

To overcome potential differences in VE estimates due to variations in observational study design, a European collaboration, the Influenza Monitoring of Vaccine Effectiveness (I-MOVE), has produced pooled estimates of influenza VE from multiple countries using shared protocols over a number of influenza seasons [11]. Most contemporary observational studies of trivalent influenza vaccine (TIV), in Europe or elsewhere, have used PCR (with or without culture)-confirmed symptomatic influenza infection as their endpoints. This facilitates comparison with the meta-analysis, where culture was most often used as an endpoint for studies of live attenuated vaccine and PCR for studies of TIV. Two main study designs have been used in the I-MOVE collaboration. The first is a prospective test-negative variant of the case–control study, where cases have a clinical illness consistent with a diagnosis of influenza and are test-positive for influenza, while controls have the same clinical illness but test negative. This is generally referred to as the test-negative design. The second is a cohort, usually assembled from administrative and/or surveillance databases. Some cohort study endpoints are not laboratory-confirmed infection, but when the same endpoint is used, VE estimates from both study designs have generally been similar for patients in the community or those admitted to hospital [11].

In the pooled test-negative design studies in Europe, the seasonal influenza VE estimate in 2010/11 for community patients was 52% (95% CI: 30 to 67), while the point estimate for adults aged 65 years and over was 59% in 2008/09 and 56% in 2010/11, with missing values imputed in the latter estimate [11]. The European estimates for 2010/11 are supported by a point estimate of 56% from Australia in 2011 where the circulating viruses and vaccine strains were the same as in Europe [12]. In Canada in 2010/11 VE among adults aged 20–49 years was 65% (95% CI: 8 to 87) for A(H1N1)pdm09, 66% (95%CI: 10 to 87) for influenza B and 39% (95%

CI: 0 to 63) for influenza A(H3N2) but VE for all ages against any influenza strain was estimated to be only 37% (95% CI: 17 to 52) [13].

Given the wide confidence intervals, the evidence suggests that, while point estimates may sometimes be lower in the observational studies in Europe and elsewhere [5-13], they are not always substantially different from the meta-analysis of VE from trials of vaccines licensed in the US [4]. This is despite the fact that the meta-analysis included only healthy adults recruited into trials while the observational studies comprised unselected adults, including those in risk groups.

When restricted to risk groups in the pooled European test-negative design studies, VE estimates reported in 2010/11 were similar to those from the meta-analysis. Among those targeted for vaccination, the point estimate of VE was 56% (95% CI: 34 to 71) [11]. The studies were performed in the community but similar VE estimates were obtained when hospitalised patients were studied in the same season in Valencia region, Spain. For all patients hospitalised with laboratory-confirmed influenza, the VE was estimated at 54% (95%CI: 11 to 76), with little difference when estimates were restricted by age or risk group [14]. VE estimates from observational studies in 2010/11 were similar to the pooled estimate from trials [4], but the effect of study design on VE is not yet clear [15,16].

In the northern hemisphere 2011/12 influenza season, considerably lower estimates of VE were reported from the Navarre region, Spain [5], the United Kingdom (UK) [6] and from pooled studies in eight European countries [7] compared with those from previous seasons using the same test-negative study design. In a mild season in the UK in 2011/12, for instance, protection against influenza A(H3N2) infection in primary care was described as poor. Adjusted VE against confirmed influenza A(H3N2) infection was only 23% (95% CI -10 to 47), with VE of 43% (95% CI -34 to 75) for October 2011 to January 2012 and 17% (95% CI -24 to 45) for February to April 2012 [6]. Researchers speculated that a late season in which influenza A(H3N2) was the dominant circulating virus might have resulted in lower VE because antibody-derived immunity waned, which resulted in reduced protection, especially evident among older people who are more likely to suffer an adverse outcome from influenza A(H3N2) virus infection. The influenza A(H3N2) strain in the vaccine was assessed as being not well matched to the circulating strain by the World Health Organization (WHO) which consequently recommended a change in the A(H3N2) strain for the vaccine in the following season [17].

Early estimates of VE, published in Eurosurveillance, against the matched influenza A(H3N2) strain in 2012/13 have shown improved protection of around 50% in community settings. In the Canadian sentinel surveillance scheme, VE estimates were driven by the dominant influenza A(H3N2) strain among adults aged 20–49 years, an age group often over represented in similar schemes. The adjusted VE against influenza A(H3N2) was 45% (95%CI: 13 to 66) [8]. In the UK, adjusted VE against laboratory-confirmed influenza in primary care was 51% (95%CI: 27 to 68); against influenza A, 49% (95%CI: -2 to 75) and against influenza B, 52% (95%CI: 23 to 70) [9]. In the pooled estimate from five European countries, adjusted VE was 62% (95% CI: 21 to 82) and 42% (95% CI: -67 to 80) against A(H3N2) for all ages [18]. The similar point estimates from Canada and the UK were also in the range of the interim point estimate of 55% protection against influenza A reported for the US, although the US estimate included children and was adjusted only for study site [19].

However, VE against influenza for the same season was not as encouraging in a study from Denmark, where influenza A(H3N2) was also circulating. The study used linked databases to construct a test-negative design for patients aged at least 65 years [10]. Eligible patients could be tested in hospitals or in the community, but 95% were tested in hospitals. VE against influenza A was estimated as -11% (95% CI: -41 to 14) and 69% (95% CI: 26 to 87) against influenza B. The investigators identified antigenic changes that may have contributed to the low VE estimate for influenza A in the hospitalised elderly.

Thus, despite the improved interim VE estimates in community settings from the UK, Canada and the US after the change of the influenza A(H3N2) vaccine antigen for the 2012/13 season, the VE estimate from predominantly hospitalised elderly patients in Denmark indicates the relationship between vaccine effectiveness and vaccine strain match may not be as clear as we had assumed. Indeed after several years of observational studies, it is apparent that a better match between circulating virus and vaccine strains does not necessarily translate into improved VE. For instance, in a recent study from Australian sentinel practices, where the four-year point estimate of VE was 62% for adults aged 20–64 years, VE was estimated at 58% (95% CI: 17 to 79) in 2007 when all strains were assessed as predominantly mismatched, but 59% (95% CI: 4 to 82), in 2010 when strains predominantly matched [20].

The apparent anomaly of VE not correlating with strain match may relate to the way match is currently evaluated or to the fact that antibody immunity measured by haemagglutinin inhibition (HI) is not the only (or even the best) correlate with protection from clinical infection. Indeed it has been suggested that HI assays may not always detect drift of the haemagglutinin antigen [8,13]. VE may also vary with the antigenic distance between circulating wild virus and the vaccine virus contained in current and previous vaccines [21].

A number of observations, many of which have been made previously and which may affect estimates of VE, have become evident again in the last few years,

but are still not well understood. These include the possibility of intra-seasonal waning of immunity as described in papers published in this journal [5-7], the predictable effect of vaccine strain match or mismatch on VE estimates [22], and the effect of repeated annual vaccination on VE [21,23].

The recent VE estimates summarised above indicate that inactivated influenza vaccine may provide levels of protection below the range of 70–90% [1] and it is becoming more widely accepted that VE is a complex measure, with variation by year, influenza type and sub-type, and by age and health status [2,3,22,24]. When reporting VE estimates in a range from 40–60% in Eurosurveillance, authors have described protection as 'sub-optimal', 'moderate to low' or 'moderate'. While it could be useful for messaging if researchers agreed on a common approach to describing estimates of VE, it is important to bear in mind that 'moderate' protection, in the order of 40 to 60%, is nonetheless protection. If vaccination with a safe vaccine decreases the risk of an adverse outcome by approximately half, vaccination can be confidently recommended. We note that all the interim VE estimates for influenza B in the 2012/13 season are generally at the top end of this range, or above, particularly evident in the study from the Navarre region, Spain, where influenza B was dominant and the vaccine and circulating strains were of the same lineage [25].

Of course it is desirable to offer better than 50% protection and this is achieved in some years for some influenza types or sub-types. We therefore continue to support the use of existing vaccines, especially in populations at risk of a severe outcome following infection. We hope that influenza vaccine researchers continue to refine study methods to estimate the benefit that can be expected from inactivated vaccines in routine practice, and agree on how best to describe this benefit. This is important for a consistent and credible public health message.

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Early estimates of influenza vaccine effectiveness in Navarre, Spain: 2012/13 mid-season analysis

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We present estimates of influenza vaccine effectiveness (VE) in Navarre, Spain, in the early 2012/13 season, which was dominated by influenza B. In a population-based cohort using electronic records from physicians, the adjusted VE in preventing influenza-like illness was 32% (95% confidence interval (CI): 15 to 46). In a nested test-negative case–control analysis the adjusted VE in preventing laboratory-confirmed influenza was 86% (95% CI: 45 to 96). These results suggest a high protective effect of the vaccine.

Background

In the 2012/13 influenza season the composition recommended for the influenza vaccine in the northern hemisphere included A/California/07/2009(H1N1) pdm09-like, A/Victoria/361/2011(H3N2)-like and B/Wisconsin/1/2010(Yamagata)-like viruses [1].

During the early 2012/13 season, influenza B virus was the predominant circulating influenza virus in Spain, and most characterised isolates belonged to the B/Yamagata lineage [2]. The aim of this study was to provide early estimates of the effectiveness of the 2012/13 seasonal vaccine in preventing medically-attended influenza-like illness (MA-ILI) and laboratory-confirmed influenza in Navarre, Spain.

Estimating influenza vaccine effectiveness

The effectiveness of the influenza vaccine varies every season. Estimates of vaccine effectiveness (VE) during the influenza season help guide health interventions aimed at reducing the impact of influenza in the population [3,4]. A multi-centre European study (I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe) was launched in 2008, including cohort and case–control studies in several settings and the work presented here for Navarre is part of this project [3,4].

We conducted a prospective cohort study based on electronic records of physicians and laboratories and a nested case–control analysis of swabbed patients in Navarre, between 5 November 2012 (week 45 of 2012 – the first week in which influenza virus was detected more than 14 days after the beginning the vaccination campaign) and 3 February 2013 (week 5 of 2013). This cohort included all persons covered by the Regional Health Service, except healthcare workers, persons living in nursing homes and children under six months of age (96% of the population of the region).

The seasonal influenza vaccination campaign took place from 15 October to 30 November 2012. The trivalent inactivated non-adjuvanted vaccine (Sanofi Pasteur MSD) was offered free of charge to people aged 60 or over and to those with major chronic conditions. Other people can also be vaccinated if they pay for the vaccine. Precise instructions for registering each dose of vaccine were communicated to all vaccination sites [5]. Influenza vaccine status was obtained from the online regional vaccination register [6]. Subjects were considered to be protected 14 days after vaccine administration.

Influenza surveillance was based on automatic reporting of cases of influenza-like illness (ILI) from all primary healthcare physicians and searching of ILI cases by public health nurses in hospitals. All of them followed the European Union case definition [7]. A sentinel network composed of a representative sample of 79 primary healthcare physicians, covering 16% of the population, was requested to take nasopharyngeal and pharyngeal swabs, after obtaining verbal informed consent from all their patients diagnosed with ILI, whose symptoms had begun preferably less than five days previously. In hospitals, an agreed protocol for influenza cases was applied, which specified early detection and nasopharyngeal and pharyngeal

Figure

Weekly incidence of medically-attended influenza-like illness and number of swabbed patients according to influenza virus test result, Navarre, Spain, 1 October 2012–3 February 2013

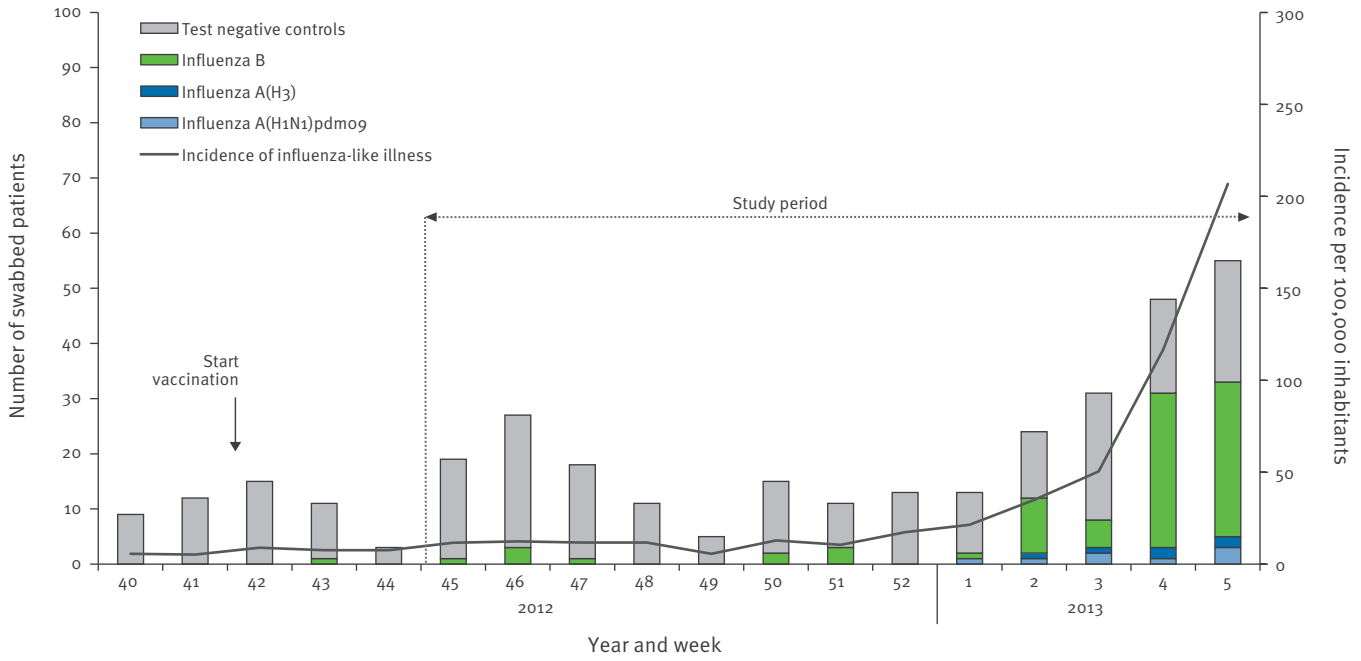

Table 1

Estimates of the effect of the seasonal influenza vaccine in preventing medically-diagnosed influenza-like illness, Navarre, Spain, 5 November 2012–3 February 2013

	Person-years	Cases of MA-ILI	Crude vaccine effectiveness, % (95% CI)	P value	Adjusted vaccine effectiveness, % (95% CI)[a]	P value
Weeks 45/2012 to 5/2013[b]						
Whole cohort						
Unvaccinated	133,499	3,100	Reference	<0.001	Reference	<0.001
Vaccinated	20,043	189	56 (46 to 64)		32 (15 to 46)	
Target population[c]						
Unvaccinated	37,870	737	Reference	<0.001	Reference	0.004
Vaccinated	17,889	144	59 (51 to 65)		32 (11 to 48)	
Weeks 1 to 5/2013[d]						
Whole cohort						
Unvaccinated	50,526	2,517	Reference	<0.001	Reference	<0.001
Vaccinated	8,436	143	66 (60 to 71)		30 (15 to 42)	
Target population[c]						
Unvaccinated	13,903	553	Reference	<0.001	Reference	0.004
Vaccinated	7,498	108	64 (55 to 71)		30 (12 to 44)	

MA-ILI: medically-attended influenza-like illness.

[a] Poisson regression model adjusted for sex, age (10-year groups), major chronic conditions, primary healthcare visits during the previous year (tertiles), hospitalisation in the previous year, urban/rural area, migrant status, children in the household and month.

[b] Whole study period which corresponds to the period between 5 November 2012 and 3 February 2013.

[c] Target population for vaccination includes people ≥60 years-old and people with major chronic conditions.

[d] Period with increasing incidence of MA-ILI.

swabbing of all hospitalised patients with ILI. Swabs were processed by reverse transcription-polymerase chain reaction (RT-PCR) assay, and samples positive for A(H1N1)pdm09, A(H3) and B virus were identified.

From the electronic primary healthcare records we obtained the following baseline variables: sex, age, migrant status, district of residence, major chronic conditions (heart disease, lung disease, renal disease, cancer, diabetes mellitus, cirrhosis, dementia, stroke, immunodeficiency, rheumatic disease and body mass index ≥40 kg/m2), hospitalisation in the previous 12 months, primary healthcare visits in the previous 12 months, and children in the household.

Table 2

Characteristics of laboratory-confirmed influenza cases (n=97) and test-negative controls (n=194), Navarre, Spain, 5 November 2012–3 February 2013

	Laboratory-confirmed influenza cases	Test-negative controls	P value
	n (%)	n (%)	
Age groups (years)			<0.001
<5	3 (3)	30 (15)	
5–14	28 (29)	29 (15)	
15–44	38 (39)	66 (34)	
45–64	26 (27)	43 (22)	
≥65	2 (2)	26 (13)	
Sex			0.901
Male	48 (49)	98 (51)	
Female	49 (51)	96 (49)	
Residence			0.384
Rural	20 (21)	50 (26)	
Urban	77 (79)	144 (74)	
Migrant status			0.521
No	90 (93)	174 (90)	
Yes	7 (7)	20 (10)	
Major chronic conditions			0.044
No	66 (68)	108 (56)	
Yes	31 (32)	86 (44)	
Hospitalisation in the previous year			<0.001
No	92 (95)	148 (76)	
Yes	5 (5)	46 (24)	
Outpatient visits in the previous year			<0.001
0 to 5	60 (62)	73 (38)	
>5	37 (38)	121 (62)	
Healthcare setting			<0.001
Primary healthcare	88 (91)	118 (61)	
Hospitalisation	8 (8)	68 (35)	
Emergency rooms	1 (1)	8 (4)	
Period			<0.001
Weeks 45/2012 to 52/2012	10 (10)	109 (56)	
Weeks 1/2013 to 5/2013	87 (89)	85 (44)	
Seasonal influenza vaccine 2012/13			<0.001
No	94 (97)	157 (81)	
Yes	3 (3)	37 (19)	
Total	**97 (100)**	**194 (100)**	

Cohort analysis

The incidence rates of MA-ILI were compared in vaccinated and unvaccinated persons. Person-years were used as the denominator, with end of follow-up at the date of MA-ILI diagnosis, death, or 3 February 2013 (end of this analysis), whichever came first. Poisson regression models were used to obtain MA-ILI-adjusted rate ratios for influenza vaccination status.

Test-negative case–control analysis

All outpatients and hospitalised patients who were swabbed during the study period were included in a case–control analysis that compared seasonal vaccination status in patients in whom any influenza virus was detected (cases) and those who were negative for influenza (controls). Crude and adjusted estimators of the effect were quantified by odds ratios (ORs) with their 95% confidence intervals (CIs), calculated using logistic regression models. The adjusted models included age group (<5, 5–14, 15–44, 45–64 and ≥65 years), major chronic conditions, three-week periods (weeks 45 to 47 of 2012, 48 to 50 of 2012, 51 of 2012 to 1 of 2013, 2 to 4 of 2013 and 5 of 2013) and healthcare setting (primary healthcare, emergency room and hospitalisation), because these were the statistically significant variables in the bivariate analyses and altered the OR by 3% or more. Separated analyses were done by type of influenza, by healthcare setting, for patients for whom influenza vaccination was indicated because they were 60 years of age or older or had some major chronic condition, and for patients diagnosed in the period of increasing incidence (weeks 1 to 5 of 2013).

Percentages were compared by chi-squared test and Fisher's exact test. VE was estimated as a percentage: (1–rate ratio)×100 or (1–OR)×100.

Mid 2012/13 season influenza vaccine effectiveness

Vaccine effectiveness in preventing medically-attended influenza-like illness

A total of 616,721 persons were included in the cohort study, of which 223,936 had an indication for vaccination because they were 60 years of age or older or had some major chronic condition. The influenza vaccine coverage was 14.2% in the whole cohort and 49.4% in subjects aged 60 years or more.

From week 45 of 2012 to week 5 of 2013, 3,289 cases of MA-ILI were diagnosed, with an increasing incidence in the last weeks (Figure).

The MA-ILI incidence rate was 9.4 per 1,000 vaccinated person-years as opposed to 23.2 per 1,000 unvaccinated person-years (p<0.001), and the adjusted VE against MA-ILI was 32% (95% CI: 15 to 46). In the target

population for vaccination the incidence rate was 8.0 per 1,000 vaccinated person-years and 19.5 per 1,000 unvaccinated person-years (p<0.001), and the adjusted VE against MA-ILI was 32% (95% CI: 11 to 48). When the analyses were restricted to the period with increasing MA-ILI incidence (weeks 1 to 5 of 2013), the estimates were similar (Table 1).

Vaccine effectiveness in preventing laboratory-confirmed influenza

During the study period, 291 ILI patients were swabbed of whom 97 (33%) were confirmed for influenza virus: 83 (86%) for influenza B, eight for influenza A(H1N1) pdm09 and six for influenza A(H3) virus (Figure). All swabs from outpatients had been taken in the first five days after symptom onset.

Compared with confirmed cases of influenza, the group of test-negative controls had a higher proportion of persons under the age of five years or 65 years and older, persons with major chronic conditions, people who had consulted a physician five or more times in the past year, who had been hospitalised in the past year, and who were treated in the hospital (Table 2).

There were three (3%) laboratory-confirmed cases in the 97 patients who had received the 2012/13 seasonal vaccine, while 37 (19%) of the 194 influenza-negative controls had received the influenza vaccine (p<0.001). In the logistic regression analysis, the adjusted estimate of the influenza VE was 86% (95% CI: 45 to 96). The comparison of influenza B cases with controls gave similar results (89%; 95% CI: 46 to 98), while the estimate of the VE in preventing influenza A cases had a wide confidence interval (68%; 95% CI: -189 to 99). Other analyses restricted to the period between weeks 1 and 5 of 2013, to the target population for vaccination or including only primary healthcare patients also found high VE (Table 3). All 14 type B viruses with known lineage were B/Yamagata, which was the same lineage included in the vaccine. Two vaccine failures were due to influenza B and happened in persons with some immunodepression, and one vaccine failure was due to influenza A(H1N1)pdm09 virus in an immunocompetent person.

Discussion and conclusion

The early estimates of this study show a high protective effect of the 2012/13 seasonal influenza vaccine in preventing laboratory-confirmed cases of influenza

Table 3

Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in Navarre, Spain, 5 November 2012–3 February 2013

	Cases; controls	Crude vaccine effectiveness, % (95% CI)	P value	Adjusted vaccine effectiveness, % (95% CI)[a]	P value
All swabbed patients					
Unvaccinated	94; 157	Reference	0.001	Reference	0.005
Vaccinated	3; 37	86 (55 to 96)		86 (45 to 96)	
Primary healthcare patients					
Unvaccinated	85; 105	Reference	0.056	Reference	0.029
Vaccinated	3; 13	71 (-3 to 92)		80 (15 to 95)	
Hospitalised patients					
Unvaccinated	8; 51	Reference	0.235	Reference	0.221
Vaccinated	0; 17	72 (-98 to 100)[b]		78 (-138 to 100)[b]	
Target population for vaccination[c]					
Unvaccinated	32; 64	Reference	0.007	Reference	0.021
Vaccinated	2; 31	87 (43 to 97)		88 (28 to 98)	
Weeks 1 to 5/2013[d]					
Unvaccinated	84; 66	Reference	0.001	Reference	0.004
Vaccinated	3; 19	88 (56 to 96)		88 (49 to 97)	
Influenza B					
Unvaccinated	81; 157	Reference	0.002	Reference	0.007
Vaccinated	2; 37	89 (55 to 97)		89 (46 to 98)	
Influenza A					
Unvaccinated	13; 157	Reference	0.470	Reference	0.531
Vaccinated	1; 37	67 (-132 to 99)[b]		68 (-189 to 99)[b]	

[a] Logistic regression model adjusted for age group (<5, 5–14, 15–44, 45–64 and ≥65 years), three-week periods, major chronic conditions, hospitalisation in the previous year and healthcare setting (primary healthcare, emergency room and hospitalisation).

[b] Exact logistic regression analysis.

[c] Target population for vaccination includes people ≥60 years-old and people with major chronic conditions.

[d] Period with increasing incidence of medically-attended influenza-like illness.

in Navarre and a notable effect against MA-ILI. During the study period influenza B virus was predominantly (86%) found, and all type B viruses with known lineage were B/Yamagata, which was the same lineage included in the vaccine [1].

Although the estimates overlap, our results might suggest a higher VE in Navarre than obtained in the early estimates in the United States, the United Kingdom, Canada and Denmark for the same season [8-11]. In these studies the proportion of influenza A cases (range: 24–91%) was higher than in Navarre (14%) and Spain (15%) [2,8-11].

The results presented here are preliminary and may have limited statistical power for some analyses. Therefore the final results for the season may be different. Cohort studies can be affected by biases if those who are vaccinated tend to have poorer health status or if, on the contrary, they tend to take better care of their health than the unvaccinated [12,13], but our analyses were controlled for the most frequently recognised confounders [14]. The case–control analysis included only laboratory-confirmed cases and compared them with controls recruited in the same healthcare settings before either patient or physician knew the laboratory result, a fact that reduced selection bias.

The analyses of VE against two outcomes provide complementary information. The effectiveness of 86% in preventing laboratory-confirmed influenza can be considered the best estimate of the actual protective effect of the trivalent 2012/13 seasonal vaccine. The effectiveness of 32% in preventing MA-ILI describes the effect as seen in clinical practice, in which not all ILI cases are confirmed for influenza virus. The consistency of the results obtained using two designs for two different outcomes reinforces their validity.

These results support a high protective effect of the seasonal vaccine against influenza disease in Navarre in the early 2012/13 season where predominantly influenza B circulates and highlight the importance of annual immunisation against influenza of high-risk populations.

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Conflicts of interest

None declared.

Authors' contributions

Jesús Castilla, Iván Marínez-Baz, Marcela Guevara, Manuel García Cenoz and Aurelio Barricarte, designed the study and coordinated the activities. Iván Marínez-Baz, Marcela Guevara and Jesús Castilla undertook the statistical analysis. Fernando Elía and Nerea Alvarez prepared the electronic databases. Víctor Martínez-Artola, Mirian Fernández-Alonso, Gabriel Reina and Carmen Ezpeleta were responsible of the virological analysis and the interpretation of laboratory results. Jesús Castilla, Iván Marínez-Baz, Marcela Guevara wrote the draft manuscript, and all authors revised and approved the final version.

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Early estimates of seasonal influenza vaccine effectiveness in Europe: results from the I-MOVE multicentre case–control study, 2012/13

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We conducted a test-negative case–control study based in five European sentinel surveillance networks. The early 2012/13 adjusted influenza vaccine effectiveness was 78.2% (95% CI: 18.0 to 94.2) against influenza B, 62.1% (95% CI: –22.9 to 88.3%) against A(H1) pdm09, 41.9 (95% CI: –67.1 to 79.8) against A(H3N2) and 50.4% (95% CI: –20.7 to 79.6) against all influenza types in the target groups for vaccination. Efforts to improve influenza vaccines should continue to better protect those at risk of severe illness or complications.

Background

Since 2008/9, the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network has estimated the effectiveness of seasonal influenza vaccine to prevent medically attended influenza-like illness (ILI) laboratory confirmed as influenza [1-7]. One of the components of I-MOVE is a multicentre case–control study based on practitioners participating in the European Influenza Surveillance Network (EISN) [8].

This season, six study sites are participating in the multicentre study: Germany, Ireland, Poland, Portugal, Romania and Spain.

Here we provide early season estimates of the 2012/13 influenza vaccine based on data collected from week 43 2012 to week 3 2013. Poland is not included in the early season estimates as there were no vaccinated individuals among the patients recruited.

Estimating influenza vaccine effectiveness

The methods of the multicentre case–control study have been described previously [1-4,9].

Participating practitioners swabbed and interviewed all or a systematic sample of patients consulting for ILI. The common variables collected in all study sites were symptoms, date of onset and swabbing, 2012/13 seasonal vaccination status and date of vaccination, sex, age, presence of chronic conditions and number of hospitalisations for the chronic condition in the past 12 months. Four of the five study sites included a question on belonging to the target groups for vaccination. In Portugal, this information was gathered using information on age, chronic conditions, pregnancy, whether the patient was a health professional or carer and a household member or carer of an at-risk patient aged less than six months.

In the pooled analysis, we included patients with a nasopharyngeal swab taken less than eight days after symptom onset and meeting the European Union case definition for ILI: sudden onset of symptoms, at least one of four systemic symptoms (fever or feverishness, malaise, headache, myalgia) and at least one of three respiratory symptoms (cough, sore throat, shortness of breath) [10]. A case of confirmed influenza was an ILI patient who was swabbed and tested positive for influenza virus using real-time reverse-transcription polymerase chain reaction or culture. Controls were ILI patients who tested negative for any influenza virus.

We defined a person as vaccinated if he or she had received at least one dose of a 2012/13 seasonal influenza vaccine more than 14 days before ILI symptom onset. All the others were classified as unvaccinated.

For each study site we included ILI patients with symptom onset up to the end of week 3 2013 and more than 14 days after the start of national or regional influenza vaccination campaigns.

We conducted a complete case analysis excluding individuals with missing information on key confounders. We estimated the pooled seasonal influenza vaccine effectiveness (VE) as 1 minus the odds ratio (OR) expressed as a percentage, using a one-stage method with the study site as fixed effect in the model.

Table 1

Study details, multicentre case–control study, study sites in five European Union countries, week 43/2012–week 3/2013

Study site	Week of start of influenza season[a]	Number of practitioners participating in the study	Number of practitioners recruiting at least one ILI patient[b]	Number of ILI patients[b] recruited by practitioners	Inclusion period for the preliminary analysis (ISO weeks)[c]	Number of included ILI patients positive for influenza and with known vaccination status[d]		Number of included ILI patients negative for any influenza and with known vaccination status[d]	
						Total	Vaccinated	Total	Vaccinated
Germany	Week 50/2012	150	109	863	Week 43/2012–week 3/2013	267	8	556	38
Ireland	Week 50/2012	28	20	126	Week 48/2012–week 3/2013	81	3	45	4
Portugal	Not started within study period	62	21	43	Week 51/2012–week 3/2013	10	0	33	5
Romania	Week 3/2013	75	7	7	Week 2/2013–week 3/2013	4	1	3	1
Spain	Week 3/2013	239	66	122	Week 50/2012–week 3/2013	54	0	68	5
Total	-	554	223	1,161	-	416	12	705	53

ILI: Influenza-like illness; ISO: International Organization for Standardization.

[a] According to the thresholds used to define the start of the influenza season in each of the countries.

[b] ILI patients meeting the European Union case definition, swabbed less than eight days after onset of symptoms within the study period.

[c] From 15 days after the start of the vaccination campaign to week 3/2013. We excluded controls with an onset of symptoms in the weeks before the first influenza case in the study site.

[d] ILI patients included in the study, after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

We used a logistic regression model to adjust for presence of at least one chronic disease, sex, age group and month of symptom onset.

We estimated VE against all laboratory-confirmed influenza, and individually against influenza A(H3N2), A(H1N1)pdm09 and influenza B. For each study site, we excluded controls with symptom onset in the weeks before symptom onset of the first influenza type/subtype case depending on the outcome used. We also estimated VE restricted to the target groups for vaccination.

Early estimates of 2012/13 influenza vaccine effectiveness

In the five countries, the influenza season, as defined by national thresholds, started at different times – in week 50 2012 in Germany and Ireland, week 3 2013 in Spain and Romania (Table 1). In week 3, the ILI incidence in Portugal was still below the threshold defining the start of the season. The first study site to recruit cases was Germany (in week 43 2012) and the last Romania (in week 2 2013).

Among 554 practitioners, 223 recruited at least one ILI patient (Table 1).

Of the 1,161 ILI patients enrolled, 271 tested positive for influenza A (23.3%), 162 for influenza B (14.0%) and one tested positive for both influenza B and influenza A(H1)pdm09. Among the 269 influenza A viruses that could be subtyped, 146 (54.3%) were A(H1)pdm09 and 123 (45.7%) were A(H3N2). Influenza A virus was predominant in Germany, and influenza B in Ireland and Spain (Table 2).

The proportion of patients who were vaccinated was 2.9% (12/416) among cases and 7.5% (53/705) among controls.

After excluding patients with missing information on 2012/13 influenza vaccination (n=40), age (n=2), sex (n=11), presence of chronic conditions (n=62), we included 1,046 individuals (396 cases and 650 controls) in the complete case analysis (Figure). There were 12 vaccinated cases: five positive for influenza A(H3N2), four for A(H1)pdm09 and three for B.

The adjusted VE was 62.2% (95% CI: 21.1 to 81.9) for influenza A and B combined, 78.2% (95% CI: 18.0 to 94.2) for influenza B, 62.1% (95% CI: −22.9 to 88.3) for A(H1)pdm09 and 41.9 (95% CI: −67.1 to 79.8) for A(H3N2) (Table 3). Among the target groups for vaccination, the VE against influenza A and B combined was 50.4% (95% CI: −20.7 to 79.6).

Discussion

These early estimates suggest a moderate VE against all influenza viruses. By type and subtype, the highest VE was against influenza B and the lowest against influenza A(H3N2).

Table 2

Details for influenza B (n=163), A(H3N2) (n=123), A(H1)pdm09 (n=146) cases and controls[a] (n=727) considered for mid-2012/13 season trivalent influenza vaccine effectiveness analysis, study sites in five European Union countries, week 40/2012–week 3/2013 (n=1,161[b,c])

Variables	Number of test-negative controls[c]/total n (%)	Number of influenza B cases[b]/total n (%)	Number of influenza A(H3N2) cases/total n (%)	Number of influenza A(H1)pdm09 cases[b]/ total n (%)
Median age (years)	20	31	11	25.5
Age groups (years)				
0–4	184/725 (25.4)	16/163 (9.8)	33/123 (26.8)	25/146 (17.1)
5–14	130/725 (17.9)	51/163 (31.3)	38/123 (30.9)	35/146 (24.0)
15–59	350/725 (48.3)	84/163 (51.5)	41/123 (33.3)	79/146 (54.1)
≥60	61/725 (8.4)	12/163 (7.4)	11/123 (8.9)	7/146 (4.8)
Sex				
Female	368/714 (51.5)	84/162 (51.9)	56/122 (45.9)	85/146 (58.2)
Days between symptom onset and swabbing				
0	60/727 (8.3)	6/163 (3.7)	2/123 (1.6)	8/146 (5.5)
1	294/727 (40.4)	34/163 (20.9)	52/123 (42.3)	55/146 (37.7)
2	171/727 (23.5)	41/163 (25.2)	34/123 (27.6)	37/146 (25.3)
3	112/727 (15.4)	43/163 /26.4)	17/123 (13.8)	23/146 (15.8)
4–7	90/727 (12.4)	39/163 (23.9)	18/123 (14.6)	23/146 (15.8)
Seasonal vaccination[d] 2012/13	53/705 (7.5)	3/161 (1.9)	5/117 (4.3)	4/136 (2.9)
At least one chronic condition	143/676 (21.2)	29/161 (18.0)	14/114 (12.3)	18/134 (13.4)
At least one hospitalisation in the previous 12 months for chronic conditions	11/584 (1.9)	2/152 (1.3)	2/103 (1.9)	0/122 (0.0)
Belongs to target groups for vaccination	175/711 (24.6)	35/163 (21.5)	22/117 (18.8)	23/143 (16.1)
Study sites				
Germany	578/727 (79.5)	51/163 (31.3)	112/123 (91.1)	122/146 (83.6)
Ireland	45/727 (6.2)	66/163 (40.5)	9/123 (7.3)	5/146 (3.4)
Portugal	33/727 (4.5)	4/163 (2.5)	0/123 (0.0)	6/146 (4.1)
Romania	3/727 (0.4)	2/163 (1.2)	0/123 (0.0)	2/146 (1.4)
Spain	68/727 (9.4)	40/163 (24.5)	2/123 (1.6)	11/146 (7.5)

[a] Controls used to compare with all influenza cases.

[b] One influenza case positive for influenza B and for influenza A(H1)pdm09 was included in both analyses.

[c] The virus from three influenza A cases could not be subtyped: these cases are not included in the descriptive analysis.

[d] Vaccination more than 14 days before onset of influenza-like illness symptoms.

Table 3

Pooled crude and adjusted 2012/13 seasonal vaccine effectiveness against laboratory confirmed influenza by influenza type/suptype, overall and among target groups for vaccination. Multicentre case–control study in five European Union study sites, week 43 (2012)–week 3 (2013), influenza season 2012/13

Influenza type/subtype	Crude vs adjusted model	Cases and controls (n/n)	Vaccinated cases and controls (n/n)	Vaccine effectiveness (%)	95% confidence intervals
All population					
A and B	Crude[a]	396/650	12/48	62.8	27.3 to 80.9
	Adjusted[b]	396/650	12/48	62.2	21.1 to 81.9
A(H1)pdm09	Crude[a]	125/477	4/37	66.1	-2.7 to 88.8
	Adjusted[c]	125/477	4/37	62.1	-22.9 to 88.3
A(H3N2)	Crude[a]	111/577	5/39	34.7	-70.1 to 74.9
	Adjusted[b]	111/577	5/39	41.9	-67.1 to 79.8
B	Crude[a]	158/523	3/41	79.8	29.2 to 94.2
	Adjusted[b]	158/523	3/41	78.2	18.0 to 94.2
Target population					
A and B	Crude[a]	73/157	9/32	46.5	-23.0 to 76.8
	Adjusted[d]	73/154	9/32	50.4	-20.7 to 79.6

[a] Study site included in the model as fixed effect.

[b] Model adjusted for presence of at least one chronic disease, sex, 10-year age group and month of symptom onset.

[c] Model adjusted for presence of at least one chronic disease, sex, 10-year age group until age 60, where age is coded as ≥60 years and month of symptom onset.

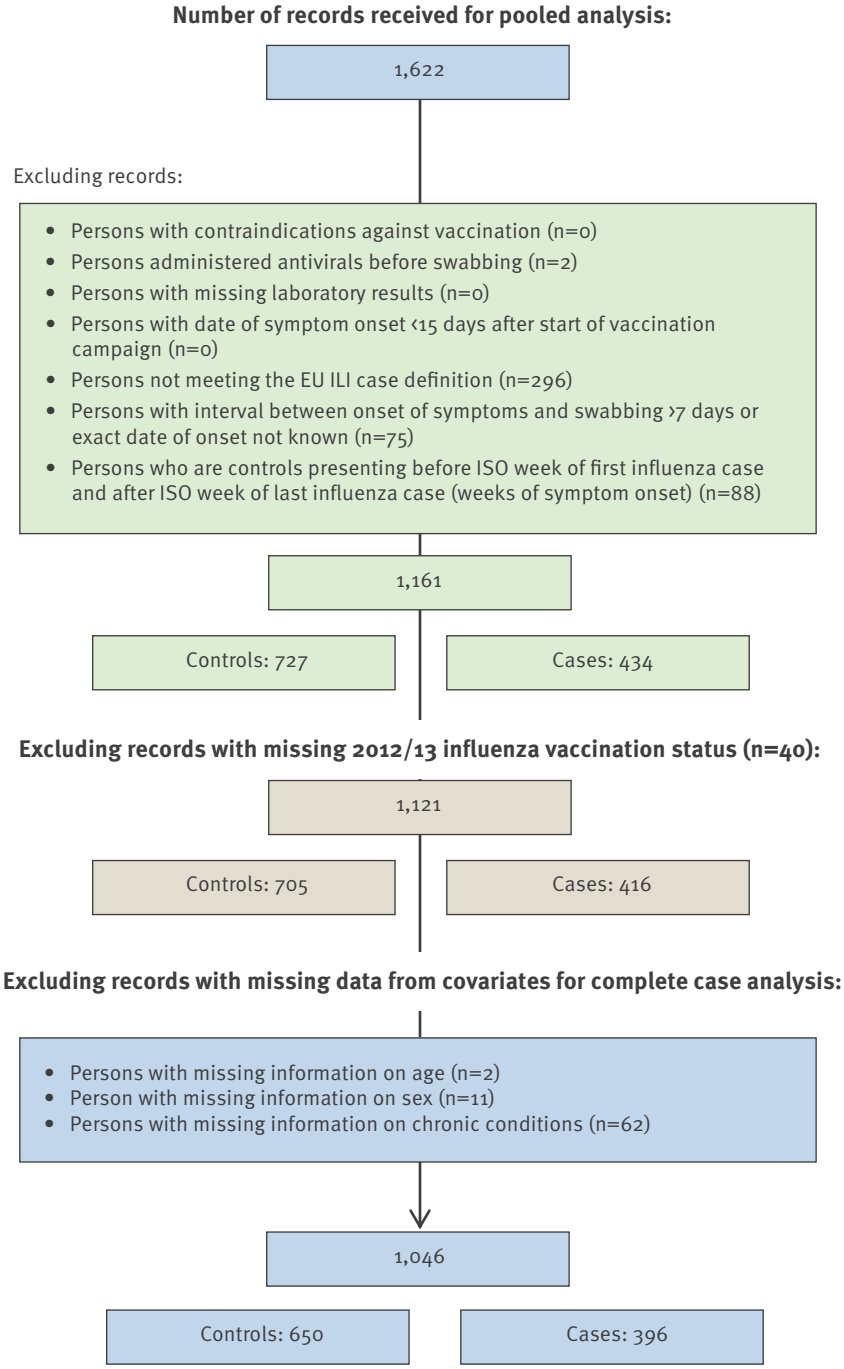
[d] Model adjusted for presence of at least one chronic disease, sex, age group (0–14; 15–59 and ≥60 years) and month of symptom onset. Three records were excluded for October.

During the study period, as of week 3-2013, two of the participating countries reported a low ILI/ARI activity (Portugal, Romania) and three medium activity (Germany, Ireland, Spain) [11].The sample size varied by study site. As most patients (863/1,161, 74.3%) were enrolled in Germany, the pooled estimates are highly influenced by the German data. When restricting the analysis to Ireland, Portugal, Romania and Spain (n=296, four vaccinated cases), the adjusted point VE against all influenza was higher (73.5%; 95% CI: 8.7 to 92.3) than the adjusted point VE including the five study sites.

As in 2011/12, the results suggests a low-to-moderate VE for influenza A(H3N2) [9]. Our point estimate is lower than that reported by Canada [12] and the United States [13], countries with a predominance of this subtype in the early phase of the 2012/13 season. Most of the influenza A(H3N2) cases included in our study were German patients. In Germany, most of

Figure

Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case–control study, influenza season 2012/13



EU: European Union; ILI: influenza-like illness; I-MOVE: Influenza Monitoring Vaccine Effectiveness; ISO: International Organization for Standardization.

the 103 influenza A(H3N2) viruses characterised at the national reference centre for influenza were similar to the A/Victoria/361/2011(H3N2) vaccine virus for the 2012/13 season [14]. This similarity was also reported by the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) [15]. This discrepancy between the apparently well-matched vaccine strain/circulating strains and low VE has also been noted this season in Canada [12].

Our 2013 early point VE estimates for influenza B are similar to estimates from the United States [13] and higher than those reported in the United Kingdom [16]. All the influenza B virus isolates genetically characterised from influenza cases enrolled in the Irish (three isolates), Portuguese (three isolates) and Spanish (four isolates) study sites were B/Yamagata, the lineage included in the 2012/13 vaccine. Data from the German national reference centre for influenza indicated that among 75 influenza B strains characterised, 68 were Yamagata and 7 Victoria.

The sample size did not allow VE estimation by type and subtype among the target population for vaccination. The low VE against all influenza types in this population is similar to the estimates the I-MOVE multicentre case–control study provided last season against influenza A(H3) [3].

This season, in which different influenza viruses are co-circulating in Europe, the I-MOVE multicentre case–control study provided early adjusted VE estimates for influenza B, A(H3N2) and A(H1N1)pdm09 viruses. However, due to small sample size, the precision around these estimates is low and should be taken into account when interpreting these preliminary results.

The results underscore the importance of providing early VE estimates against virus subtype regardless of the reported relatedness between circulating viruses and administered vaccines. The early VE estimates could be useful when defining the recommendations for next season's vaccine composition.

In conclusion, our early season estimates suggest that the 2012/13 influenza vaccine is effective in preventing medically attended laboratory-confirmed influenza, with a higher VE against influenza B than against influenza A subtypes. The lower VE among the target groups and against influenza A(H3N2) underlines that efforts to improve the influenza vaccine should continue in order to better protect those at risk of severe illness or complications.

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None declared. EpiConcept analyses pooled data of a hospital-network multicentre case–control (HNMCC) study measuring influenza VE. The HNMCC analysis is co-funded by Pasteur, Sanofi Pasteur MSD, GlaxoSmithKline and EpiConcept.

Authors' contributions

Marta Valenciano led the writing of the rapid communication. Esther Kissling undertook the statistical analysis on which the rapid communication is based. All authors participated in the interpretation of the study and contributed to the revision of the draft manuscript and approving the final version. Alain Moren, Marta Valenciano, Esther Kissling were involved in the original methodological design of the multicentre case–control study. Amparo Larrauri, Silvia Jiménez-Jorge, Joan O'Donnell, Emilia Lupulescu, Daniela Pitigoi, Baltazar Nunes, Ausenda Machado, Annicka Reuss, Udo Buchholz have had a role in modification of this design over the years.
Germany: Annicka Reuss, Udo Buchholz and Silke Buda are responsible for validation of data and interpretation of results. **Ireland:** Justyna Rogalska was involved in the collection and collation of the data. Joan O'Donnell was involved in the original methodology and final review of the paper. She was also coordinating the project in Ireland. Lisa Domegan was involved in collection, collation and analysis of clinical and virological data from all sentinel GPs. Darina O'Flanagan was involved in the original initiation of the ILI surveillance system and approved the final communication. Claire Collins was involved in the original study design. In this round, she contributed to the preparation of the ethical submission and coordinated the invitation letter to participating GPs and the GP payments. Michael Joyce was involved in the collection and collation of the data. Joanne Moran and Suzie Coughlan - Extraction of sentinel influenza I-MOVE data from the National Virus Reference Laboratory information system (NVRL LIMs) on a weekly basis for distribution to the Health Protection Surveillance Centre (HPSC). **Portugal:** Baltazar Nunes, Ausenda Machado, Raquel Guiomar and Pedro Pechirra were responsible for the study design in Portugal study site. Ausenda Machado, Inês Batista, were responsible for the field work, study monitoring, data validations and preparation. Pedro Pechirra, Paula Cristovão and Patricia Conde were responsible for the laboratory analysis: virus sub-typing, genotyping and laboratory data validation. **Romania:** Daniela Pitigoi, Emilia Lupulescu, Viorel Alexandrescu coordinated the Romanian study. Daniela Pitigoi and Emilia Lupulescu were responsible for the study design in Romania study site. Daniela Pitigoi, Emilia Lupulescu, Gheorghe Necula collected data. Daniela Pitigoi, Alina Ivanciuc enrolled patients. **Spain:** Amparo Larrauri and Silvia Jiménez-Jorge participated in the coordination of the Spanish study and the national database. Salvador de Mateo was involved in the interpretation and analysis of the Spanish study. Francisco Pozo and Inmaculada Casas were involved in genetic characterisation of influenza virus from the Spanish Influenza Surveillance System.

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Real-time laboratory surveillance of sexually-transmissible infections in Marseille university hospitals reveals rise of gonorrhoea, syphilis and human immunodeficiency virus seroconversions in 2012

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Real-time systematic monitoring of the number of infections diagnosed in our clinical microbiology laboratory in Marseille recently drew attention to the fact that the incidence of gonorrhoea was 10-fold greater from September through December 2012 than during same months of previous years. We also found an increase in the annual incidence of syphilis and human immunodeficiency virus seroconversion. Our system allowed timely identification of an increase in sexually-transmitted infections in Marseille for the whole year of 2012.

Routine laboratory surveillance in Marseille, France identified a rise in the number of diagnosed gonococcal infections in the last quarter of 2012. We therefore analysed the annual incidence data of sexually transmitted infections (STI) and noted an increase not only in the incidence of gonorrhoea but also of syphilis and human immunodeficiency virus (HIV) infections.

Laboratory surveillance in Marseille

Systematic monitoring of the number of infections diagnosed through tests performed by the laboratories is a new monitoring mode to detect seasonality and variations in the incidence of infectious and contagious diseases [1]. We have since 2002 been using such a system in our clinical microbiology laboratory [2], which is the sole laboratory for Marseille University hospitals and performs annually for the diagnosis of infections approximately 145,000 serological tests, 200,000 PCR tests, as well as cultures of bacteria, yeasts or viruses from 220,000 samples. Our computer tool gives a signal when the weekly incidence of a given disease is greater than the mean plus two standard deviations [2].

Marseille is the second largest city in France with about 850,000 inhabitants in the city itself and 1,560,000 inhabitants in the entire Marseille urban unit (2.5% of the metropolitan population in France). The annual activity of Marseille University hospitals includes about 890,000 consultations, 125,000 admissions, 151,000 persons seen in emergency wards, and 112,000 hospitalised patients. No data on the recent incidence or prevalence of diagnosed STI are available for other laboratories that cover our geographical area, nor, to our best knowledge, are any national data.

Increase in diagnosed sexually transmitted infections

Seven cases of gonorrhoea were diagnosed in September 2012, whereas the mean number was 1.2 cases (range: 0–3 cases) from January 2005 through August 2012 (Figure, panel A), which prompted us to investigate the data from our surveillance system for other STIs. This analysis confirmed that there was an increase in the annual incidence of serologically diagnosed active syphilis, which was 2.7-fold higher in 2012 (164 cases) compared to the period from 2005 to 2011, during which it ranged from 44 to 84 (mean: 62 cases) (Figure, panel B). Concurrently, the annual number of HIV seroconversion was 1.8-fold higher in 2012 (16 cases) than during the period from 2005 to 2011 (mean: 9 cases) (Figure, panel C). In addition, we confirmed a 10-fold increase in the number of gonorrhoea cases diagnosed from September to December 2012

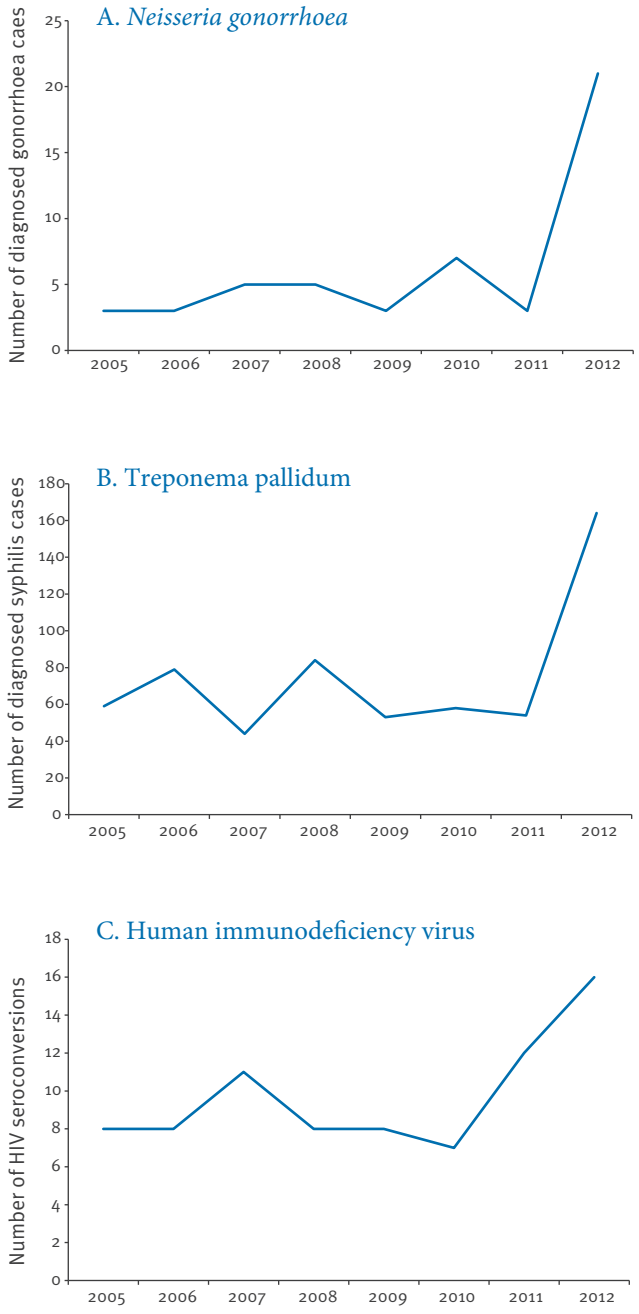
compared with the same months of the seven previous years. Regarding Chlamydia trachomatis infections, we have not noticed any significant increase in numbers, but our monitoring for this particular pathogen only started in January 2011.

There have not been any recent changes in testing procedures for STI in our laboratory.

We looked at the sex and age of all patients who experienced gonorrhoea, active syphilis or HIV seroconversion. It was found that they were mostly young men. Indeed, in 2012, 38 of 47 gonorrhoea cases were diagnosed in men whose mean age (±standard deviation) was 29±10 years (range: 16–51 years); 89% of syphilis were diagnosed in men whose mean age was 46±14 years (range: 21–87 years); and all 16 cases diagnosed with HIV seroconversion were men whose mean age was 39±15 years (range: 21–72 years) and among whom 6 of 16 were younger than 30 years. Among persons who experienced HIV seroconversion, we found a significant rise of the male/female sex ratio in the period from 2005 to 2010 (37 men among 50 cases) and the period 2011 and 2012 (27 men among 28 cases) (p=0.014), and a 2.2-fold rise of the annual number of men having sex with men who experienced HIV seroconversion in the period from 2005 to 2010 (31 cases) and the period 2011 and 2012 (23 cases).

Figure

Culture isolation of *Neisseria gonorrhoeae* (A), serology indicating active syphilis (B) and primary infection with human immunodeficiency virus (C), Marseille, 2005–2012



HIV: human immunodeficiency virus.

Trends in other countries

Interestingly, other countries in Europe also described recent increases in the incidence of several STIs, for instance in England, Germany and Sweden, particularly among MSM [3]. In France, a 52% increase in gonorrhoea was described between 2008 and 2009 [4], but not in the following years. In Europe, a rise of gonorrhoea notifications has been reported in several countries [3]. In England, the increase was 25% in the general population, and as high as 61% among men who have sex with men among whom 42% of diagnoses were in those aged 25–34 years [5]. The number of syphilis cases in France nationally declined in 2008 and 2009 after an earlier increase in 2007 [6], which is in contrast to our data for Marseille. In England, a 10% increase in syphilis was noted in 2011, reaching 28% among young men who have sex with men [5]. In Germany, syphilis cases rose by 22% in 2011, mainly in men [7]. Finally, regarding HIV, a significant increase of the number of positive serology results was reported in some regions of metropolitan France between 2007 and 2011 [8]. The estimated yearly HIV incidence among MSM was 3.8% person-years in France in 2009 and 2.5% in Europe, North America and Australia for the period 1995–2005 [9,10].

In conclusion, our monitoring system based on laboratory diagnoses, which mimics the system implemented in England and Wales can detect early changes in the incidence of STIs. Such real-time systematic laboratory surveillance of infectious diseases is critical for an accurate appreciation of incidence and for appropriate prevention and treatment, and is currently lacking in France. In addition, among the STIs analysed here, notification is only mandatory for HIV infection. Finally, our system is unique in that it can pick up signals in real time, which allowed analysis of the full 2012 data already in January 2013 and led to the identification of the increasing trend in STIs in Marseille.

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Authors' contributions

DR, FG and PC conceived the study and wrote the manuscript. DR, PC, FG, SB, CT and/or AS provided and analysed the data.

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Letter to the editor: influenza vaccine effectiveness: heterogeneity in estimates for the 2012/13 season

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To the editor: In the past few weeks, there have been several publications on influenza vaccine effectiveness (VE) during the 2012/13 influenza season. Having robust VE estimates as soon as possible during the season is of great public health benefit. Indeed, to optimise the design of such studies and increase the precision of (early) estimates by pooling of data, the European Centre for Disease Prevention and Control (ECDC) has supported the European Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network [1].

However, the recently published studies provide very different estimates: A study from the United Kingdom (UK) showed a VE against laboratory-confirmed influenza in a general practitioner (GP) network of 51% (95% confidence interval (CI): 27% to 68%) [2]. In contrast, a study from Denmark using national registries showed a dramatically low VE of -11% (95% CI: -41% to 14%) against laboratory-confirmed influenza A among those aged 65 years and over [3]. VE against influenza B in the Danish study was much higher at 69% (95% CI: 26% to 87%).

Both studies used the test-negative case–control method, which has become a standard method for estimating influenza VE and in which the study population consists of people tested for suspected influenza [4]. Those with a positive test for influenza virus are cases and those with a negative test are controls. VE is then calculated based on the influenza vaccination status of cases and controls. Most studies estimate VE from GP networks, in which patients presenting with influenza-like illness (ILI) are swabbed for surveillance purposes. In the Netherlands, we routinely estimate VE with the test-negative approach from the sentinel GP network of the NIVEL Netherlands Institute for Health Services Research [5]. The information it collects is indicative only, as the number of swabs from ILI patients is often too low to obtain robust estimates.

The Table shows the most recent VE estimates for the Netherlands for the 2012/13 season. VE was estimated using logistic regression on all medically attended ILI patients in the sentinel GP network swabbed between 3 December 2012 and 3 February 2013. We excluded cases if the period between disease onset and date of swabbing was seven days or more. For type- and subtype-specific VE, controls were defined as negative for any influenza virus. The adjusted VE point-estimates for all ages early in the 2012/13 influenza epidemic

Table

Influenza vaccine effectiveness estimates in all age groups for the 2012/13 influenza epidemic in the Netherlands

Number of ILI patients swabbed[a]	Influenza virus (sub)type	Crude VE (95% CI)	Age- and comorbidity- adjusted VE (95% CI)[b]
176	All (sub)types	59% (15% to 81%)	90% (68% to 97%)[c]
117	A(H1N1)pdm09	82% (35% to 95%)	96% (79% to 99%)[d]
111	A(H3N2)	42% (-51% to 78%)	82% (17% to 96%)[e]
100	B	39% (-82% to 80%)	87% (20% to 98%)[d]

CI: confidence interval; ILI: influenza-like illness; VE: vaccine effectiveness.

[a] Numbers represent all influenza virus-negative patients plus the patients positive for the indicated influenza virus type and subtype.

[b] Adjusted for age and the following comorbidities reported by the general practitioner on the swabbing form: respiratory allergy including asthma, immunodeficiency, and chronic diseases including chronic obstructive pulmonary disease.

[c] Information on comorbidity missing for three patients.

[d] Information on comorbidity missing for two patients.

[e] Information on comorbidity missing for one patient.

were remarkably high, suggesting that the vaccine was effective against all circulating influenza virus (sub) types in the Netherlands. Adjusted VE for those aged 60 years and older was also high, although the confidence interval was very wide and included zero (VE: 92%; 95% CI: -27% to 99%).

The Danish study by Bragstad et al. is unique, in that it used laboratory and vaccination registries with nationwide coverage [3]. These are generally not available in other countries and provide exciting opportunities for epidemiological studies. However, as the authors indicated, information on some important variables such as comorbidity was not available from the national registries. The authors argue that comorbidity is unlikely to be an important confounder and that selection bias is unlikely to have played a role. However, our data showed a significant effect after correction for comorbidity, and other Dutch data show that influenza vaccination coverage is likely to be higher among elderly with underlying medical conditions compared to elderly who consider themselves healthy. In the Netherlands, over the past few years, this difference has consistently been larger than 20% [6].

One could further speculate that in comparison with healthy elderly peoply, those with underlying medical conditions are more likely to seek medical care in case of acute febrile illness, more likely to be admitted to hospital, and more likely to get an influenza diagnostic laboratory test. If this is true, then a larger proportion of influenza virus infections would be detected in the vaccinated group compared to the non-vaccinated group, and the VE estimate would be biased. Such bias is less likely when the study population consists of patients visiting their GP for ILI.

In the context of ongoing controversies about the usefulness of influenza vaccination, there is a great need to further develop optimal methodologies for the rapid assessment of influenza VE. The Innovative Medicines Initiative, a public-private partnership of the European Union and the pharmaceutical industry aims to develop a framework for rapid assessment of vaccination benefit/risk in Europe over the coming years. For influenza VE, the I-MOVE network has already shown that significant progress and harmonisations across the participating European countries was feasible [4]. Considering the heterogeneity in VE estimates that to some extent may depend on the used methodology and the sources of information, this process of harmonisation needs to continue to provide optimal and rapid assessment of influenza vaccine effectiveness.

Conflict of interest

None declared.

Authors' contributions

W van der Hoek, MA van der Sande, F Dijkstra and MM de Lange conceived the idea to respond to the recent articles on influenza vaccine effectiveness in Eurosurveillance. A Meijer provided the virological test data and MM de Lange and F Dijkstra did the data analysis for the Dutch VE estimates. W van der Hoek drafted the letter. The text was revised by the co-authors, and all authors approved the final version of the letter.

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Authors' reply: influenza vaccine effectiveness: heterogeneity in estimates for the 2012/13 season

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To the editor: We thank Wim van der Hoek and colleagues for their interest in our work [1] and for sharing the preliminary data on influenza vaccine effectiveness (VE) for the 2012/13 season in the Netherlands. When we wrote our article, we emphasised that the findings were based on analysis of data from elderly people mainly admitted to hospital. We cannot make any inference as regards VE among younger, unselected individuals seen in primary healthcare. However, the main public health objective with the influenza vaccination campaign is to prevent morbidity and premature mortality among the frail and the elderly. With this in mind, our observations do have relevance.

We found a low VE of -11% (95% confidence interval: -41% to 14%) against influenza A among patients 65 years and older. This is not a stand-alone observation but is corroborated by other lines of evidence. In the period we studied, influenza A(H3N2) was the dominant influenza subtype in Denmark, and genetic characterisation of the strain revealed a clade that, compared with vaccine strain A/Victoria/361/2011, contained seven amino acid substitutions in the haemagglutinin (HA) gene. It is possible that widespread circulation in Denmark of this clade may be a biological explanation of the disappointing VE against influenza A. In our paper, we mention that this clade was demonstrated in patients who had been vaccinated with seasonal influenza vaccine. Further support to our findings is provided from registration of influenza cases in Danish intensive care units (ICU). Current data suggest that 22 of 58 patients admitted with influenza A this season had been vaccinated, corresponding to 38% vaccine failures. In the three previous seasons, the proportion of vaccine failures among patients in ICUs ranged between 15% and 19%. Finally, an estimated VE against influenza B of 69% renders credibility to our epidemiological methodology and data.

We agree with van der Hoek et al. that it is important to consider sources of bias and confounding. It is argued that patients with underlying medical conditions are more likely to seek medical care in case of acute febrile illness, more likely to be admitted to hospital, and more likely to get an influenza diagnostic laboratory test. We consider these arguments reasonable. Age can be regarded as a crude proxy of comorbidity. In the study period, the national testing rate for influenza was age-dependent and ranged from 119 per 100,000 population in 65-69 year-olds to 179 per 100,000 among patients 80 years and older (Table). Indirectly, this suggests that the very old and frail are tested more often than the healthy seniors, as argued above. The advantage of the test-negative design is that both cases and controls are subject to the same selection process (i.e. seeking medical care and being tested)

Table 1

National testing activity for influenza, number and proportion of samples tested positive for influenza A, and age-specific crude vaccine effectiveness estimated on the figures provided in [1]

Age group (years)	Population[a]	Number of tests	Test rate per 100,000 population	Number positive for influenza A	Proportion of all tests positive for influenza A (%)	Vaccine effectiveness in age strata % (95% CI)
65–69	350,623	416	119	75	63	15.1% (-44.9 to 50.3)
70–74	239,485	321	134	70	52	1.7% (-70.2 to 43.3)
75–70	171,586	290	169	84	50	-29.3% (-116 to 22.3)
≥80	232,821	416	179	135	76	-24.9% (-89.0 to 17.4)

CI: confidence interval.
a Danish population data from www.statistikbanken.dk, last quarter of 2012.

and therefore the concerns raised by van der Hoek are to a large extent covered by the analytical design.

Van der Hoek et al. argue further that a larger proportion of influenza virus infections would be detected in the vaccinated group compared to the non-vaccinated group. This would only be an issue of confounding if both being tested positive and the VE estimate was dependent on comorbidity (e.g. poor VE among those with severe comorbidity). In principle, this cannot be ruled out. Our data do indicate a trend of higher VE estimates in the younger population, but a formal test of heterogeneity of the odds ratio fails to show significant effect-modification (p=0.66).

In conclusion, we consider that the test-negative design combined with the adjustment for age addresses most concerns about bias and confounding, but needless to say, it would be even better to have valid indicators of underlying illness. We note with interest that our Dutch colleagues report a considerable difference between the crude and adjusted VE estimates. It is of methodological interest to learn how much of this adjustment could be accomplished by adjusting for age alone.

For the future we hope to expand our registers to include indicators of underlying illness and to obtain complete and timely data on vaccination uptake among younger individuals. This will allow us to obtain rapid estimates of VE covering a wider range of age groups and potentially also to stratify for different groups of comorbidities. We acknowledge the advantages of VE estimates obtained from networks of primary health physicians, but keeping the objective of the seasonal influenza vaccinations in mind, it is important also to assess the effectiveness among other populations.

Conflict of interest

None declared.

Authors' contributions

K Mølbak wrote a draft response, H-D Emborg and S Gubbels verified the data and the analysis, T K Fischer, T G Krause and K Bragstad provided comments, and all authors approved the final version.

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