Residual immunity in older people against the influenza A(H1N1) – recent experience in northern Spain

E Pérez-Trallero (mikrobiol@terra.es)[1,2,3], L Piñeiro[1], D Vicente[1,2], M Montes[1,2], G Cilla[1,2]

1. Microbiology Service and Reference Laboratory for Influenza Infections of the Basque Country, Hospital Donostia, San Sebastián, Spain
2. Biomedical Research Centre Network for Respiratory Diseases (CIBERES), San Sebastián, Spain
3. Department of Preventive Medicine and Public Health, Faculty of Medicine, University of the Basque Country, San Sebastián, Spain

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The 2009 pandemic influenza A(H1N1) virus has a higher incidence in children and young adults, a pattern that has also been reported in seasonal influenza caused by the influenza A(H1N1) virus. We analysed age at infection in symptomatic patients with influenza in the Basque Country (northern Spain), reported through the sentinel influenza surveillance system which monitors 2.2-2.5% of the population. Between September 1999 and August 2009, influenza A(H3N2) or seasonal influenza A(H1N1) was detected in 941 patients, and from April to August 2009, pandemic influenza A(H1N1) was detected in 112 patients. The H3/H1 seasonal influenza ratio was between 3.3 and 3.4 in the under 60 year-olds, but 9.8 in older individuals, suggesting that people born before 1950 have residual immunity against the influenza A H1N1 subtype (both seasonal and pandemic).

Introduction

In 1957, the *Asian influenza* pandemic was caused by influenza A(H2N2) virus, which circulated until 1968 when it was displaced by the influenza A(H3N2) virus which was responsible for the *Hong Kong* pandemic. Before 1957, direct descendants of the influenza A(H1N1) virus that had caused the 1918 pandemic (*Spanish flu*) had circulated. In 1977, an influenza A(H1N1) strain re-emerged, which, together with the dominant influenza A(H3N2) strain, has been the cause of seasonal human influenza for more than three decades [1]. Despite the prolonged co-circulation of both subtypes, few studies have analysed their ability to affect distinct age groups.

The current pandemic influenza A(H1N1) virus, influenza A(H1N1)v, which emerged in the spring of 2009, has spread throughout the world. The aim of this study was to compare the distribution in distinct age groups of infections caused by the two subtypes of seasonal influenza in the past 10 seasons and relate this to recent infections due to influenza A(H1N1)v.

Methods

The virological study was performed in the Microbiology Department of Hospital Donostia, which is the Reference Laboratory for influenza infections in the Basque Country and part of the Spanish influenza surveillance system. The sentinel physicians in this system attend to 2.2%-2.5% of the 2.1 million inhabitants of the region. The age and sex of subjects to be monitored represent the normal distribution of people in our region.

Samples (pharyngeal swabs with viral transport medium) were obtained from patients with symptoms of influenza according to the International Classification of Primary Care (ICPC) definition (code 487). This definition includes four (in epidemic seasons) or six (in non-epidemic seasons) of the following criteria: sudden symptom onset, fever of >38 ºC, cough, chills, general malaise, muscle and joint ache, upper respiratory tract involvement, or contact with an infected person. We included patients between week 40 of one year and week 20 of the following year in the seasons from 1999 to 2008. The 2008 9 season was extended until 31 August 2009 due to the pandemic.

In the study period, influenza vaccination was recommended for individuals older than 65 years (ca. 65% coverage was reached during the study period) and individuals with risk factors. Seasonal influenza viruses were identified through virus culture and/or detection of two or more viral genes in a reverse transcriptase-polymerase chain reaction (RT-PCR) assay directed at the matrix and nucleoprotein genes [2], and positive samples were further subtyped by PCR as H1 or H3 [3]. RT-PCR assays were also done for the nucleoprotein [4], haemagglutinin and M2 matrix protein (Influenza A/H1N1 Detection Set®, Roche) of the pandemic influenza A(H1N1)v strain.

Results

A total of 1,106 laboratory-confirmed influenza A virus infections were detected in the 2,801 symptomatic patients who had consulted a physician of the surveillance network. Of these 1,106 infections, 994 were caused by seasonal influenza A viruses (733 H3, 208 H1 and 53 not subtyped) and 112 by the pandemic influenza A(H1N1) v virus. The distribution of the two seasonal influenza subtypes (H1 and H3) according to age is shown in Table 1.

The ratio between the subtypes H3 and H1 (total numbers) was 3.5. In people under and over the age of 60 years, it was 3.4 and 9.8, respectively (chi-squared test=4.29, p=0.038).

The results according to year of birth are shown in Table 2.

The first case of pandemic influenza A(H1N1)v infection was detected in the Basque Country on 26 April 2009. Of 263 patients suspected to have pandemic influenza who were studied by the influenza surveillance system between that date and 31 August 2009, 112 were laboratory-confirmed as influenza A(H1N1)v cases. These 112 infections affected mainly children and young adults (see Table 1), similar to a further 219 influenza A(H1N1)v infections that were not detected as part of the influenza surveillance system and are not included in this study.

Among the seasonal influenza patients, there were 55 vaccination failures, 47 cases of A(H3N2) and eight cases of A(H1N1) infection. The ratio was 4.5 (27 H3N2 and six H1N1) and 10 (20 H3N2 and two H1N1) in people under and over the age of 60 years, respectively (Fisher 0.45, non significant).

Discussion

Only two (1.8%) of the 112 patients with 2009 pandemic H1N1 influenza who were included in this study were older than 59 years. This percentage was 4.1% (9/219) among patients with a 2009 pandemic H1N1 influenza infection not detected through the sentinel surveillance system. The low proportion of people born before 1950 who are infected with this virus has also been observed in other parts of the world [5,6].

Among the symptomatic cases of seasonal influenza who consulted a physician and were detected by the sentinel surveillance system in the Basque Country in the past 10 seasons, symptomatic infections caused by the H3 subtype were 3.5 times more frequent than those caused by the H1 subtype. This H3/H1 ratio was seen in all age groups until the age of 59 years, but in older individuals the ratio tripled (from 3.4 to 9.8), with 91% of the over 60 year-old patients infected with H3 strains.

That the two subtypes are not equally distributed in different age groups was initially reported in the 1980s [7,8] and more recently in a study from the United States and Oceania based on strains sequenced in the past 15 years (1995-2008) [9]. Unlike earlier studies reporting that the H1 subtype rarely affected people older than 30 years [7,8], the present study found that approximately one third of the patients with influenza A(H1N1), both pandemic and seasonal, were between 30 and 59 years-old, suggesting that young adults today do not have the residual immunity of persons

Table 1

Seasonal influenza A subtypes detected in the seasons from 1999 to 2009 (n=941*) and pandemic influenza A(H1N1) virus detected from 26 April to 31 August 2009 (n=112) in the Basque Country Influenza Surveillance System, by age group

Age group (years)	Seasonal influenza A			Pandemic influenza
	A(H3N2)	A (H1N1)	*Ratio H3/H1*	A(H1N1)v
0 a 4	110	31	*3.5*	4
5 a 9	105	33	*3.2*	7
10 a 14	92	26	*3.5*	31
0 to 14	**307**	**90**	***3.4***	**42**
15 a 19	52	15	*3.5*	15
20 a 24	48	15	*3.2*	16
25 a 29	60	16	*3.8*	14
15 to 29	**160**	**46**	***3.5***	**45**
30 a 34	40	9	*4.4*	3
35 a 39	46	17	*2.7*	5
40 a 44	48	15	*3.2*	3
30 to 44	**134**	**41**	***3.3***	**11**
45 a 49	38	11	*3.5*	7
50 a 54	27	10	*2.7*	4
55 a 59	28	6	*4.7*	1
45 to 59	**93**	**27**	***3.4***	**12**
60 a 64	11	0	-	1
65 a 69	8	1	*8*	0
70 a 74	8	1	*8*	0
60 to 74	**27**	**2**	***13.5***	**1**
>74	12	2	*6.0*	1
Total	**733**	**208**	***3.5***	**112**
Mean age	25.2	23.6		23.2

* 53 isolates were not subtyped and are not included.

of the same age in previous decades. Since this study included 10 influenza seasons, data by birth year gave a clearer indication of residual immunity than age in years.

Vaccination failures due to the influenza H3 subtype were six times more frequent than those due to H1, suggesting greater genetic variability of the H3 subtype. The antigenic drift proceeds at a slower pace in the H1 haemagglutinin gene than in the H3 gene [10]. This greater variability of the influenza A(H3N2) virus could also explain the greater frequency and severity of infections caused by this subtype [7].

Residual immunity against seasonal and pandemic influenza A(H1N1) virus in people born before 1950 is probably due to the lower capacity for drift of the H1N1 subtype, combined with the wide circulation of this virus between 1918 and 1957.

Table 2

Seasonal influenza A subtypes detected in the seasons from 1999 to 2009 (n=941) in the Basque Country Influenza Surveillance System, by year of birth

Year of birth	Seasonal influenza A		
	H3	H1	Ratio H3/H1
2005-2009	32	11	2.9
2000-2004	94	30	3.1
1995-1999	104	22	4.7
1995-2009	**230**	**63**	**3.7**
1990-1994	80	23	3.5
1985-1989	57	22	2.6
1980-1984	54	16	3.4
1980-1994	**191**	**61**	**3.1**
1975-1979	43	13	3.3
1970-1974	53	11	4.8
1965-1969	44	18	2.4
1965-1979	**140**	**42**	**3.3**
1960-1964	47	18	2.6
1955-1959	39	7	5.6
1950-1954	26	9	2.9
1950-1964	**112**	**34**	**3.3**
1945-1949	23	4	5.8
1940-1944	8	0	-
1935-1939	11	2	5.5
1935-1949	**42**	**6**	**7.0**
1930-1934	6	0	-
1925-1929	7	0	-
1920-1924	0	1	0.0
1920-1934	**13**	**1**	**13.0**
1900-1919	**5**	**1**	**5.0**
Total	**733**	**208**	**3.5**
Mean age	25.2	23.6	

Chi-squared test=4.55 in persons born before and after 1950; p=0.033; odds ratio 2.23 (95% confidence interval: 1.04 to 5.49).

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