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Residual immunity in older people against the influenza A(H1N1) – recent experience in northern 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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Early estimates of 2009 pandemic influenza A(H1N1) virus activity in general practice in France: incidence of influenza-like illness and age distribution of reported cases

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In the end of August 2009, an unusually elevated level of influenza-like illness (ILI) activity was reported to the French Sentinel Network. We quantified the observed excess in ILI cases in France during summer 2009 and characterised age patterns in reported cases. An excess of cases has been observed since 5 July, with a time increasing trend. The cumulated estimated excess number of ILI cases was 269,935 [179,585; 316,512], corresponding to 0.5% French population over the period. Compared to the same period in the past years, relative cumulated incidence was greater among young subjects and lower among subjects over 65 years-old. Compared to past epidemics, the relative cumulated incidence was greater in children less than five years-old. This excess of cases may reflect the current spread of the A(H1N1) virus in France, subject to the following limitations: estimates were based on clinical cases consulting a GP; large media coverage may have led to a non specific increase in consultation rates.

Background

Cases of infection with the 2009 pandemic influenza A(H1N1) virus have been reported in France since May 2009, with first evidence of local secondary transmission in July 2009.

By the end of August, an unusually elevated level of influenza-like illness (ILI) had been reported to the French Sentinel Network (FSN), an epidemiological surveillance system based on general practitioners (GPs) and operating since 1984 in France.

The objective of the present study was to quantify the excess in ILI cases in France during the 2009 summer and to examine age patterns in the reported cases using, for comparison, data reported to a long-running routine surveillance system.

Method

Sentinel network and estimation of ILI incidence

Sentinel GPs report ILI cases to the FSN in real time. The ILI case definition is sudden onset of fever (39°C or above) with myalgia and respiratory signs [1]. Weekly ILI incidence is estimated using the average number of ILI cases reported by GPs, and then extrapolated to national ILI incidence using the ratio of all French GPs to participating sentinel GPs [2]. Characteristics of the GPs in the Sentinel Network are similar to those of all French GPs as regards the regional distribution, the proportion of GPs in rural practice and the type of practice [3].

Expected and excess ILI cases

Starting on 1 June 2009, the expected ILI incidence was calculated for each week as the average of weekly ILI incidences reported in the preceding, current and following weeks in the period 1985 to 2008 [4]. A 90% confidence interval was derived from the 5th and 95th percentiles of these values (Q_5 and Q_{95}, respectively) for each week.

For a given week, an excess in ILI incidence was defined when the observed incidence was above Q_{95}. The number of excess cases was calculated as the difference between the observed and expected incidences. The inferior bound (respectively superior bound) of this excess was calculated as the difference between the observed incidence and Q_{95} (respectively Q_5).

Relative cumulated incidence according to age

Incidence according to age was determined by apportioning extrapolated cases according to the age distribution in reported cases, using the following age groups: <5 years, 5-17, 18-49, 50-64 and ≥65 years. However, it is difficult to compare directly these incidences with past epidemics as the A(H1N1) pandemic is still in its early phase. Therefore, we extracted the age pattern of reported cases by computing relative incidence rates as the ratio of incidence in an age group to incidence in the whole population. Relative incidences larger than 1 indicate that the corresponding age class experienced larger incidence than the population as a whole.

The relative cumulated incidence rates according to age of ILI cases were calculated for: a) the current period, b) the

same weeks in the past years and c) the past seasonal epidemic periods, as determined by the FSN and d) the 1986-7 and 1988-9 seasonal epidemics during which influenza A(H1N1) virus was the predominant circulating influenza virus [5].

Results

As shown in Figure 1, the current estimated ILI incidence has been in excess of expected incidences of ILI cases in France since week 28 of 2009 (6 to 12 July), with an increasing time trend.

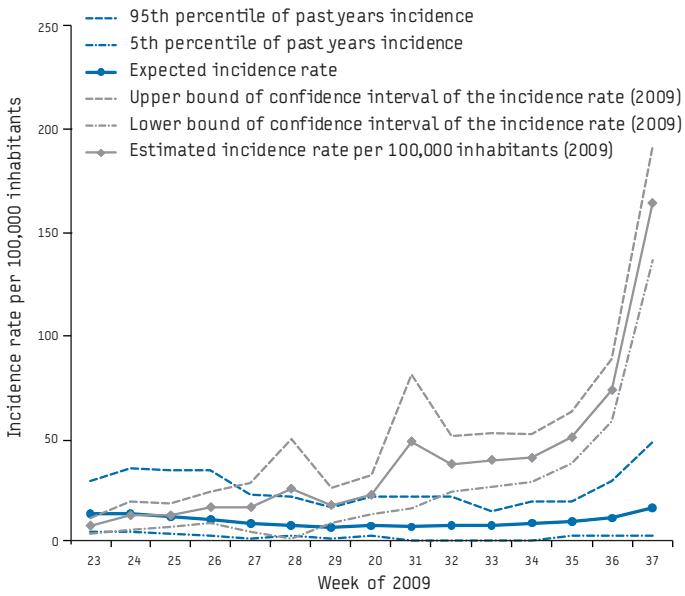
Weekly estimated excess of ILI cases (90% CI bounds are presented in brackets) increased from 6,805 [654; 10,076] cases in week 29, to 92,505 [72,563; 101,456] cases in week 37, the time of writing this article (Table). Overall, the cumulated excess number of ILI cases between week 28 and week 37 of 2009 was 269,935 [179,585; 316,512] (323,420 reported ILI cases minus the expected 53,485 over the period).

The median age of ILI reported cases was 26 years (range: 1-103 years), and 48% were male. Compared to weeks 28 to 37 of past years since 1985, age group-relative incidence rates of ILI between weeks 28 and 37 of 2009 were greater among subjects less than 18 years-old and smaller in those older than 65 years (Figure 2A).

Compared to past epidemic periods and A(H1N1) epidemics, age group-relative incidence rates of ILI between weeks 28 and 37 of 2009 was higher among subjects less than 5 years of age and lower among subjects aged 5 to 17 years (Figure 2B).

FIGURE 1

Estimated and expected incidence rates and their confidence interval, pandemic influenza A(H1N1) 2009, France



Discussion

An excess of 270,000 ILI cases has been reported to the French Sentinel Network since 1 July 2009, with a specific age pattern, compared to cases usually reported at this time of year. Compared to the past seasonal epidemics, (including those with predominant A(H1N1) circulating), the excess in ILI cases was largest among children less than 5 years-old.

In the past 24 years of surveillance, upper respiratory tract infections have been uncommon in summer, making the last weeks exceptional. Besides the pandemic influenza A(H1N1) virus, no unusual circulation of an infectious agent, nor seasonal influenza viruses have been reported in France since 1 June 2009 [6]. The recent excess of ILI cases must therefore reflect the developing pandemic in France.

Some pitfalls arise in the interpretation of this increasing incidence. First, cases reported by GPs are based on a clinical definition without virological confirmation. This case definition had positive predictive value for approximately 40% influenza virus infections in the past seasonal epidemics [1]. It has been in use

TABLE

Estimated and expected number of cases of influenza-like illness and calculated excess of cases in France between week 28 (6 to 12 July) and 37 (7 to 13 September) of 2009

Week number	Observed incidence	Expected incidence			Excess of cases		
		Expected	5th percentile	95th percentile	Average	Inferior bound	Superior bound
28	15,516	4,545	1,256	13,190	10,971	2,326	14,260
29	10,704	3,899	628	10,050	6,805	654	10,076
30	13,868	4,388	1,256	13,190	9,480	678	12,612
31	30,255	4,083	0	13,190	26,172	17,065	30,255
32	23,151	4,493	0	13,190	18,658	9,961	23,151
33	24,435	4,528	0	8,793	19,907	15,642	24,435
34	24,985	5,217	0	11,934	19,768	13,051	24,985
35	31,660	5749	1,256	11,934	25,911	19,726	30,404
36	46,134	6,778	1,256	18,215	39,356	27,919	44,878
37	102,712	9,805	1,256	30,149	92,907	72,563	101,456
Total	**323,420**	**53,485**	**6,908**	**143,835**	**269,935**	**179,585**	**316,512**

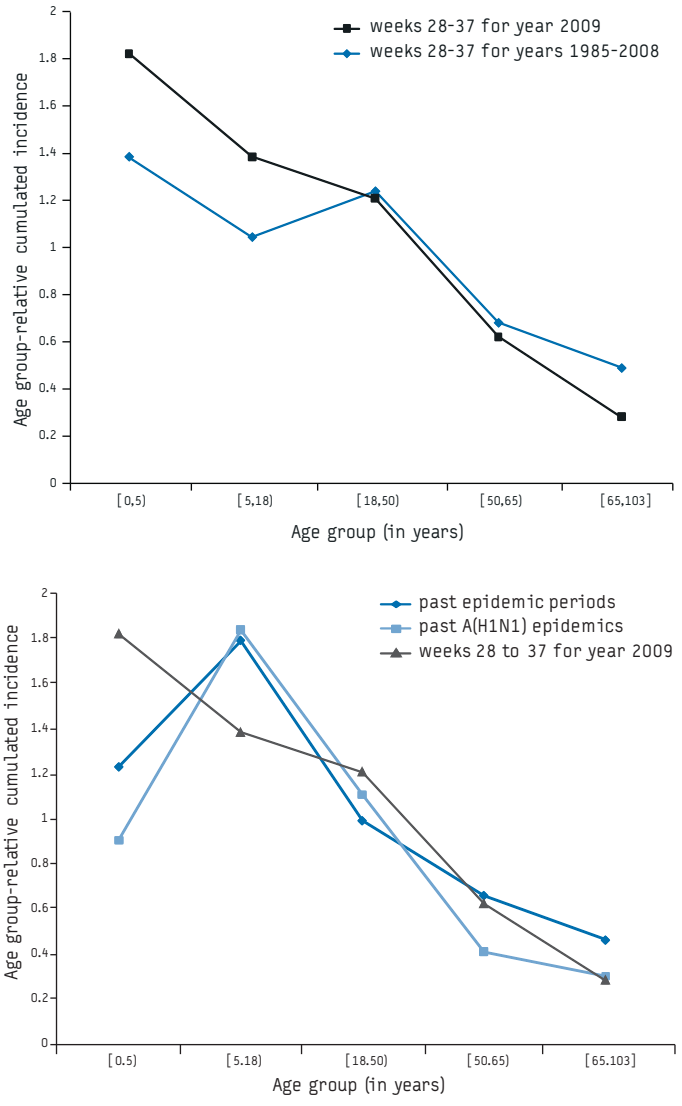
for 25 years in the FSN, making it likely that it is currently well applied by GPs. To further improve specificity, we retained only cases in excess of the expected incidence at this time of year in the calculations. Second, the heavy media coverage of the pandemic may have increased the propensity to visit a GP in case of symptoms, leading to an upward bias in the number of excess ILI cases. The change in age pattern of patients consulting their GPs argues against a mere change in consultation frequency; however an age-specific change in propensity to consult may also lead to this change. Last, cases of 2009 pandemic influenza A(H1N1) virus infection with mild disease and/or not seeking care are not taken into account in the estimates. We did not change the case definition to include milder cases so that direct comparison with the past years was possible.

As reported in other countries, a relatively higher incidence of 2009 pandemic influenza A(H1N1) virus infection is observed in the young. In most reports, the increased incidence among young subjects could be ascribed to case finding and ascertainment, with more young people being tested, for example as part of outbreaks of influenza in schools [7-9]. Cases seen by the sentinel network GPs may provide a better picture of what is happening in the population at large. Using the same definition as before makes it possible to compare the current situation with the past.

The data confirmed and quantified an epidemic of ILI that started during the recent summer months in France, and had never been observed in the previous 25 years, with an age-specific incidence different from previous epidemic periods. These preliminary data highlight the heavy burden of this ILI epidemic on small children, relatively to older persons [10].

FIGURE 2

Age group-relative cumulated incidence rates* of influenza-like illness cases reported by the French Sentinel Network general practitioners between weeks 28 and 37 of 2009, compared to weeks 28 and 37 of past years since 1985 (2A)* and to past seasonal epidemic periods and past A(H1N1) epidemics (1986-7, 1988-9) (2B)



*Ratio of incidence in an age group to incidence in the whole population: relative incidence >1 indicates that the corresponding age class experienced larger incidence than the population as a whole.

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* Authors correction

The legend of Figure 2A was corrected after the publication of the article, on 6 October 2009.

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Ongoing rubella outbreak in Bosnia and Herzegovina, March-July 2009 - preliminary report

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Between 24 March and 31 July 2009, 342 clinically diagnosed cases of rubella were notified in five municipalities in Republika Srpska, Bosnia and Herzegovina. Eight cases were laboratory-confirmed by positive IgM against rubella virus*. Four virus isolates were obtained and identified as genotype 2B strains, with one isolate differing by a single mutation in the region of the E1 gene. This ongoing outbreak revealed gaps in the immunisation programme during the war in BiH (1992-1995) and highlights the need to revise legislation to permit immunisation of children above 14 years of age with measles, mumps, rubella (MMR) vaccine and to introduce supplemental immunisation activities.

Introduction

Rubella is a notifiable disease in Bosnia and Herzegovina (BiH; estimated population 3,9 million) and is reported on the basis of clinical symptoms. Rubella immunisation was introduced in the 1980s. In 1999-2000 a two-dose schedule with the measles, mumps, rubella (MMR) vaccine was implemented, with the first dose given at the age of 12 months (since 2008 at 11 months) and the second dose at the age of seven years and no later than 14 years.

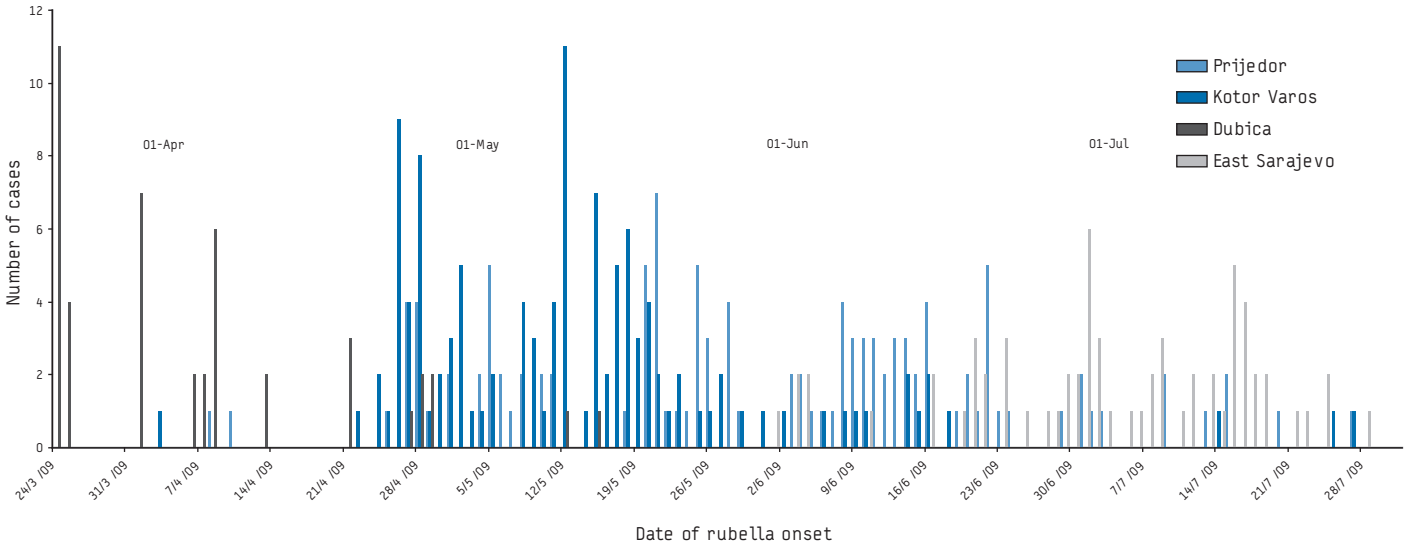
Between 24 March and 31 July 2009, 342 clinically diagnosed cases of rubella were notified in five municipalities in Republika Srpska (RS) which is one of two governing entities in BiH. At the time of publication of this report, the outbreak is ongoing, with ca. four cases per week. Epidemiological and laboratory investigation was started in early May 2009. Preliminary results are presented below.

Materials and methods

Serum samples were collected from 20 suspected rubella cases (six from Dubica, five from Kotor Varos, three from Prijedor, four from East Sarajevo-Pale and two from Trebinje). Throat swabs were obtained from the three patients from Prijedor and from two of the five patients from Kotor Varos. All sera were tested for IgM against measles and rubella and for rubella IgG (Dade Behring Enzygnost® immunoassays) at the Regional Reference Laboratory (RRL) of

Figure 1

Rubella cases, Bosnia and Herzegovina, 24 March - 31 July 2009 (n=342)



the World Health Organization Regional Office for Europe (WHO/Europe) in Luxembourg, and ten serum samples were also analysed for rubella IgM at the laboratory of the Public Health Institute of Republika Srpska (PHI RS). The throat swabs were used for PCR analysis as described previously [1] and for virus isolation [2]. Phylogenetic analysis based on the rubella virus E1 glycoprotein gene was done with MEGA [3] and sequences were compared to published sequences by BLAST.

Results

Outbreak profile

On 28 May 2009 the PHI RS declared a rubella outbreak in three municipalities in the Banja Luka Region: Prijedor, Dubica and Kotor Varos. Later, an outbreak occurred in the East Sarajevo region including the municipalities Pale and Sokolac. In addition, four suspected cases were reported in Banja Luka and eight in Doboj.

In Dubica, 44 rubella cases were reported between 24 March and 15 May 2009 (Figure 1) on the basis of a clinical case definition, i.e. acute onset of generalised maculopapular rash, body temperature higher than 37.2 °C and arthralgia/arthritis, lymphadenopathy, or conjunctivitis. The outbreak in this area appears to be over. The index case was not identified.

In Kotor Varos, Prijedor and East Sarajevo, where the outbreaks are still ongoing, 117, 116 and 65 rubella cases, respectively, were reported until the end of July. The last case to date was reported on 15 September 2009 in Sokolac, East Sarajevo.

Forty-five percent of the cases were male. The age ranged from those born in 1971 to those born in 2007. Most cases (82%, n=282) were observed among teenagers born between 1990 and 1994 still attending high school (Figure 2): 66% (29/44) in Dubica, 90% (105/117) in Kotor Varos, all of them attending the same school, 87% (101/116) in Prijedor and 72% (47/65) in East Sarajevo.

In Prijedor only five of the notified rubella cases had received one dose of MMR, while all the other patients were not immunised. The vaccination status of the cases in Dubica, Kotor Varos and East Sarajevo is still under investigation.

Laboratory findings

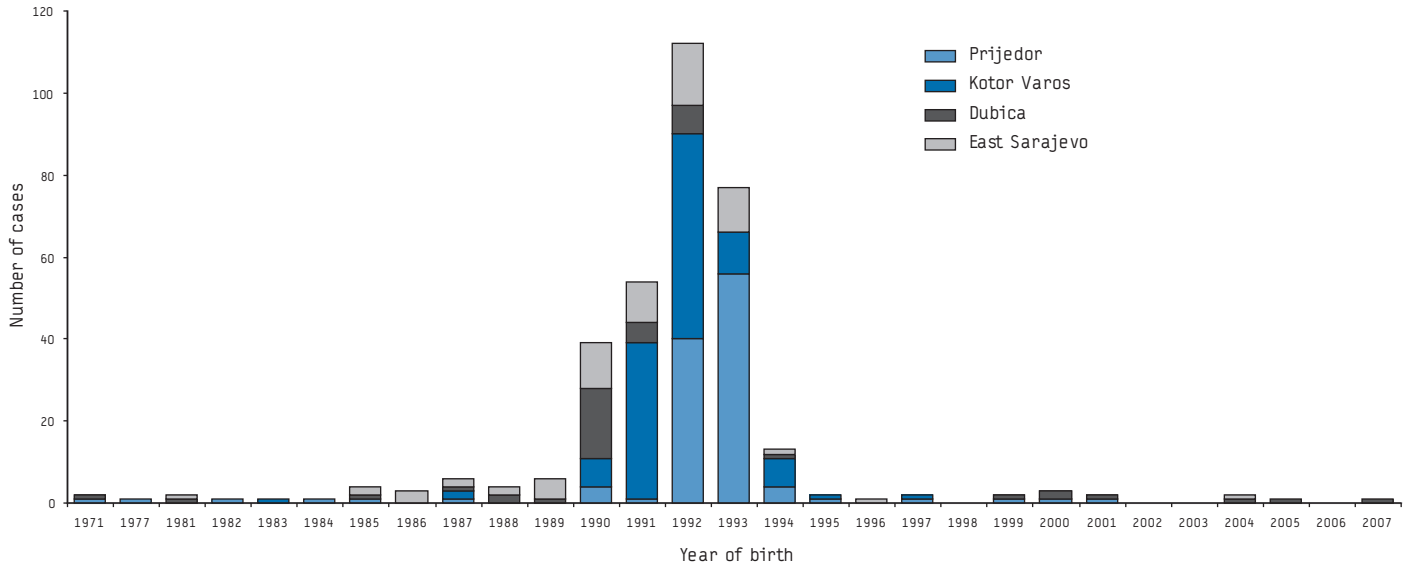
Eight samples were positive for rubella IgM, including three from Kotor Varos, one from Prijedor and four from East Sarajevo-Pale, confirming that the outbreaks in these regions were caused by rubella. Four sera were equivocal, and eight were IgM-negative for rubella (Table). There was a 100% concordance between the test results obtained at PHI RS and the Luxembourg RRL for the ten sera tested in both laboratories.

The rubella-positive samples were from seven 15-17 year-olds and from one 24 year-old. Five of them had received one dose of rubella vaccine, two were not vaccinated against rubella and for one patient no information on the vaccination status was available (Table). One rubella IgM-positive patient was negative for rubella IgG, while the other seven showed relatively low titres of rubella IgG (<77 IU/ml). In total 14 patients were positive for rubella IgG and six were negative. All 20 serum samples were negative for measles IgM.

Four of the five throat swabs were positive in the diagnostic PCR and for all four positives virus isolates were obtained. These samples were collected between one and four days after onset of rash from 16 or 17 year-olds of whom only one reported to have been vaccinated against rubella more than nine years ago. Of all four PCR-positive samples nearly complete E1 gene sequence data were obtained. Three of the sequences were identical and from Prijedor and the fourth showed one mutation at position 303 of the E1 gene and was from Kotor Varos. Phylogenetic analysis attributed the sequences to genotype 2B. According to a BLAST analysis, the most similar previously published sequence was an isolate obtained in the United States nine years ago (RVi/WA.USA/16.00, GenBank accession number AY968220) with a Kimura distance of more than 2%.

Figure 2

Rubella cases by year of birth, Bosnia and Herzegovina, 24 March - 31 July 2009 (n=342)



Discussion

This preliminary report describes a fairly large laboratory-confirmed outbreak of rubella affecting mainly unvaccinated or partially vaccinated 16-17 year-old school children in three contiguous municipalities and one distant region in RS. As the clinical diagnosis of rubella is unreliable, the real number of cases may be somewhat overestimated as for a few suspected cases there may have been different reasons for the symptoms observed. This may also explain why some of the sera tested negative for rubella IgM. On the other hand, several cases may have remained undetected due to a subclinical course of disease. No cases of rubella were diagnosed in BiH in 2008 nor in January and February 2009.

Due to lack of laboratory confirmation, the outbreak was recognised in the first community (Dubica)on 24 March 2009, The index case was not identified and therefore it is not clear when and from where the virus was introduced. As the most similar published sequence was found in the United States in 2000 and the genetic distance to that isolate was more than 2%, the origin of the virus remains obscure.

In early April 2009, the first cases were observed in two other municipalities, Kotor Varos and Prijedor, and in June in another two located 250-400 km away. In all of these areas, the epidemic is ongoing. Local epidemiologists speculate that the virus may have spread among teenagers during their stay in Mrakovica, Kozara mountain (56 km south from Dubica), which is a very popular place for regular school excursions in spring.

To date there is no information on occurrence of rubella in pregnant women or abortion in connection to the current rubella outbreak. Due to the risk of congenital rubella infection during the first trimester of pregnancy, which can lead to miscarriage, stillbirth, or infants with birth defects, rubella is of high public health importance.

Before the war in 1990, coverage with MMR vaccine was 93.6% in BiH. Vaccine procurement and implementation of the immunisation programme were difficult during the war, and in the last two years of war, MMR vaccine coverage was only 56.8%. The age groups primarily affected in the current outbreak were born during the war and most of them were not even vaccinated with the first dose of MMR. Surveys done in RS in 1999 and in 2006 showed MMR vaccination coverage rates of only 54% and 79%, respectively, among 12-23 months-old children [4]. Annual statistics from PHI RS show varying vaccination coverage rates in recent years (2006: first dose 83%, second dose 83%, 2007: 92% and 93%, 2008: 78% and 52%), indicating that other age groups may also contain people at risk for infection.

As a result of the outbreaks, the Minister of Health and Social Welfare and the PHI RS have initiated immediate actions to improve the coverage with the second dose of MMR vaccine in children under the age of 14 years, and have alerted the Regional Public Health Institutes and primary health care providers of the emerging outbreak. An action plan to initiate supplementary immunisation of children and young adults with measles and rubella vaccine or rubella vaccine is presently being developed with support from WHO/Europe. The ongoing rubella outbreak also highlights the need for a revised legislation that permits MMR vaccination in children older than 14 years as well as the need to improve the surveillance of congenital rubella syndrome.

Table

Laboratory results, rubella outbreak in Bosnia and Herzegovina, 24 March - 31 July 2009 (n=20)

Patient	Vaccination status	Rubella virus IgM	Rubella virus IgG	PCR
1	not vaccinated	negative	negative	positive
2	not vaccinated	positive	positive	positive
3	not vaccinated	equivocal	negative	positive
4	1 dose	positive	negative	positive
5	1 dose	equivocal	negative	negative
6	1 dose	negative	negative	not done
7	1 dose	positive	positive	not done
8	1 dose	positive	positive	not done
9	1 dose	negative	positive	not done
10	no information	negative	negative	not done
11	1 dose	negative	positive	not done
12	1 dose	negative	positive	not done
13	1 dose	equivocal	positive	not done
14	1 dose	equivocal	positive	not done
15	not vaccinated	negative	positive	not done
16	not vaccinated	negative	positive	not done
17	no information	positive	positive	not done
18	1 dose	positive	positive	not done
19	not vaccinated	positive	positive	not done
20	vaccinated	positive	positive	not done

* Author's correction: On request of the authors, this sentence was corrected on 2 October 2009

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Results of a vaccination campaign against human papillomavirus in the province of La Spezia, Liguria, Italy, March-December 2008

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Sexually transmitted diseases caused by human papillomavirus (HPV) are being diagnosed more frequently than others. It is accepted that HPV infection is a necessary cause for all cases of cervical carcinoma and a large number of other anogenital and oral cancers. Two vaccines have been developed and were licensed in 2007, which can prevent infections and pre-cancerous lesions due to HPV. In Italy pre-adolescent age (12 years-old) was identified as the ideal age for vaccination against HPV. In Liguria, the first free HPV vaccination campaign was started on 8 March 2008 in 12 year-old girls. We assessed the adherence to the vaccination during the 2008 campaign as 80.6%, 79.0% and 64.1%, respectively, for the first, second and third dose of vaccine in the target population.

Introduction

Sexually transmitted diseases caused by human papillomavirus (HPV) are being diagnosed more frequently than others. Today it is universally accepted that HPV infection is the necessary, although not sufficient, cause of all cases of cervical carcinoma and of a large number of other anogenital cancers and oral squamous cell carcinoma [1].

Certain viral genotypes, defined as high-risk (HR) carcinogenic genotypes (e.g. HPV types 16, 18, 31, 33, 35, 45, 52, 58) are associated more strongly with the development of tumours than others [4], and among these, genotypes 16 and 18 are most relevant in the context of cervical carcinogenesis [5-8]. The low-risk viral genotypes, including HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, cause benign laesions such as anogenital condyloma and laryngeal papilloma [9].

Cervical cancer affects approximately 1.4 million women in the world, with an annual incidence of 500,000 cases [2] and causes an estimated 274,000 deaths each year. In Europe, cervical cancer affects approximately 60,000 women and 30,000 die because of this disease every year [3]. In Italy, recent numbers indicate that an estimated 3,500 women are diagnosed with cervical cancer every year and approximately 1,200 die. Cervical cancer occupies the tenth position for cancers affecting women in Italy and is the third most common cancer in women between the ages of 15 and 44 years. It is estimated that about 10.3% of women in Italy have an HPV infection and that 71.7% of invasive cervical cancers are attributable to the high-risk HPV genotypes 16 and 18 [3].

Vaccines

Two vaccines have been developed, Cervarix and Gardasil, that can prevent infections and pre-cancerous laesions caused by HPV infection. They consist of recombinant viral capsid protein L1 (or a combination of L1 and L2) of HPV genotypes 6, 11, 16 and 18, assembled into virus-like particles (VLPs), and induce the production of neutralising antibodies against these genotypes. Since these vaccines do not contain HPV DNA they cannot cause infection or have an oncogenic effect by integrating into the DNA of the host cell [10-12]. Cervarix is a bivalent vaccine developed by GlaxoSmithKline, containing VLPs of the L1 proteins of HPV16 and 18, 20 µg of each, with an adjuvant of aluminium salts and a lipid agent (ASO4). The vaccination protocol foresees three intramuscular doses of 0.5 ml (at 0, 1 and 6 months) for girls from 10 to 25 years of age. The quadrivalent vaccine Gardasil was developed by Sanofi Pasteur MSD. The vaccine contains 20 µg L1 VLPs of HPV6 and 18 and 40 µg L1 VLPs of HPV11 and 16. The purified particles were adsorbed with aluminium salts that act as adjuvant. The protocol for the vaccine foresees three intramuscular doses of 0.5 ml (at 0, 2 and 6 months) for girls from nine to 26 years of age [13,14].

Both vaccines are considered to be safe and several studies document seroconversion to all types of HPV contained in the vaccine in more than 98% of cases. The antibody peak occurs a month after the third dose, then it decreases slowly until 18 months. In general, the antibody titres decrease 10-fold in the first one or two years post vaccination and stabilise after three to five years at levels higher than those induced by the natural infection. The quadrivalent vaccine showed 100% and 99% efficacy, respectively, against cervical intraepithelial neoplasia grade 2/3 and condyloma. The bivalent vaccine proved 100% effective in the prevention of cervical dysplasia [15-18]. At this point in time, it is not known how long the protection by the HPV vaccine lasts and whether a later booster vaccination will be necessary. However, preliminary results have shown that a booster with monovalent HPV16 vaccine induced a quick, very high and prolonged immune response [19].

The bivalent vaccine shows cross-reactivity to other HPV types, in particular to HPV45 and 31, which are phylogenetically similar to HPV18 and 16, respectively [17].

Target population

Genital HPV infection is usually transmitted sexually, and immunisation should therefore precede the start of sexual activity. It implies that the target population for vaccination is prepubertal girls or young adolescents. In addition, the antibody response induced by vaccines is generally higher in prepubertal children [20].

The United States Advisory Committee on Immunization Practices (ACIP) recommends the routine use of the vaccine for 11-12 year-old girls (minimum age nine years) and a catch-up vaccination for women between 13 and 26 years of age, regardless of whether they are sexually active or not [20]. The Canadian National Advisory Committee on Immunization (NACI) advises that girls aged between nine and 13 years should be vaccinated before their sexual debut and that women between 14 and 26 years of age should be vaccinated, regardless of whether they are sexually active or not [21].

The target populations in some European countries are shown in Table 1. In Germany and in the United Kingdom, the HPV vaccine is offered to the target population free of charge. In France, 65% of the cost is borne by the welfare system and the remaining 35% are paid by the individual or by a voluntary private insurance [22].

A recent survey on the sexual habits of young Italians indicates that 4% of girls report to have had their first sexual intercourse at the age of 14 years and 10% at the age of 15 years. Moreover, the data stratified by age showed that the age of the first sexual intercourse is decreasing within the cohort of 18-29 year-olds (both in men and in women) [23].

Another study compared 16 vaccine strategies in different age cohorts and the corresponding number of infections prevented by HPV. It found that vaccinating 12 year-old girls can be effective in the prevention of HPV infections. Indeed, the majority of 12 year-old girls are not yet sexually active and therefore represent the best target for vaccination [24]. The Superior Council of Health in Italy identified in its opinion on 11 January 2007 pre-adolescence (12 years) as the ideal age for vaccination because of the following considerations:

- Almost none of the children have previously had any sexually transmitted infections;
- The immune response at that age tends to be stronger;
- Children of that age attend the first two classes of secondary school where parents are still much involved and therefore both children and parents can be reached with adequate and relevant information about infection and vaccination;
- There is the possibility to catch up on missed doses of the vaccine in the third class of secondary school;
- Children of that age are under the responsibility of their parents who may insure adherence to the vaccination course;
- The vaccination can be included in the national vaccination schedule [25].

On 22 February 2008, the Italian Minister of Health announced the start of the first public vaccination campaign against HPV for 12 year-old girls [26].

The HPV vaccination campaign in Liguria

As foreseen in the Regional Decree (DRG) No. 54 on 25 January 2008, the vaccination campaign started on 8 March 2008 and targeted 12 year-old girls (born in 1997) who were offered free vaccination. Moreover, a free not active offer is in place for girls at the age of 13 years (born in 1996), and girls and women between the ages of 14 and 26 years can get the vaccine at a partial price of EUR 105, the cost of the vaccine and its administration incurred for the local public health authority (Azienda Sanitaria Locale, ASL). The objective was to achieve a coverage of >95% of the 12 year-old-girls with three doses of vaccine within five years after the start of the vaccination programme [27]. The bivalent vaccine was chosen for the campaign.

The aim of this work was to assess the adherence to HPV vaccination in 12 and 13 year-old girls during the vaccination campaign in the ASL 5 "Spezzino", from March to December 2008. The study analysed all girls (12-13 years-old-girls) vaccinated as part of the active free offer as well as the not active free offer, and also noted the adherence to vaccination in people who paid the partial costs for their vaccination.

Materials and methods

This study shows the results of the HPV vaccination in the province of La Spezia in the region of Liguria. This province is served by the ASL 5 "Spezzino". The resident population of La Spezia on 31 December 2007 was 218,032 people [28]. Healthcare is provided by four hospitals and three social health districts.

The recruitment of birth cohorts 1996 and 1997 for vaccination was made using the municipal registers. The other birth cohorts were not recruited, but signed up for the vaccination themselves. An invitation letter was sent to the girls' parents to explain the campaign. It included a regional information brochure, the informed consent form, and the date on which to present to the outpatient clinics for vaccination. A second invitation letter was sent if parents did not respond. Moreover, if girls stopped the vaccination cycle after the first or second dose of vaccine, a reminder letter was sent, containing a consent or dissent form to be completed and returned.

Table 1

Details of HPV vaccination programmes introduced in some European countries as of 31 October 2007*

Characteristics	Austria	France	Germany	United Kingdom
Target population	Girls and boys before sexual debut	14 year-old girls	12-17 year old girls	12-13 year-old girls
Catch-up	No	15-23 year-old women, sexually active or who started sexual activity in the 12 previous months	No	16-18 year-old women from autumn 2009 and 15-17 year-old women from autumn 2010

HPV: human papillomavirus
*According to reference [22]

A similar invitation letter was sent to the 1996 birth cohort together with the regional information brochure and a phone number to call for an appointment.

Information campaigns on prevention interventions and health promotion targeting adolescents are often fragmented and without continuity. They often do not integrate the work of health and education services and voluntary associations. Therefore, the ASL 5 coordinated the activities for the HPV vaccination campaign, involving different areas of expertise such as general practitioners, paediatricians, local nursery and infant health services, school authorities, local press and families.

The general practitioners, paediatricians, and local nursery and infant health services received posters to be displayed in their waiting rooms, containing the email addresses and internet links of where to obtain information about the vaccination. They also actively informed parents and girls about transmission, consequences of HPV infection and the protection the new vaccine could offer. ASL staff also prepared and distributed brochures in all schools in the province of La Spezia. In a simple and understandable way, the girls were informed about the benefits of vaccination and invited to ask their paediatricians for further information.

Gynaecologists and local public health experts held a press conference explaining in detail how the immunisation campaign was organised and the benefits it offered. Local newspapers reported on the beginning of the immunisation campaign, with an invitation to call the vaccination clinics for any information about it. Finally, the ASL 5 website posted a link to the HPV vaccination campaign site containing frequently asked questions about vaccination (prepared by the National Screening Observatory) and the procedures for access to the public health clinics throughout the territory.

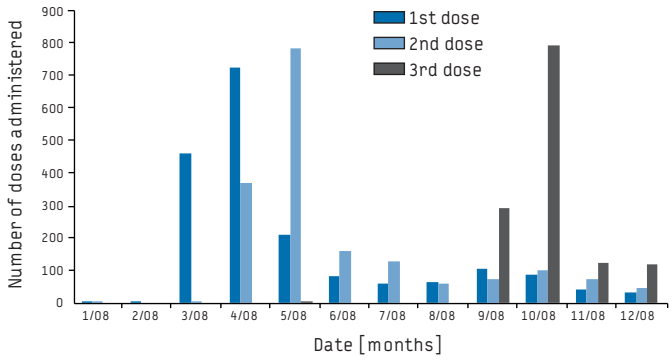
Vaccination teams were established to reduce outpatient waiting times. These vaccination units consisted of a physician, a nurse and an administrative technician. In addition, compensation was provided for staff working outside normal office hours to enable vaccination sessions in the afternoon. Data were collected from March to December 2008 in a computerised vaccination registry. The percentage of adherence to the vaccination was calculated as the number of doses administered per target resident population x 100. Adverse reactions to the vaccine were reported to the regional Department of Health, following the established routine for adverse reactions to other vaccines.

Results

The figure shows the number of doses administered between March and December 2008. The majority of first doses were

Figure

HPV vaccine doses administered from March to December 2008 to girls born in 1997 and 1996, by month, in La Spezia province



HPV: human papillomavirus.

Table 2

Number of HPV-vaccinated girls per birth cohort (1997-1982) and relative vaccination adherence, Italy, March to December 2008

Birth cohorts	Resident girls (no.)	Vaccinated girls first dose (%)	Vaccinated girls second dose (%)	Vaccinated girls third dose (%)
1997	825	80.6	79.0	64.1
1996	854	74.5	73.5	58.1
1995	782	12.3	11.9	7.2
1994	761	10.1	8.9	5.4
1993	753	10.1	9.6	5.8
1992	841	12.5	11.7	6.3
1991	782	8.2	7.5	3.6
1990	836	6.7	6.2	5.0
1989	844	2.3	2.1	1.3
1988	842	2.5	2.0	1.2
1987	797	1.9	1.6	0.9
1986	846	1.7	1.4	0.7
1985	852	1.8	1.2	0.8
1984	902	1.4	1.2	0.6
1983	862	1.3	1.3	0.8
1982	978	0.9	0.6	0.4
total 1982-1995	**11,678**	**5.0**	**4.6**	**2.7**

HPV: human papillomavirus

administered by the vaccination clinics during the months of March and April, following the administration of the first dose on 19 March, with a slight increase in September, which, according to statements from girls and parents, may be related to the Nobel Prize in Medicine awarded to Harald zur Hausen who is dedicated to the study of HPV.

The percentage of adherence to the vaccination was 80.6%, 79.0% and 64.1%, respectively, for the first, second and third dose in the 1997 birth cohort, and 74.5%, 73.5% and 58.1% in the 1996 birth cohort. As expected, the adherence in older age groups was lower: 5.0%, 4.6% and 2.7%, respectively, in those born between 1995 and 1982. Table 2 shows the number of vaccinated girls born between 1982 and 1997 and the relative vaccination adherence.

As of 31 December 2008, only three girls born in 1997 had stopped taking the vaccine after the first dose. Twenty girls had stopped after taking the second dose. In the 1996 birth cohort were two girls hat stopped after the first dose, one of them due to an adverse reaction, and 22 had interrupted the vaccination after the second dose (one due to an adverse reaction).

In the assessment of side effects due to the vaccine (data not shown) that occurred within seven days after administration, local effects were the most frequent, especially pain and redness in the inoculation site. The most frequently observed systemic side effects were fatigue, general malaise and gastrointestinal symptoms, which is in agreement with the literature [15-17].

Two adverse reactions involved girls born in 1996. One was characterised by redness and induration at the breast ipsilateral to the inoculated arm. It appeared about 12 hours after the first vaccination and resolved spontaneously within a few days. This reaction led to the decision to suspend the vaccination cycle. The other one, following administration of the second dose of vaccine, was characterised by a severe form of atopy which resolved spontaneously in a girl with a history of atopic dermatitis. This girl had already presented erythema and itching with lower intensity after the first dose of vaccine. Again, as a precaution, it was decided to suspend the vaccination course.

Discussion and conclusion

HPV vaccination is a new important instrument to prevent the occurrence of a specific cancer. The success of a vaccination campaign depends on several factors including support from policy makers, the presence of qualified and expert health professionals and the cost-effectiveness of the vaccine. It is necessary to provide the population with clear, concise and simple information about HPV infections, cervical cancer, prevention and vaccination. It is important that healthcare workers are well trained in communicating with patients to insure professional credibility and aid the promotion and implementation of coordinated vaccination campaigns.

There are as yet no published national or international data on how many vaccine doses were administered in countries that have already run HPV vaccination campaigns, and how many people were vaccinated or completed the vaccine course. It is estimated that the target population, 12 year-old girls, was about 280,000 in Italy [26] and 6,000 in the region of Liguria [27]. Considering the expected objective for Liguria to achieve a coverage of >95% of the 12 year-old girls with three doses of vaccine within five years after the start of the vaccination programme [27] and the Ligurian pooled data which show an adherence to HPV vaccination of about 62% among 12 year-old girls [29], the results obtained during the HPV vaccination campaign in 2008 in the ASL 5 "Spezzino" (80% adherence) are to be considered very good.

Adverse reactions to all vaccines have to be reported to the regional Department of Health to ensure post-licensure monitoring of the safety of the vaccine. In the 2008 HPV vaccination campaign the ASL 5 "Spezzino" observed only two moderate adverse reactions that did not require hospitalisation or medication and resolved spontaneously. With regard to the tolerability of the vaccine, these side effects were comparable to those observed in the literature [15-17] and the number of girls who interrupted their vaccination course was limited (two girls).

The involvement of girls and their parents in the vaccination campaign was very high and they showed a considerable interest in HPV and the consequences that the infection may have. General practitioners and paediatricians received many requests for information from parents of girls involved in the campaign and their number of patients increased. In the first month of the campaign the website was accessed more than 500 times and 300 phone calls were made to the dedicated numbers. The main points of our programme were the implementation of educational campaigns targeted according to age and sex, the involvement of educational institutions, information about the transmission of the infection and an increase in staff at vaccination clinics during the campaign.

In conclusion, we can say that the information campaign carried out throughout the province was conducted successfully and appropriately. However, this is only a starting point. To further raise the awareness of girls and parents regarding HPV vaccination, the quality of the information and especially the quality of healthcare and vaccination services needs to be improved.

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Laboratory support for the diagnosis and surveillance of sexually transmitted infections (STIs) in Eastern Europe

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This report outlines the proceedings of the 4th Annual Meeting of the Eastern European Network for Sexual and Reproductive Health (EE SRH Network) [1,2], which took place at Uppsala University in Uppsala, Sweden between 30 May and 3 June, 2009. The meeting was attended by 65 network participants from 14 Eastern European countries (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Lithuania, Russian Federation, Ukraine, Uzbekistan and Tajikistan), representatives of the World Health Organization (WHO) and invited experts from Sweden, United States, Denmark, and United Kingdom. The plenary session was followed by workshops on: (a) the development of sexually transmitted infections (STI) laboratory diagnosis guidelines, (b) surveillance of antimicrobial resistance of Neisseria gonorrhoeae and (c) epidemiological surveillance systems.

During the conference, it was emphasised, that STIs remain an unrecognised, but significant public health problem in the majority of Eastern European (EE) countries. WHO in its "Global strategy for prevention and control of STIs for 2006-2015" states that it is crucial to increase the commitment of national governments and to use integrated approaches in order to address the problem [3]. The EE SRH Network has endorsed these aims and contributed to the work of WHO by promoting cooperation on both national and regional levels and by developing international consensus approaches for the diagnosis of STIs [4].

It has long been recognised that laboratory testing plays an essential role in patient management and epidemiological surveillance of STIs. However, a survey of laboratory diagnostic methods among the network countries demonstrated that individual tests and approaches used to establish a diagnosis often do not achieve recommended international standards. For example, serological tests are used to diagnose chlamydial infection in up to 70% of clinical laboratories in several EE countries, while screening for gonococcal infections in women is largely conducted by using microscopy of Gram-stained cervical smears. In addition, few laboratories use type-specific herpes simplex virus (HSV) serology for the diagnosis of genital herpes [5].

In order to improve the quality of STI diagnostic services in the region, the EE SRH network has prepared "consensus" guidelines for the laboratory diagnosis of gonorrhoea, syphilis and chlamydial infections. These guidelines were formulated by the network participants during previous meetings, using evidence-based principles. This approach stimulated direct communication between leading experts from "East" and "West", resulting in consensus documents which were first published internationally [6-8] and then subsequently adopted and published at the national level [1,2].

During the meeting reported here, workshop participants reached consensus on further guidelines for the laboratory diagnosis of four specific infections, namely, bacterial vaginosis (BV), infections caused by Mycoplasma genitalium, trichomoniasis and genital herpes. International and national publications of these guidelines are currently in preparation [9].

It is recognised that both the quality of test kits used and the implementation of quality assurance systems contribute to the confidence in results provided and reputation of diagnostic services. STI diagnostic test kits manufactured in EE countries have rarely been internationally validated. The network has conducted a number of studies comparing Russian-manufactured tests for the detection of *N. gonorrhoeae, Chlamydia trachomatis* and *Mycoplasma genitalium* with internationally acknowledged methods, which yielded promising results [10-13]. It is clear that the regional biomedical industry has the potential for producing reliable reagents and tests kits at affordable prices; however, strict quality assurance is crucial [14]. Comprehensive evaluations of locally manufactured tests should be conducted according to internationally accepted guidelines as a prerequisite to marketing products in the region. In addition, other issues related to laboratory quality assurance have emerged as a high priority for many EE countries. The establishment of an extensive external quality assurance programme for the serological diagnosis of syphilis in Russia has revealed a number of difficulties, including lack of willingness to participate and high rates of false-positive/negative

results [15]. Such programmes should be extended to include all laboratory testing, with appropriate sanctions being implemented for those laboratories that consistently fail to provide satisfactory results.

Another factor which is necessary to assure high-quality laboratory practices is the establishment of national or regional reference laboratories for STIs, preferably supported and financed by the state authorities. At present, there are no such institutions in Eastern Europe. Such institutions could provide a source of expertise to support national or regional STI initiatives, perform reference testing and collect surveillance data. In addition, these laboratories could maintain external quality assurance (EQA) programmes, supervise updating of national STI laboratory guidelines and establish international collaborations [16].

The emergence and spread of antimicrobial resistance (AMR) among isolates of *N. gonorrhoeae* is recognised as a major concern globally. However, in the majority of the EE countries AMR testing of *N. gonorrhoeae* isolates is performed only occasionally, because gonococcal culture is rarely undertaken [17]. At the EE SRH meeting, a workshop to establish AMR surveillance of *N. gonorrhoeae* in the network countries was conducted at the Swedish Reference Laboratory for Pathogenic Neisseria (Örebro University Hospital). Representatives from Russia, Belarus, Estonia, Georgia, Ukraine and Kazakhstan adopted WHO protocols regarding culture, identification and AMR testing for *N. gonorrhoeae* and received WHO quality control strains and reagents to enable them to initiate collection of *N. gonorrhoeae* strains for AMR testing. The remaining countries will be supported in order to overcome some technical difficulties before the collection of strains can commence.

Most EE countries inherited complicated and labour-intensive communicable disease surveillance systems. STI surveillance is mostly suboptimal owing to old-fashioned, non-standardised, paper-based surveillance systems and the absence of computer-based statistical tools [18]. Furthermore, legal constraints have shown to be a potential barrier for good STI surveillance [19]. Surveillance systems for STIs differ from one country to another depending on the availability of laboratory services and the accessibility of healthcare-provider institutions. However, all countries should strive to nationwide establish, implement, and maintain as high quality laboratory service as possible considering resource constraints [20].

During a one-day epidemiological surveillance workshop, participants were introduced to a computer-based system for communicable disease surveillance (ULISAS), developed as a result of a joint Lithuanian-Swedish project [21]. Lithuanian and Belarusian epidemiologists presented their recent experiences with this programme. The system is already being used as a national tool in Lithuania; while in Belarus, it has been fully implemented in the capital, Minsk and is currently being introduced in other parts of the country [22]. Discussions on the adaptation and implementation of the system by other EE SRH countries are in progress.

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ECDC in collaboration with the VAESCO consortium to develop a complementary tool for vaccine safety monitoring in Europe

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A consortium of researchers aiming for development of vaccine safety monitoring through linkage of large computerised clinical databases and immunisation registries (VAESCO-project) has recently signed a contract with the European Centre for Disease Prevention and Control (ECDC). This new tool will complement the routine monitoring of adverse events through National Regulatory Agencies reporting to the large European Medicines Agency (EMEA) EudraVigilance database.

The consortium with participants from eight European Union Member States will utilise common software (the Jerboa Vaccine module) to look for possible events in each participating database. Aggregated data on specific events will be shared across country borders. The consortium had its start-up meeting a few weeks ago in Basel, where the coordinating institution is located.

The vaccine safety data linkage system will be used immediately to develop age- and sex-specific background incidence data on rare and more common conditions in larger European populations that possibly could be related to administration of vaccines. Brighton case definitions for events will be used when available [2].

Such data will be valuable when mass vaccination campaigns will start against the pandemic influenza A (H1N1) 2009 virus, if there is a need to perform analyses of observed versus expected events. The information will be available in the end of October for use by National Regulatory Agencies or EMEA and will later be published in a peer-reviewed scientific journal.

Infectious diseases such as measles and polio are now close to being eliminated through large immunisation programmes. Vaccines are provided to individuals of all ages. The mere fact that large numbers of doses of vaccines are administered to healthy individuals creates conditions for events which are temporally associated with vaccination. These events can either be real or coincidental. To maintain public confidence in the immunisation programs, vaccine safety must be a focus for all stakeholders including manufacturers, vaccine providers and governments.

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