Interim effectiveness of trivalent influenza vaccine in a season dominated by lineage mismatched influenza B, northern Spain, 2017/18

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The 2017/18 interim estimate of trivalent influenza vaccine effectiveness (VE) was 39% (95% confidence interval: 20–54) in Navarre. Compared with individuals unvaccinated in the current and five previous seasons, VE against influenza B was 41% for current and any prior doses, 67% for current vaccination only, and 22% for any prior doses, and 43%, 51% and 54%, respectively against influenza A(H3N2). This suggests moderate VE despite predominance of lineage mismatched influenza B.

The early 2017/18 influenza season in Europe was characterised by co-circulation of influenza B, A(H3N2) and A(H1N1)pdm09, with lineage mismatched influenza B(Yamagata) virus predominating in many countries [1,2]. Concerns arose due to the low influenza vaccine effectiveness (VE) reported in the 2017 influenza A(H3N2) epidemic in Australia [3] and the warning about low VE of the trivalent influenza vaccine (TIV) against a lineage mismatched influenza B(Yamagata) virus [4]. Influenza vaccination in previous seasons may retain some preventive effect and modify the effect of the current season vaccination so the vaccination history should be considered in the VE assessment [5,6].

We present the 2017/18 interim effectiveness estimates of different combinations of current and prior season influenza vaccination in preventing laboratory-confirmed influenza.

Study design and information sources
A test-negative case–control study was used for the estimations. Cases and controls were identified through the influenza epidemiological and virological surveillance in primary healthcare and hospitals in Navarre, northern Spain. In October and November 2017, the trivalent inactivated non-adjuvanted vaccine was offered free of charge to the target population for vaccination, which included people aged 60 years or more and people with major chronic conditions. The TIV comprised influenza A/Michigan/45/2015(H1N1)-like, A/HongKong/4801/2014(H3N2)-like and B/Brisbane/60/2008(Victoria-lineage)-like antigens [7]. The TIV had contained B(Yamagata) antigens in the 2012/13 to 2015/16 seasons [8]. Influenza vaccine status in the current and five prior influenza seasons, 2012/13 to 2017/18, was obtained from the regional vaccination register, where all vaccines administered in healthcare centres are registered online [9]. Persons were considered to be protected by the vaccine 14 days after receiving it.

Influenza surveillance relied on all primary healthcare physicians and hospitals automatically reporting influenza-like illness (ILI) cases [6]. A sentinel network of primary healthcare physicians collected nasopharyngeal and pharyngeal swabs from their patients diagnosed with ILI, when symptoms had appeared less than five days before. In hospitals, early detection and swabbing of all hospitalised patients with ILI was specified by the protocol. Samples were processed by reverse-transcription PCR assay. A selection of representative strains of each week and virus type/subtype was sent to the National Influenza Centre–Madrid laboratory to be completely genetically characterised.

Statistical analysis
The study population included individuals covered by the Navarre Health Service since 2012 (96% of the population). All ILI patients who were swabbed in

TABLE 1

Characteristics of the patients with medically-attended influenza-like illness included in the test-negative case–control analysis, Navarre, Spain, December 2017–January 2018 (n = 1,268 patients)

Characteristics	Test-negative controls		All influenza cases		Influenza B		Influenza A(H3N2)		Influenza A(H1N1)pdm09	
	N	%	N	%	N	%	N	%	N	%
Age groups (years)										
9–24	14	2	35	5	30	6	2	2	3	8
25–44	89	15	150	23	109	22	27	22	14	39
45–64	123	20	170	26	136	27	25	21	8	22
65–84	271	44	203	31	158	32	37	32	8	22
≥85	117	19	96	15	65	13	27	23	3	8
Sex										
Male	336	55	311	48	230	46	62	52	18	50
Female	278	45	343	52	268	54	56	48	18	50
Major chronic conditions										
No	167	27	278	43	221	44	37	31	19	53
Yes	447	73	376	57	277	56	80	69	17	47
Month of swabbing										
December	178	29	91	14	76	15	11	9	4	11
January	436	71	563	86	422	85	107	91	32	89
Target group for vaccination[a]										
No	110	18	210	32	164	33	27	23	18	50
Yes	504	82	444	68	334	67	91	77	18	50
Healthcare setting										
Primary healthcare	131	21	329	50	264	53	43	37	22	61
Hospitalization	483	79	325	50	234	47	75	63	14	39
2017/18 season vaccine										
No	283	46	423	65	328	66	66	56	28	78
Yes	331	54	231	35	170	34	52	44	8	22
Total	614	100	654	100[b]	498	100	118	100	36	100

[a] Target group for vaccination includes people ≥60 years-old and people with major chronic conditions.
[b] Two cases were influenza A not subtyped.

December 2017 and January 2018 were considered. We excluded healthcare workers, people living in nursing homes, children under 9 years of age and patients hospitalised prior to ILI symptom onset. The seasonal vaccination status of patients testing positive for influenza virus (cases) was compared to that of those who were negative for this virus (controls). Logistic regression models were employed to derive crude and adjusted odds ratios (OR) with their 95% confidence intervals (CI). Adjusted models included sex, age group (9–24, 25–44, 45–64, 65–84 and ≥85 years), major chronic conditions, month of swabbing and healthcare setting. Four categories combining the current-season and five prior season vaccination were considered: current-season vaccination and any prior doses, current-season vaccination and no prior doses, no current-season vaccination and any prior doses, and no current-season vaccination and no prior doses (reference group). VE was estimated as a percentage: (1 − OR) x 100.

Influenza vaccine effectiveness interim estimation

A total of 1,268 ILI patients were included, 808 (64%) inpatients and 460 (36%) primary healthcare patients. A total of 654 (52%) were confirmed cases for influenza virus: 498 (76%) for influenza B, 118 (18%) for A(H3N2), 36 (6%) for A(H1N1)pdm09 and two non-subtyped influenza A viruses.

The sequence derived from the amplification product of the HA1 fragment of the haemagglutinin gene was characterised for 51 viruses. Of 40 influenza B viruses, 35 were B/Phuket/3073/2013(Yamagata-lineage)-like, three B/Brisbane/60/2008(Victoria-lineage)-like and two B/Norway/2409/2017(Victoria-lineage)-like. The four A(H1N1)pdm09 strains were A/Michigan/45/2015-like. Among seven A(H3N2) strains, five were A/HongKong/4801/2014-like and two A/Singapore/16–0019/2016-like.

Compared with test-negative controls, influenza cases comprised a lower proportion of individuals aged

Table 2

Influenza vaccine effectiveness in preventing laboratory-confirmed influenza among individuals aged 9 years or older in Navarre, Spain, December 2017–January 2018 (n = 1,268 patients)

Models	Controls Vaccinated/unvaccinated	Cases Vaccinated/unvaccinated	Crude vaccine effectiveness % (95% CI)	Adjusted vaccine effectiveness % (95% CI)[a]
All swabbed patients	331/283	231/423	53 (42 to 63)	39 (20 to 54)
Target group for vaccination[b]	318/186	216/228	45 (28 to 57)	39 (17 to 54)
Age group				
9–64 years	54/172	41/314	58 (35 to 73)	55 (26 to 73)
≥65 years	277/111	190/109	30 (4 to 49)	30 (2 to 50)
Virus type/subtype				
Influenza B	331/283	170/328	56 (43 to 65)	41 (20 to 56)
Influenza A(H3N2)	331/283	52/66	33 (0 to 55)	29 (−15 to 57)
Influenza A(H1N1)pdm09	331/283	8/28	76 (46 to 89)	59 (−6 to 84)
Primary healthcare patients				
All influenza viruses	35/96	56/273	44 (9 to 65)	51 (13 to 73)
Influenza B	35/96	47/217	41 (2 to 64)	52 (12 to 74)
Influenza A(H3N2)	35/96	6/37	56 (−14 to 83)	54 (−44 to 85)
Influenza A(H1N1)pdm09	35/96	3/19	57 (−55 to 88)	49 (−120 to 88)
Hospitalised patients				
All influenza viruses	296/187	175/150	26 (2 to 45)	35 (11 to 53)
Influenza B	296/187	123/111	30 (4 to 49)	37 (11 to 55)
Influenza A(H3N2)	296/187	46/29	0 (−65 to 39)	20 (−40 to 54)
Influenza A(H1N1)pdm09	296/187	5/9	65 (−6 to 88)	63 (−27 to 89)

CI: confidence interval.

[a] Logistic regression model adjusted for sex, age group (9–24, 25–44, 45–64, 65–85 and ≥85 years), major chronic conditions, month of swabbing and healthcare setting (primary healthcare and hospital).

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

65 years or older, of persons with comorbidities or who were attended in hospitals. Among cases, 35% (231/654) had been vaccinated in the 2017/18 season vs 54% (331/614) among controls (p < 0.001) (Table 1).

Regardless of the vaccination history, the overall adjusted estimate of influenza VE was 39% (95% CI: 20 to 54). In persons less than 65 years-old the estimates were higher (55%) than in the older age group (30%), and in outpatients (51%) than inpatients (35%). VE was 41% (95% CI: 20 to 56) against influenza B, 29% (95% CI: −15 to 57) against A(H3N2), and 59% (95% CI: −6 to 84) against A(H1N1)pdm09 (Table 2).

Nevertheless, better levels of protection were observed in the analysis considering the vaccination history. Compared with persons never vaccinated in the current and five previous seasons, the preventive effect was 42% (95% CI: 20 to 58) in those vaccinated in the current and any prior seasons, 65% (95% CI: 32 to 82) in those vaccinated only in the current season, and 28% (95% CI: −11 to 53) in those vaccinated only in any prior seasons. The corresponding estimates against influenza B were 41% (95% CI: 17 to 59), 67% (95% CI: 31 to 84) and 22% (95% CI: −24 to 51), and against A(H3N2)

were 43% (95% CI: −1 to 67), 51% (95% CI: −51 to 84) and 54% (95% CI: −7 to 80), respectively (Table 3).

Discussion

These results suggest a protective effect of the TIV of 42% to 65% in the early 2017/18 season in Navarre, depending on the vaccination status in prior seasons. Moderate VE was observed against influenza B, A(H1N1)pdm09 and A(H3N2).

Our results on influenza B are consistent with those recently reported from Canada [10] and contrast with the low VE expected in a season dominated by lineage mismatched influenza B virus [4]. Although we observed some preventive effect of previous vaccinations in individuals unvaccinated in the current season, the highest VE against influenza B was seen in people vaccinated in the current season but not vaccinated in prior ones, ruling out the possibility that the observed VE is due to the residual effect of previous vaccines containing B(Yamagata). Instead, this notable effectiveness of the TIV against influenza B suggests important cross-lineage protection [10-15].

Effectiveness of current season influenza vaccination and of vaccination in the five prior seasons in preventing laboratory-confirmed influenza cases among people aged 9 years or older, Navarre, Spain, December 2017–January 2018 (n = 1,268 patients)

Vaccination history by type of patients or influenza	Cases/controls	Crude vaccine effectiveness % (95% CI)	Adjusted vaccine effectiveness % (95% CI)[a]
All patients			
Never vaccinated	366/211	Reference	Reference
No current+any prior dose	57/72	54 (33 to 69)	28 (−11 to 53)
Current only	17/28	65 (35 to 81)	65 (32 to 82)
Current+any prior dose	214/303	59 (48 to 68)	42 (20 to 58)
Primary healthcare patients			
Never vaccinated	261/87	Reference	Reference
No current+any prior dose	12/9	56 (−9 to 82)	51 (−25 to 81)
Current only	8/11	76 (38 to 91)	79 (42 to 92)
Current+any prior dose	48/24	33 (−15 to 61)	39 (−20 to 69)
Hospitalised patients			
Never vaccinated	105/124	Reference	Reference
No current+any prior dose	45/63	16 (−34 to 47)	20 (−31 to 52)
Current only	9/17	38 (−46 to 73)	47 (−28 to 78)
Current+any prior dose	166/279	30 (3 to 49)	41 (13 to 59)
Influenza B			
Never vaccinated	283/211	Reference	Reference
No current+any prior dose	45/72	53 (30 to 69)	22 (−24 to 51)
Current only	13/28	65 (32 to 83)	67 (31 to 84)
Current+any prior dose	157/303	61 (50 to 70)	41 (17 to 59)
Influenza A(H3N2)			
Never vaccinated	28/211	Reference	Reference
No current+any prior dose	8/72	60 (11 to 82)	54 (−7 to 80)
Current only	4/28	48 (−54 to 83)	51 (−51 to 84)
Current+any prior dose	48/303	42 (11 to 82)	43 (−1 to 67)

CI: confidence interval.

[a] Vaccine effectiveness adjusted by age groups (9–24, 25–44, 45–64, 65–84 and ≥85 years), sex, major chronic conditions, healthcare setting (primary healthcare and hospital), and month of swabbing.

The moderate VE against influenza A(H3N2) observed in the analysis adjusted for vaccination history contrasts with the lower estimate from the analysis that only considers current season vaccination, indicating that the vaccination history may be a confounding factor [6]. By including in the analyses any vaccination in the five prior seasons, the reference category was not affected by residual vaccine effect.

Our results from two independent groups, i.e. hospitalised patients and primary healthcare patients, were broadly consistent. The lower point estimates among inpatients in some analyses might be explained by the poorer immune response of patients who required hospitalisation.

This study has some limitations. The number of influenza B cases with known lineage was too small to obtain estimates by lineage, although 88% of known lineages were Yamagata. The results are preliminary and for some analyses, the statistical power is limited. Nevertheless, selection bias was reduced by recruiting laboratory-confirmed cases and controls in the same settings before either patient or physician was aware of laboratory results [16]. We also included outpatients and inpatients, thus obtaining broad representation of patients with influenza. The analyses were adjusted for the healthcare setting as this variable could have acted as a confounding factor.

In conclusion, these results suggest moderate effectiveness of the trivalent inactivated influenza vaccine against the three circulating viruses in the early 2017/18 season in northern Spain. The TIV effectiveness against influenza B suggests an important cross-lineage protection.

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Conflict of interest

None declared.

Authors' contributions

J Castilla, A Navascués, I Casado and I Martínez-Baz designed the study and coordinated the activities. I Martínez-Baz, I Casado and J Castilla undertook the statistical analysis. A Navascués, A Aguinaga, A Pérez-García, C Ezpeleta and F Pozo were responsible of the virological analysis and the interpretation of laboratory results. G Ezpeleta, I Casado, the Primary Health Care Sentinel Network, and the Network for Influenza Surveillance in Hospitals of Navarre participated in the data collection. J Castilla, I Casado and I Martínez-Baz wrote the draft manuscript, and all authors revised and approved the final version.

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