Vaccine effectiveness in preventing laboratory-confirmed influenza in Navarre, Spain: 2013/14 mid-season analysis

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We estimate mid-2013/14 season vaccine effectiveness (VE) of the influenza trivalent vaccine in Navarre, Spain. Influenza-like illness cases attended in hospital (n=431) and primary healthcare (n=344) were included. The overall adjusted VE in preventing laboratory-confirmed influenza was 24% (95% CI: –14 to 50). The VE was 40% (95% CI: –12 to 68) against influenza A(H1)pdm09 and 13% (95% CI: –36 to 45) against influenza A(H3). These results suggest a moderate preventive effect against influenza A(H1)pdm09 and low protection against influenza A(H3).

2013/14 influenza season: early assessment of vaccine effectiveness

Spain was one of the European countries affected earliest by influenza in the 2013/14 season. During the early part of the season (October 2013 to January 2014), influenza A(H1N1)pdm09 and A(H3N2) viruses co-circulated in Spain and elsewhere in Europe: most characterised isolates were A/StPetersburg/27/2011(H1N1)pdm09-like and A/Texas/50/2012(H3N2)-like [1-3]. The composition of the influenza vaccine in the northern hemisphere for 2013/14 comprises an A/California/7/2009(H1N1)pdm09-like virus, an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 and a B/Massachusetts/2/2011-like virus [4]. We provide early indicators of the effectiveness of the 2013/14 seasonal vaccine in preventing laboratory-confirmed influenza in Navarre, Spain, by assessing patients in three settings: primary healthcare, hospitalised patients and nursing homes.

Setting and information sources

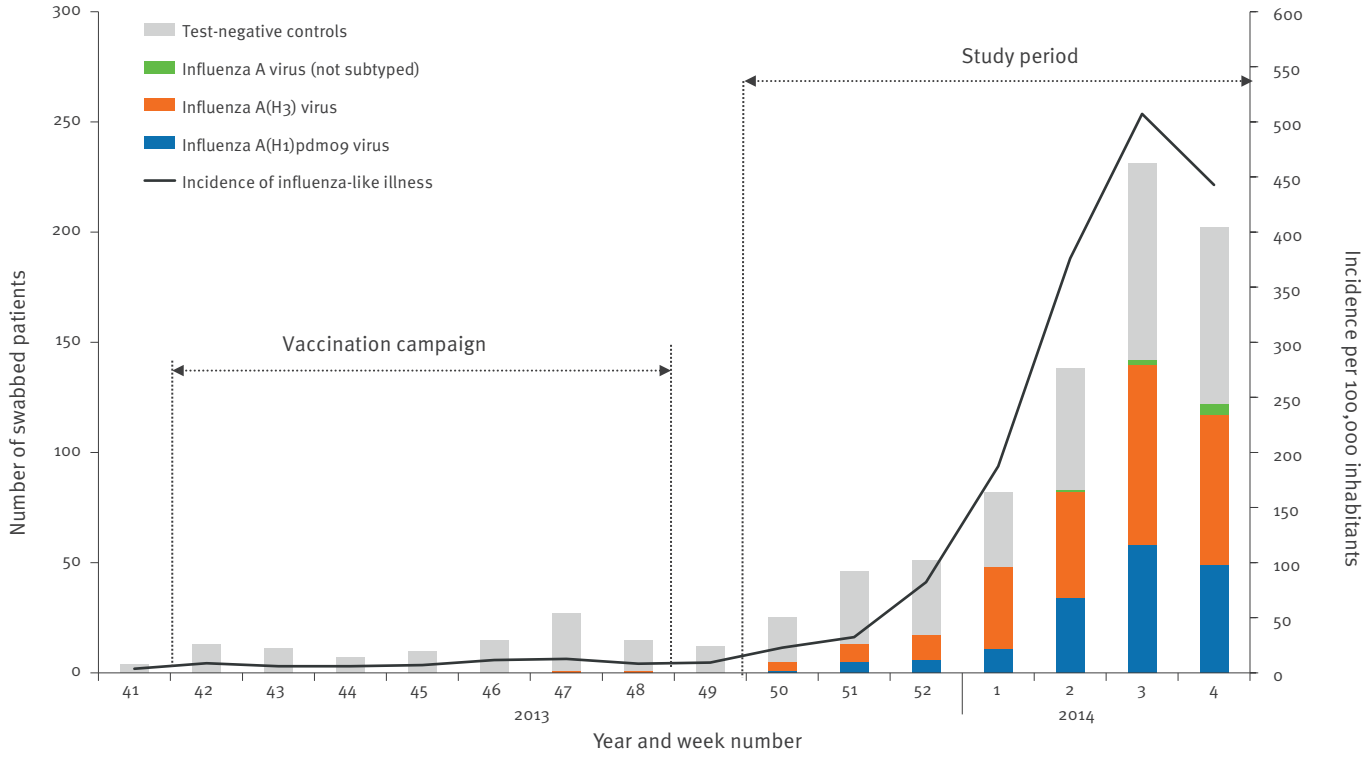
Estimates of vaccine effectiveness (VE) during the influenza season help guide health interventions aimed at reducing the impact of influenza in the population [5,6]. As part of a multicentre European study Influenza Monitoring Vaccine Effectiveness (I-MOVE) [5], Navarre, an autonomous community in northern Spain, has since 2009 provided regular mid-season estimates of influenza VE, which have been supported by estimates at the end of the season [6]. This evaluation of VE is based on electronic clinical records and on epidemiological and virological surveillance of influenza in primary healthcare, hospitals and nursing homes.

In Navarre, the seasonal influenza vaccination campaign took place from 14 October to 30 November 2013. The trivalent inactivated non-adjuvanted vaccine (Vaxigrip, Sanofi Pasteur MSD) was offered free of charge to people aged 60 years or over, to those with major chronic conditions (outlined below) and to people living in institutions. Other people could also be vaccinated if they paid for the vaccine. Precise instructions for registering each dose of vaccine were communicated to all vaccination sites [7]. Influenza vaccine status was obtained from the online regional vaccination register [8] and people were considered to be protected 14 days after vaccine administration. Those for whom the period between vaccination and symptom onset was less than 14 days were excluded, as their immune status is unknown.

Influenza surveillance was based on automatic reporting of cases of influenza-like illness (ILI) from all primary

Figure

Weekly incidence of medically attended influenza-like illness patients and number of swabbed patients by test result, Navarre, Spain, 7 October 2013–26 January 2014



healthcare physicians and searching of ILI cases by public health nurses among admitted patients in hospitals. All of them followed the European Union ILI case definition [9]. A sentinel network composed of a representative sample of 80 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 less than five days previously. In hospitals, an agreed protocol was applied, which specified early detection and nasopharyngeal and pharyngeal swabbing of all hospitalised patients with ILI, but only swabs taken within 10 days of symptom onset were considered in our analysis. Swabs were processed by RT-PCR assay and samples positive for influenza A(H1)pdm09, A(H3) and B viruses were identified.

From the electronic primary healthcare records, we obtained the following baseline variables: sex, age, migrant status, district of residence and 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).

Interim estimation of influenza VE in non-institutionalised inpatients and outpatients

This analysis included 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). All primary healthcare patients and hospitalised patients who were swabbed between 9 December 2013 (the first week with continuous influenza virus detections) and 26 January 2014 were included in an interim test-negative case–control analysis. We compared the seasonal vaccination status of patients in whom any influenza virus was detected (cases) and those who tested negative for influenza (controls). Crude and adjusted estimators of the effect of vaccination were quantified by odds ratios (ORs) with their 95% CIs, calculated using logistic regression models. The adjusted models included sex, age group (<5, 5–14, 15–44, 45–64 and ≥65 years), major chronic conditions, month of sample collection and healthcare setting (primary healthcare and hospital). Separate analyses were carried out by type/subtype of influenza, age group, healthcare setting, and for patients for whom influenza vaccination was indicated because they were 60 years of age or older or had a major chronic condition.

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

During mid-2013/14 season in Navarre, the incidence of ILI cases, number of swabbed patients and number of influenza-positive cases followed a similar trend,

peaking in week 3 (which began on 13 January) of 2014 (Figure).

During the study period, a total of 1,112 ILI patients were swabbed: 775 were included in the VE analysis, of whom 431 were hospitalised patients and 344 were primary healthcare patients recruited by sentinel practitioners. The distribution of these patients by age group (<15, 15–64 and ≥65 years) was, respectively, 21%, 29% and 50% in hospitalised patients, and 13%, 80% and 7% in primary healthcare patients (p<0.001). Influenza virus was laboratory confirmed in 430 (56%) cases: all were infected with influenza A virus. Influenza A(H3) virus was detected in 258 cases, influenza A(H1)pdm09 in 164, and eight remained non-subtyped.

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 and persons treated in hospital. As compared with influenza A(H1)pdm09 detections, influenza A(H3) was more frequently detected in persons aged 65 years or older, persons with major chronic conditions and individuals who were hospitalised. The percentage of hospitalised patients was similar in cases infected with influenza A(H1)pdm09 virus (43%) and those with A(H3) virus (46%, p=0.623) (Table 1).

Among the 430 laboratory-confirmed influenza cases, 98 (23%) had received the 2013/14 seasonal vaccine, versus 113 (33%) of the 345 influenza-negative controls (p=0.002) (Table 1).

In the logistic regression analysis, the overall adjusted estimate of the influenza VE was 24% (95% CI: −14 to 50). The VE estimates were similar in the analysis restricted to primary healthcare patients (23%; 95% CI: −87 to 68), to hospitalised patients (22%; 95% CI: −25 to 52), or to the target population for vaccination (23%; 95% CI: −20 to 51). However, the estimated VE in persons aged 65 years or over (11%; 95% CI: −53 to 48) was lower than the estimate in persons younger than 65 years (39%; 95% CI: −15 to 68) (Table 2).

The VE against influenza A(H1)pdm09 virus was 40% (95% CI: −12 to 68) and against influenza A(H3) was 13% (95% CI: −36 to 45). The estimates restricted to primary healthcare patients, to hospitalised patients and to the target population for vaccination were quite similar (Table 2). However, relevant differences were found in the VE against influenza A(H1)pdm09 virus between persons younger than 65 years (59%; 95% CI: 4 to 83) and those aged 65 or more (4%; 95% CI: −162 to 65) (Table 2).

Influenza outbreaks in nursing homes

Influenza surveillance in Navarre includes the detection and study of influenza outbreaks in nursing homes for elderly people or people with physical or mental disabilities. Outbreaks are passively reported by physicians, actively detected by sentinel general practitioners who cover six nursing homes or actively searched when a nursing home resident is confirmed with influenza in a hospital. Influenza vaccine coverage is usually near 90% or higher in all these institutions (unpublished data from the Vaccination Register of Navarre). From 2009 to 2013, outbreaks of laboratory-confirmed influenza in nursing homes were only detected in the 2011/12 season [10], a season with predominance of influenza A(H3) and low VE in the general population [11]. In the other seasons, the estimated VE

Table 1

Characteristics of patients with medically attended influenza-like illness included in test-negative case–control analysis, by test result, Navarre, Spain, 9 December 2013–26 January 2014 (n=775)

Characteristic	Test-negative controls n (%)	Influenza cases[a] n (%)	Influenza virus	
			A(H1) pdm09 n (%)	A(H3) n (%)
Age groups in years				
<5	69 (20)	22 (5)	7 (4)	14 (5)
5–14	25 (7)	21 (5)	10 (6)	11 (4)
15–44	70 (20)	141 (33)	63 (38)	75 (29)
45–64	61 (18)	127 (30)	64 (39)	61 (24)
≥65	120 (35)	119 (28)	20 (12)	97 (38)
Sex				
Male	170 (49)	212 (49)	76 (46)	132 (51)
Female	175 (51)	218 (51)	88 (54)	126 (49)
Month				
December	98 (28)	49 (11)	15 (9)	34 (13)
January	247 (72)	381 (89)	149 (91)	224 (87)
Residence				
Rural	90 (26)	138 (32)	52 (32)	84 (33)
Urban	255 (74)	292 (68)	112 (68)	174 (67)
Migrant status				
No	325 (94)	398 (93)	143 (87)	248 (96)
Yes	20 (6)	32 (7)	21 (13)	10 (4)
Major chronic conditions				
No	159 (46)	233 (54)	103 (63)	126 (49)
Yes	186 (54)	197 (46)	61 (37)	132 (51)
Healthcare setting				
Primary healthcare	107 (31)	237 (55)	93 (57)	140 (54)
Hospital	238 (69)	193 (45)	71 (43)	118 (46)
Seasonal influenza vaccine 2013/14				
No	232 (67)	332 (77)	142 (87)	183 (71)
Yes	113 (33)	98 (23)	22 (13)	75 (29)
Total	**345 (100)**	**430 (100)[a]**	**164 (100)**	**258 (100)**

[a] Includes eight cases of infection with influenza A virus that was not subtyped.

Table 2

Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in Navarre, Spain, 9 December 2013–26 January 2014

Category of patients	Controls	All influenza viruses		Influenza A(H1)pdm09 virus		Influenza A(H3) virus	
	Number vaccinated/ total	Cases Number vaccinated/ total	VE % (95% CI)[a]	Cases Number vaccinated/ total	VE % (95% CI)[a]	Cases Number vaccinated/ total	VE % (95% CI)[a]
All swabbed patients	113/345	98/430	–	22/164	–	75/258	–
Crude	–	–	39 (17 to 56)	–	68 (47 to 81)	–	16 (–19 to 41)
Adjusted	–	–	24 (–14 to 50)	–	40 (–12 to 68)	–	13 (–36 to 45)
Target population for vaccination[b]	105/204	91/232	–	20/73	–	70/154	–
Crude	–	–	39 (11 to 58)	–	64 (36 to 80)	–	21 (–19 to 48)
Adjusted	–	–	23 (–20 to 51)	–	36 (–28 to 68)	–	15 (–37 to 47)
Age <65 years	35/225	25/311	–	9/144	–	16/161	–
Crude	–	–	53 (18 to 73)	–	64 (22 to 83)	–	40 (–12 to 68)
Adjusted	–	–	39 (–15 to 68)	–	59 (4 to 83)	–	15 (–77 to 59)
Age ≥65 years	78/120	73/119	–	13/20	–	59/97	–
Crude	–	–	15 (–45 to 50)	–	0 (–170 to 63)	–	16 (–45 to 52)
Adjusted	–	–	11 (–53 to 48)	–	4 (–162 to 65)	–	10 (–59 to 49)
Primary healthcare patients	12/107	22/237	–	5/93	–	17/140	–
Crude	–	–	19 (–70 to 62)	–	55 (–33 to 85)	–	–9 (–140 to 50)
Adjusted	–	–	23 (–87 to 68)	–	42 (–97 to 83)	–	11 (–123 to 41)
Hospitalised patients	101/238	76/193	–	17/71	–	58/118	–
Crude	–	–	12 (–30 to 40)	–	57 (22 to 77)	–	–31 (–104 to 16)
Adjusted	–	–	22 (–25 to 52)	–	34 (–41 to 69)	–	14 (–45 to 49)

CI: confidence interval; VE: vaccine effectiveness.

[a] Logistic regression model adjusted for sex, age group (<5, 5–14, 15–44, 45–64 and ≥65 years), month, major chronic conditions and healthcare setting (primary healthcare and hospital).

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

was higher and only sporadic cases were detected in nursing homes [12-14].

In mid-2013/14 season, influenza outbreaks in five nursing homes in Navarre were detected (Table 3). All five had carried out an influenza vaccination campaign in October and November 2013, reaching coverages of 89% to 100%. The influenza outbreaks occurred in January 2014, coinciding with the epidemic wave in the region. In each institution, influenza was laboratory confirmed for three or more ILI patients. Influenza virus A(H3) was identified in 18 patients in four outbreaks in homes for elderly people. Another outbreak occurred in a home for persons with physical disabilities aged 18 to 64 years old, where influenza A(H1)pdm09 virus was detected in the three swabbed patients. In total, 20 of the 22 laboratory-confirmed cases had received the trivalent 2013/14 seasonal vaccine.

Virus characterisation

Although, to date, antigenic tests are pending, we found some genetic differences between circulating and vaccine viruses. Sequence analysis of the product of amplification (HA1 fragment of the haemagglutinin gene) showed that all four influenza A(H1N1)pdm09 viruses studied clustered into the group 6B [15], represented by A/Norway/2417/2013 and defined by D97N, K163Q, S203T, S185T, A256T and K283E amino acid mutations compared with the vaccine virus A/California/07/2009. Nevertheless, all six mutations had already been detected in previous seasons and did not have an important influence on the VE.

All 17 influenza A(H3N2) viruses studied clustered into the group 3C [15], which includes the A/Texas/50/2012 vaccine virus strain, but harbouring some amino acid changes that make it possible to find some genetic differences. All 17 A(H3N2) viruses clustered within the

Table 3

Interim description of influenza outbreaks in five nursing homes, Navarre, Spain, January 2014

Characteristic	Nursing home				
	1	2	3	4	5
Number of residents	40	82	523	55	78
2013/14 influenza vaccine coverage	100%	91%	89%	100%	96%
Number of influenza-like illness cases	8	19	10	6	26
Swabbing criteria	Cases referred to hospital	Hospitalised cases	All cases	All cases[a]	Hospitalised cases
Number of patients with nasopharyngeal swab	3	4	10	5	4
Number of patients confirmed with influenza virus infection	3	3	8	4	4
Number vaccinated/unvaccinated	3/0	3/0	6/2	4/0	4/0
Age range in years	28–44	85–90	69–92	82–90	85–93
Virus type/subtype	A(H1)pdm09	A(H3)	A(H1)pdm09 A(H3)[b]	A(H3)	A(H3)
Influenza-related hospitalisations	2	3	1	2	3

[a] The first case could not be swabbed.

[b] The first laboratory-confirmed case was infected with influenza A(H1)pdm09 virus and the other seven cases with A(H3) virus.

subgroup 3C.3, represented by A/Samara/73/2013 and defined by N128A and R142G amino acid substitutions. Interestingly, we could differentiate 16 viruses within the 3C.3 subgroup with an additional double L157S and N122D mutation. Another virus harbouring the K160R amino acid substitution could be identified within the 3C.3 subgroup. Changes in influenza A(H3N2) viruses are referred to the A/Texas/50/2012 vaccine virus strain.

Discussion and conclusion

In mid-2013/14 influenza season, our analysis suggests low effectiveness of the trivalent influenza vaccine in preventing laboratory-confirmed influenza in Navarre. Similar estimates were obtained for hospitalised patients and primary healthcare patients. In both groups, estimates suggest a moderate VE against influenza A(H1)pdm09 virus and a low VE against influenza A(H3) virus.

We also detected an unusually high number of outbreaks of laboratory-confirmed influenza A(H3) in nursing homes in Navarre with high vaccination coverage, which also suggests low VE. Information on influenza virus infection and vaccine coverage in nursing home workers could not be systematically collected, although it can be related to the occurrence of outbreaks. The outbreaks and lower VE in older people could be due to immunosenescence; however, the VE against influenza A(H3) virus was also low in people under 65 years. Some pre-existing immunity and the higher VE that we found against A(H1N1)pdm09 virus can explain the absence of outbreaks caused by this virus subtype in older people.

In the 2013/14 influenza season to date, influenza activity has peaked in Spain, but it is still increasing in many other European countries. Influenza A(H3) and A(H1)pdm09 viruses are co-circulating in Europe, with different proportions in different countries [1-3]. Both virus components were the same in the 2013/14 and 2012/13 seasonal vaccines. In the 2012/13 season, low VE against influenza A(H3N2) virus was also observed among elderly people in Denmark [16]. Although antigenic tests of influenza A(H3) strains from Navarre are pending, we have found some genetic differences between circulating and vaccine viruses.

In a recent report from Canada, the interim estimate of 2013/14 VE was 74% against A(H1N1)pdm09 viruses. Relative to vaccine, these viruses were antigenically similar and genetically well conserved [17]. Our results suggest a lower VE against this serotype in Navarre, but as yet, we do not have final antigenic results.

The estimates of the VE in Navarre are not representative of Europe, and studies in other countries or regions are necessary to draw conclusions about the influenza VE in Europe in the 2013/14 season.

The results presented here are preliminary, and have limited statistical power and wide CIs for some analyses. Therefore the final results for the season may be different. The case–control analysis included only laboratory-confirmed influenza cases and compared them with controls recruited in the same healthcare settings before either patient or physician knew the laboratory result, a feature that reduces selection bias [18].

The differences between crude and adjusted VE estimates were, in general, greater in the analysis of the influenza A(H1)pdm09 cases. This can be explained because the controls and the influenza A(H3) cases were more similar in their characteristics. In any event, the differences in these characteristics were controlled for in the adjusted analysis.

In our analysis, we included patients recruited in primary healthcare and in hospitals in Navarre, thus achieving representation of the whole spectrum of influenza patients seeking medical care. As the healthcare setting could have acted as a confounding factor, the analyses were stratified or adjusted for this variable. The possibility that the healthcare setting might have modified the effect or biased the results can be ruled out given the similarity of the estimates obtained in these two patient groups separately and in the joint analysis.

These results support a moderate protective effect of the trivalent seasonal vaccine against influenza A(H1) pdm09 virus and a low effect against A(H3) virus in Navarre mid-2013/14 season. These results should serve as a stimulus to design better influenza vaccines [19], to improve the selection of strains contained in the vaccine and to highlight the importance of other preventive measures that complement vaccination in high-risk populations, such as promotion of basic hygiene measures, use of face masks and avoidance of contact with influenza cases [20]. Early treatment with antiviral drugs should be considered in persons diagnosed with influenza who have a high risk of complications, regardless of vaccination status [21].

Even in seasons in which the effectiveness of influenza vaccine is low, vaccination may appreciably reduce the number of cases and hospitalisations in high-risk persons. In the 2013/14 season in Navarre, vaccination resulted in avoiding almost a quarter of the possible influenza cases in the vaccinated at-risk population; while not entirely satisfactory, this result is important in terms of individual and public health.

Network members

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Conflict of interest

None declared.

Authors' contributions

J Castilla, I Martínez-Baz and M Guevara designed the study, coordinated the activities and undertook the statistical analysis. E Albeniz coordinated the activities in primary healthcare. A Navascués, M Fernández-Alonso, G Reina and C Ezpeleta were responsible for the virological analysis and interpretation of laboratory results. J Chamorro and MT Ortega coordinated the activities in hospitals. E Albeniz coordinated the activities in primary healthcare. F Pozo was responsible for the virus characterisation. J Castilla, I Martínez-Baz and M Guevara wrote the draft manuscript, and all authors revised and approved the final version.

References

1. Adlhoch C, Broberg E, Beauté J, Snacken R, Bancroft E, Zucs P, et al. Influenza season 2013/14 has started in Europe with influenza A(H1)pdm09 virus being the most prevalent subtype. Euro Surveill. 2014;19(4):pii=20686.
2. Sistema de Vigilancia de la Gripe en Espa-a. Informe semanal de Vigilancia de la Gripe en Espa-a. Semana 04/2014 (20 - 26 de enero 2014). [Weekly report of the influenza surveillance system in Spain 4/2014]. No 378. Madrid: Instituto de Salud Carlos III; 30 January 2014. Spanish. Available from: http://vgripe.isciii.es/gripe/documentos/20132014/boletines/grn042014.pdf
3. European Centre for Disease Prevention and Control (ECDC). Weekly influenza surveillance overview. 7 February 2014. Stockholm: ECDC: 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/influenza-surveillance-overview-7-feb-2014.pdf
4. Recommended composition of the influenza virus vaccines for use in the 2013–2014 northern hemisphere influenza season. Wkly Epidemiol Rec. 2013;88(10):101-14.
5. Valenciano M, Ciancio B; I-MOVE study team. I-MOVE: a European network to measure the effectiveness of influenza vaccines. Euro Surveill. 2012;17(39):pii=20281.
6. Castilla J, Morán J, Martínez-Artola V, Reina G, Martínez-Baz I, García Cenoz M, et al. Effectiveness of trivalent seasonal and monovalent influenza A(H1N1)2009 vaccines in population with major chronic conditions of Navarre, Spain: 2010/11 mid-season analysis. Euro Surveill. 2011;16(7):pii=19799.
7. Instituto de Salud Pública y Laboral de Navarra. Protocolo de vacunación antigripal 2013-2014. [Influenza vaccination protocol 2013-2014]. Boletín Informativo. 2013;74:1-4. Spanish. Available from: http://www.navarra.es/NR/rdonlyres/AECCD760-AB2A-4841-818A-FA53478FD6DC/265602/BOL74INTCampana20132014.pdf
8. Aguilar I, Reyes M, Martínez-Baz I, Guevara M, Albéniz E, Belza MJ, et al. Use of the vaccination register to evaluate influenza

vaccine coverage in seniors in the 2010/11 influenza season, Navarre, Spain. Euro Surveill. 2012;17(17):pii=20154.

9. European Commission. Commission Decision of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Official Journal of the European Union. Luxembourg: Publications Office of the European Union. 18.6.2008:L 159. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:159:0046:0090:EN:PDF
10. Castilla J, Cía F, Zubicoa J, Reina G, Martínez-Artola V, Ezpeleta C. Influenza outbreaks in nursing homes with high vaccination coverage in Navarre, Spain, 2011/12. Euro Surveill. 2012;17(14):pii=20141.
11. Castilla J, Martínez-Baz I, Martínez-Artola V, Reina G, Pozo F, García Cenoz M, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. Euro Surveill. 2013;18(5):pii=20388.
12. Martínez-Baz I, Martínez-Artola V, Reina G, Guevara M, Cenoz MG, Morán J, et al. Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010-2011: a population-based test-negative case-control study. BMC Public Health. 2013;13:191. http://dx.doi.org/10.1186/1471-2458-13-191
13. Castilla J, Martínez-Baz I, Martínez-Artola V, Fernández-Alonso M, Reina G, Guevara M, et al. Early estimates of influenza vaccine effectiveness in Navarre, Spain: 2012/13 mid-season analysis. Euro Surveill. 2013;18(7):pii=20404.
14. Instituto de Salud Carlos III. Informe de Vigilancia de la Gripe en Espa-a. Temporada 2012-2013 (Desde la semana 40/2012 hasta la semana 20/2013). Sistema de Vigilancia de la Gripe en Espa-a. [Report of the Influenza surveillance in Spain, season 2012-2013]. Madrid: Instituto de Salud Carlos III; 2013. Spanish. Available from: http://vgripe.isciii.es/gripe/documentos/20122013/InformesAnuales/Informe_Vigilancia_GRIPE_2012-13_18sep2013.pdf
15. European Centre for Disease Prevention and Control (ECDC). Influenza virus characterization. Summary Europe, December 2013. Stockholm: ECDC; 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/influenza-virus-characterisation-dec-2013.pdf
16. Bragstad K, Emborg HD, Fischer TK, Voldstedlund M, Gubbels S, Andersen B, et al. Low vaccine effectiveness against influenza A(H3N2) virus among elderly people in Denmark in 2012/13 – a rapid epidemiological and virological assessment. Euro Surveill. 2013;18(6):pii=20397.
17. Skowronski DM, Chambers C, Sabaiduc S, De Serres G, Dickinson JA, Winter AL, et al. Interim estimates of 2013/14 vaccine effectiveness against influenza A(H1N1)pdm09 from Canada's sentinel surveillance network, January 2014. Euro Surveill. 2014;19(5):pii=20690.
18. Valenciano M, Kissling E, Ciancio BC, Moren A. Study designs for timely estimation of influenza vaccine effectiveness using European sentinel practitioner networks. Vaccine. 2010;28(46):7381-8. http://dx.doi.org/10.1016/j.vaccine.2010.09.010
19. Lambert LC, Fauci AS. Influenza vaccines for the future. N Engl J Med. 2010;363(21):2036-44. http://dx.doi.org/10.1056/NEJMra1002842
20. Godoy P, Castilla J, Delgado-Rodríguez M, Martín V, Soldevila N, Alonso J, et al. Effectiveness of hand hygiene and provision of information in preventing influenza cases requiring hospitalization. Prev Med. 2012;54(6):434-9. http://dx.doi.org/10.1016/j.ypmed.2012.04.009
21. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza -- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(1):1-24.