



Eurosurveillance

Volume 14, Issue 35 - 3 September 2009

Rapid communications

- Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009** 2
by F Odaira, H Takahashi, T Toyokawa, Y Tsuchihashi, T Kodama, Y Yahata, T Sunagawa, K Taniguchi, N Okabe
- Epidemiological analysis of the influenza A(H1N1)v outbreak in Bolivia, May-August 2009** 7
by A Gianella, A Walter, R Revollo, R Loayza, J Vargas, Y Roca
- Sporadic cases of chikungunya, Réunion Island, August 2009** 11
by E D'Ortenzio, M Grandadam, E Balleydier, JS Dehecq, MC Jaffar-Bandjee, A Michault, SF Andriamandimby, JM Reynes, L Filleul
- Finland introduces rotavirus vaccine into the national vaccination programme in September 2009** 13
by H Nohynek, H Salo, M Renko, T Leino

Research articles

- Universal varicella vaccination in the Sicilian paediatric population: rapid uptake of the vaccination programme and morbidity trends over five years** 16
by G Giammanco, S Ciriminna, I Barberi, L Titone, M Lo Giudice, LR Biasio

ASSESSMENT OF SECONDARY ATTACK RATE AND EFFECTIVENESS OF ANTIVIRAL PROPHYLAXIS AMONG HOUSEHOLD CONTACTS IN AN INFLUENZA A(H1N1)v OUTBREAK IN KOBE, JAPAN, MAY–JUNE 2009

F Odaira (ochang@nih.go.jp)^{1,2}, H Takahashi^{1,2}, T Toyokawa^{1,2}, Y Tsuchihashi^{1,2}, T Kodama², Y Yahata³, T Sunagawa³, K Taniguchi³, N Okabe³

1. Field Epidemiology Training Programme, National Institute of Infectious Diseases Tokyo, Japan

2. National Institute of Public Health, Saitama, Japan

3. Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan

This article was published on 3 September 2009.

Citation style for this article: Odaira F, Takahashi H, Toyokawa T, Tsuchihashi Y, Kodama T, Yahata Y, Sunagawa T, Taniguchi K, Okabe N. Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May–June 2009. *Euro Surveill.* 2009;14(35):pii=19320. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19320>

This report describes the assessment of the secondary attack rate (SAR) and the effectiveness of post-exposure antiviral prophylaxis among household contacts in the first domestic outbreak of a novel influenza A(H1N1)v between mid-May and early June 2009 in Kobe city, Japan. Of the 293 subjects, 14 (4.8%) household contacts met the case definition and most secondary cases were probably infected around the time of symptom onset date of the respective index case. The SAR among household contacts who did not receive prophylaxis was 7.6%, similar to the rate of seasonal influenza, and the attack rate in siblings was significantly higher than that in parents. We conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. We could not conclude whether antiviral prophylaxis was effective or not. However, among close contacts with underlying disease who received prophylaxis, nobody developed a severe form of the disease.

Introduction

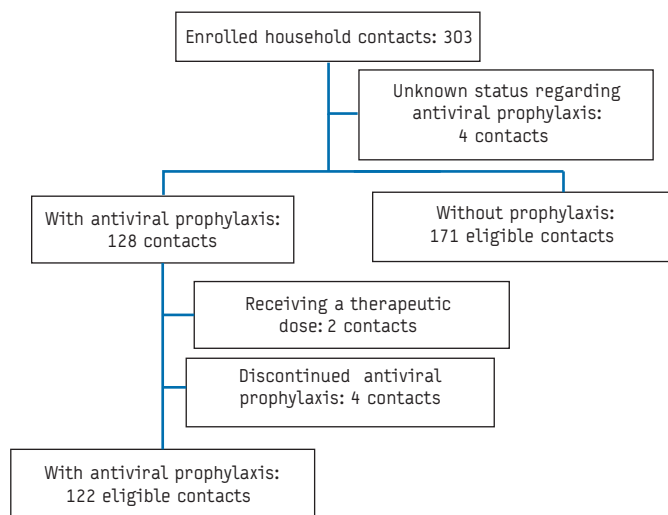
Between 16 May and 5 June 2009, 110 laboratory-confirmed cases of influenza A(H1N1)v, affecting mainly high school students, were reported from the Public Health Centre of Kobe City (PHCKC), Japan. The PHCKC provided post-exposure antiviral prophylaxis (oseltamivir or zanamivir) primarily to household contacts with underlying disease, in addition to implementing aggressive school closure throughout the city for one or two weeks from 16 May. The number of new laboratory-confirmed cases decreased in late May following the school closures [1], and community transmission was limited. No severe cases were reported during this period. We suppose that preventing the spread of influenza among household contacts effectively prevented the development of severe disease in each household and the transmission to the community. In this study, we assess the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis and the effectiveness of post-exposure antiviral prophylaxis in preventing the spread of influenza A(H1N1)v among household contacts in this particular outbreak.

Methods

Subjects and case definition

We included 303 household contacts from 97 households with the exception of three households with one person living alone. The median number of household members including index cases was four, ranging from two to eight. We defined an index case (IC) as the first person in each household who met the case definition described below according to the epidemiological investigation. The PHCKC followed up on these household contacts every day for approximately eight days either from the date when the ICs started antiviral therapy or from the date the PHCKC began to observe household contacts in case the ICs did not take antiviral therapy. In addition, household contacts were requested to stay

FIGURE 1
Flow diagram of enrolled household contacts, pandemic H1N1 influenza outbreak, Japan, May–June 2009



home but to avoid close contact with the patient in their household during the follow-up period. Household members with influenza-

like symptoms were instructed to wear face masks. Along with the PHCKC, we collected data on the symptoms and the use of antiviral prophylaxis. We excluded four contacts for whom information about antiviral prophylaxis was not available, four contacts who had discontinued antiviral prophylaxis and two contacts who were receiving a therapeutic dose (oseltamivir, 150 mg/day, or zanamivir, 20 mg/day; for five days). Overall, our study subjects comprised 122 household contacts receiving and 171 not receiving antiviral prophylaxis (Figure 1)..

TABLE 1

Demographic data for index cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=97)

Total no. of index cases		97
Sex	Women, no. (%)	40(41)
	Men, no. (%)	57(59)
Age, median (range)		17(1-53)
<20 years-old, no. (%)		87(90)
Cases with antiviral medication, no. (%)		89(92)
Interval from symptom onset to treatment, median days (range)		1(0-7)

Cases were confirmed by using the following case definition for household contacts, which is similar to the definition established by the Ministry of Health, Labour and Welfare at that time [1]:

Suspected case: a person who displayed high fever of ≥ 38 °C or at least two acute respiratory symptoms (nasal obstruction/

TABLE 2

Demographic data for household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

Total no. of subjects		Without prophylaxis	With prophylaxis			P-value*
			Total	Oseltamivir	Zanamivir	
		171	122	100	22	
Sex	Women, no. (%)	80(47)	65(53)	53(53)	12(55)	P=0.33**
	Men, no. (%)	91(53)	57(47)	47(47)	10(45)	
Age, median (range)		39(0-83)	45 (2-85)	48 (2-85)	14(7-41)	P<0.05***
Age unknown, no.		14	8	8	0	
Relationship to index case, no.						
Parent		85	73	71	2	
Sibling		64	31	11	20	
Child		4	3	3	0	
Spouse		2	2	2	0	
Grandparent		11	11	11	0	
Other		5	2	2	0	
Underlying disease, no.		n=167	n=122			
Asthma		0	9	7	2	
Hypertension		0	13	13	0	
Cardiovascular disease		1	2	2	0	
Diabetes		0	2	2	0	
Neoplasm		0	1	1	0	
Rheumatism		0	4	4	0	
Total		1	31	29	2	P<0.01**
The interval from symptom onset of index cases to prophylaxis, median day (range)			4 (0-8)	4(1-8)	3.5(0-8)	
0			3	0	3	
1			7	7	0	
2			21	19	2	
3			27	21	6	
4			23	20	3	
5			17	13	4	
6			3	2	1	
7			12	10	2	
8			9	8	1	

* Comparing total household contacts receiving prophylaxis to those not receiving prophylaxis

** Chi-square test

*** Wilcoxon rank-sum test

rhinorrhoea, sore throat, cough, fever of ≥ 37 °C), excluding individuals with negative RT-PCR for influenza A(H1N1)v virus;

Confirmed case: a suspected case with laboratory-confirmed influenza A(H1N1)v infection as tested by RT-PCR.

TABLE 3

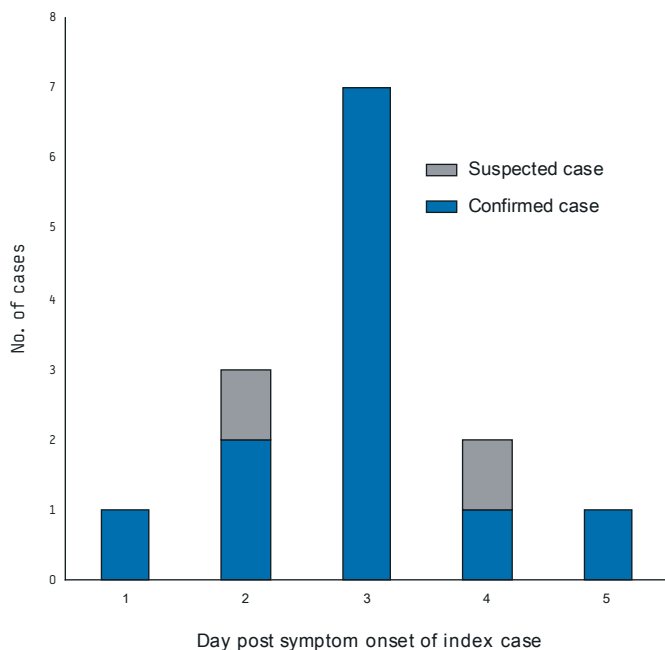
Demographic data for confirmed and suspected cases, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)

		Confirmed case	Suspected case	Total
No. of cases		12	2	14
Sex	Women, No. (%)	7 (58)	1 (50)	8 (57)
	Men, No. (%)	5 (42)*	1 (50)	6 (43)
Age, years				
0-9				
		2	2	4
10-19				
		8	0	8
40-49				
		1	0	1
50-59				
		1	0	1
Relationship to index case				
Parent				
		2	0	2
Sibling				
		10	1	11
Child				
		0	1	1
Spouse				
		0	0	0
Grandparent				
		0	0	0
Other				
		0	0	0
Underlying disease				
		0	0	0

* Including one case who received antiviral prophylaxis

FIGURE 2

The interval from symptom onset of index cases to symptom onset of household contacts, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=14)



Antiviral prophylaxis

Either oseltamivir (75 mg/day for adults or 2mg/kg/day for children*) or zanamivir (10 mg (two inhalers)/day) was administered household contacts for a period of 7–10 days, provided that they had underlying diseases (e.g. asthma or diabetes).

Statistical analyses

We calculated the secondary attack rate (SAR) among household contacts who did not receive antiviral prophylaxis. We also compared the attack rate among siblings and parents who did not receive antiviral prophylaxis in households where the ICs were under 20 years-old. We further compared the attack rate among household contacts receiving and not receiving antiviral prophylaxis to assess its effectiveness. Inter-group comparisons were made using Chi-square test or Fisher's exact test.

Results

Of the 97 ICs, 89 (92%) were treated with antiviral medication (Table 1) and 80 (82%) ICs began antiviral therapy within two days of symptom onset (e.g. nasal obstruction/rhinorrhoea, sore throat, cough or fever of ≥ 37 °C); 87 (90%) ICs were under 20 years-old.

Zanamivir was prescribed particularly to household contacts in their teens (Table 2), because there are concerns about the association between oseltamivir and abnormal behaviour in this age group in Japan [2].

The gender distribution of household contacts was not significantly different between the groups receiving and not receiving antiviral prophylaxis. However, the household contacts receiving prophylaxis were significantly older ($P < 0.05$, Table 2).

Of the 293 subjects, 14 (4.8%) in 13 households (representing 13 ICs) met the case definition: 12 confirmed cases (4.1%) and two suspected cases (0.7%) (Table 3). All 13 ICs took antiviral medication within two days of symptom onset. The median interval from symptom onset of ICs to symptom onset of the 14 contacts was three days (range: 1–5 days; Figure 2).

Only one suspected case (female, under five years old) had a history of receiving prophylaxis during this outbreak. The interval from symptom onset of her IC to the administration of antiviral prophylaxis was two days. The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)*.

In those households in which the ICs were under 20 years-old, 10 (16.4%)* cases in siblings and two (2.4%)* cases in parents met the case definition. The attack rate in siblings was significantly higher than that in parents. The odds ratio (OR) was 7.84 (95% confidence interval (CI): 1.52–54.2; Table 4).

The difference in the attack rate between household contacts who had received prophylaxis and those who had not was statistically significant. However, the household contacts receiving prophylaxis were significantly older, so we stratified household contacts according to age (≥ 20 years-old or < 20 years-old). After that, there was no statistical significance in either group (Table 5).

Discussion

The United States Centers for Disease Control and Prevention (US CDC) have estimated that the incubation period of influenza A(H1N1)v could be between one and seven days, but more likely

between one and four days [3]. Our investigation showed that the median interval from symptom onset of ICs to symptom onset among the 14 cases in the household contacts was three days (range: 1–5 days). These results indicate that most secondary cases were probably infected around the time of symptom onset of the ICs. Therefore, routine infection control measures for each household should be established because it is sometimes difficult for public health authorities to intervene in affected households immediately after ICs develop symptoms.

The World Health Organization (WHO) reported that the current estimate of the SAR of influenza A(H1N1)v was 22–33%, and the SAR of seasonal influenza was 5–15% [4]. Our investigation showed a SAR of 7.6%. This rate was lower than that for influenza A (H1N1) v reported by WHO and similar to the rate of seasonal influenza. The PHCKC and the mass media actively provided information to the public about influenza A(H1N1)v and emphasised the importance of infection control measures (such as hand washing, cough etiquette including wearing masks) at home during the outbreak period. These measures or social pressure might have been effective in reducing the number of secondary cases.

We could not conduct sero-epidemiological examinations in this investigation. Therefore, mild or asymptomatic cases that did not

meet the case definition were possibly overlooked, and the SAR may have been underestimated. This issue requires further investigation.

The attack rate among siblings was significantly higher than the attack rate for parents, indicating greater contact between siblings or that infection control measures might not have been satisfactorily practiced by the younger household contacts. We conclude that it is necessary to effectively convey infection control advice among young household members, as well as to their parents, to prevent the virus from spreading in the household and, possibly, to the community. Both the public health sector and the mass media can play an important role in this responsibility.

Antiviral prophylaxis for seasonal influenza among household contacts has been shown to be effective [5–8]. Our data indicated no significant difference in the SAR in households stratified by age and age was considered to be a confounding factor. However, only one contact who had received antiviral prophylaxis met the case definition, so it was impossible to conclude whether antiviral prophylaxis was effective or not. Moreover, because no severe cases were reported among these households, we think that post-exposure antiviral prophylaxis can be given to close contacts at high risk for developing influenza complications, as recommended by the European Centre for Disease Prevention and Control (ECDC) and the US CDC [9,10]. The effectiveness of antiviral prophylaxis warrants further study and discussion, regarding its potential to prevent severe cases and the cost-benefit relationship.

TABLE 4

Comparison between the secondary attack rate in siblings and parents, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=143)

	Cases	Not cases	Total	OR(95%CI)	P-value
Siblings	10	51	61	7.84	<0.01*
Parents	2	80	82	(1.52-54.2)	
Total	12	131	143		

CI: confidence interval; OR: odds ratio.
*Chi-square test

TABLE 5

Comparison between household contacts receiving antiviral prophylaxis and those not, pandemic H1N1 influenza outbreak, Japan, May-June 2009 (n=293)

	Cases	Not cases	Total	OR(95%CI)	P-value
With prophylaxis	1	121	122	0.10	<0.05*
Without prophylaxis	13	158	171	(0-0.75)	
Total	14	279***	293		
With prophylaxis < 20 years-old	1	23	24	0.15	0.09**
Without prophylaxis < 20 years-old	11	39	50	(0.01-1.30)	
Total	12	62	74		
With prophylaxis ≥ 20 years-old	0	90	90	0	0.50**
Without prophylaxis ≥ 20 years-old	2	105	107	(0-4.86)	
Total	2	195	197		

CI: confidence interval; OR: odds ratio.
* Chi-square test
** Fisher's exact test
*** Including 14 without prophylaxis and eight with prophylaxis for whom the age was not known.

Conclusion

From the results of this study, we conclude that it is important to establish routine infection control measures for households in order to prevent the spread of the virus among household contacts and, possibly, to the community. In future outbreaks, educating young household contacts on infection control measures through public notification and the media may be effective in controlling the outbreak. The effectiveness of prophylaxis for household contacts was not determined. However, close contacts with underlying disease who received prophylaxis did not develop a severe form of the disease.

Acknowledgements

We are grateful for the cooperation and support of the members and staff of the Public Health Centre of Kobe City and the Kobe Institute of Health.

*Authors' correction: On request of the authors, the two percentages in this sentence were corrected on 4 September 2009. Further, the sentence "The SAR in household contacts was 7.6%." was changed to read "The SAR in household contacts who did not receive antiviral prophylaxis was 7.6% (13/171)" on 7 September 2009 on request of the authors, information on oseltamivir dosage was added ("75 mg/day for adults or 2mg/kg/day for children"), and the percentage of confirmed male cases in Table 3 was corrected to read 5(42).

References

1. Shimada T, Gu Y, Kamiya H, Komiya N, Odaira F, Sunagawa T, et al. Epidemiology of influenza A(H1N1)v virus infection in Japan, May - June 2009. *Euro Surveill.* 2009;14(24):pii=19244. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19244>
2. United States Food and Drug Administration. Tamiflu (oseltamivir phosphate). Safety information. 3 April 2008. Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095044.htm>
3. Centers for Disease Control and Prevention (CDC). Interim guidance for clinicians on identifying and caring for patients with swine-origin influenza A(H1N1) virus infection. 4 May 2009. Available from: <http://www.cdc.gov/h1n1flu/identifyingpatients.htm>
4. World Health Organization (WHO). New influenza A (H1N1) virus: global epidemiological situation, June 2009. *Wkly Epidemiol Rec.* 2009;84(25):249-57. Available from: <http://www.who.int/wer/2009/wer8425/en/index.html>
5. Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliot MJ, Hammond JM, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med.* 2000;343(18):1282-9.
6. Monto AS, Pichichero ME, Blanckenberg SJ, Ruuskanen O, Cooper C, Fleming DM, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis.* 2002;186(11):1582-8.
7. Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis.* 2004;189(3):440-9.
8. Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA.* 2001;285(6):748-54.
9. European Centre for Disease Prevention and Control (ECDC). On public health use of influenza antivirals during influenza pandemics (with particular reference to the pandemic (H1N1) 2009). August 2009. Available from: http://www.ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_On_Public_Health_Use_of_Influenza_Antivirals_during_Influenza_Pandemics.pdf
10. Centers for Disease Control and Prevention (CDC). Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A (H1N1) Virus Infection and Their Close Contacts. 6 May 2009. Available from: <http://www.cdc.gov/h1n1flu/recommendations.htm>

EPIDEMIOLOGICAL ANALYSIS OF THE INFLUENZA A(H1N1)v OUTBREAK IN BOLIVIA, MAY-AUGUST 2009

A Gianella (algianella@cotas.com.bo)¹, A Walter², R Revollo¹, R Loayza¹, J Vargas¹, Y Roca¹

1. Centro Nacional de Enfermedades Tropicales (National Center of Tropical Diseases, CENETROP), Santa Cruz, Bolivia

2. Institut de Recherche pour le Développement (Research Institute for Development, IRD), representation at La Paz, Bolivia

This article was published on 3 September 2009.

Citation style for this article: Gianella A, Walter A, Revollo R, Loayza R, Vargas J, Roca Y. Epidemiological analysis of the influenza A(H1N1)v outbreak in Bolivia, May-August 2009. *Euro Surveill.* 2009;14(35):pii=19323. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19323>

The outbreak of pandemic influenza (H1N1) began in Bolivia on 25 May 2009. Between May and August, the National Center of Tropical Disease (CENETROP) analysed by RT-PCR 7,060 samples of which 12.7% were positive. A preliminary analysis of the 895 confirmed cases identified between May and August 2009 describes epidemiological and clinical characteristics. After the first imported cases from the United States and Peru, the locally acquired infections predominated (90%). The number of cases was highest in the age group of 10 to 29 year-olds, and 89.6% of cases were observed in people under the age of 40 years. Fever, cough, nasal discharge and headache remained the main symptoms.

Introduction

In response to the health emergency declared by the World Health Organization (WHO) on 29 April 2009, the Bolivian Ministry of Health activated a warning system to monitor the presence of influenza within its territory. An active surveillance system was established at all international airports and bus terminals (trains being of low importance in public transport in Bolivia). The current net of sentinel sites established throughout the country for virological surveillance of influenza and respiratory virus was alerted, as well as all other health centres on national territory, with the obligation to report all patients with fever and respiratory symptoms. A number of health facilities were prepared to receive suspected cases. In addition, the Bolivian authorities initiated an educative campaign in the media and distributed informative leaflets on measures to control the epidemic. A free telephone line was set up for health professionals and the public to report suspected cases or obtain information. The Immunology and Molecular Biology laboratory at the National Center for Tropical Diseases (CENETROP) was prepared for testing influenza A(H1N1)v as described by the United States Centers for Disease Control and Prevention (US CDC). All reagents and material for the real-time RT-PCR test were provided from CDC and WHO. This laboratory was the only laboratory in Bolivia accredited to perform this test.

This short report presents the epidemiological characteristics of the early stage of the influenza A(H1N1)v outbreak in Bolivia, from 5 May to 2 August 2009, on the basis of data collected by CENETROP.

Methods

A suspected case was defined as a person with sudden onset of fever (≥ 38 °C) and respiratory symptoms detected in any part of the Bolivian health system. Suspected cases were examined

at the nearest healthcare facility for clinical evaluation. Nasal samples were taken from symptomatic people and submitted to the CENETROP laboratory for testing, together with a case report form containing clinical and epidemiological data that were collected for all suspected cases. Nasal swabs were received from all suspected cases from 5 May until 31 July 2009. From 1 August, the protocol was changed and nasal samples were only taken from severe cases, following a WHO recommendation to that effect.

If the sample was PCR-positive for influenza A(H1N1)v and the clinical manifestations were severe, the patients were hospitalised and specific treatment was administered. In the beginning of the outbreak, antiviral drugs were given to all suspected cases and their contacts. From 1 August, antiviral drugs were given only to symptomatic high-risk groups.

Data collected by the Immunology and Molecular Biology laboratory at CENETROP were immediately entered in a database. Data from the samples registered until 31 July are analysed here with SPSS (Chi-square tests, Mann and Whitney tests and T-test).

Results

On 25 May 2009, the surveillance group of the Departmental Health Services (SEDES) in Bolivia identified the first two cases of influenza A (H1N1)v at Santa Cruz international airport by checking all arriving passengers, airplane personnel informing the healthcare staff at the airport about passengers with symptoms of fever, cough or others symptoms of respiratory disease. A woman in her late 30s returning from New York had symptoms of fever, cough and a sore throat. She was accompanied by her seven year-old child who was still asymptomatic. Nasal swabs of mother and child were taken at the airport and sent to the CENETROP laboratory. Both were placed under medical observation in a clinic especially organised to receive suspected cases from the airport, and the child subsequently developed symptoms. The RT-PCR was positive for both of them and treatment was administered in a second level reference hospital.

Between 29 May and 11 June 2009, six further cases were confirmed in Santa Cruz, La Paz and Montero, all with a history of international travel (to the United States (US), Peru and Argentina) or of contact with travellers returning from affected countries. On 12 June, the first case without travel history or known close contact with a suspected case was confirmed in Santa Cruz. From

FIGURE 1

Number of cases of influenza A(H1N1)v by week of disease onset analysed at CENETROP, Bolivia, 5 May-2 August 2009 (n=7,060 analysed samples)

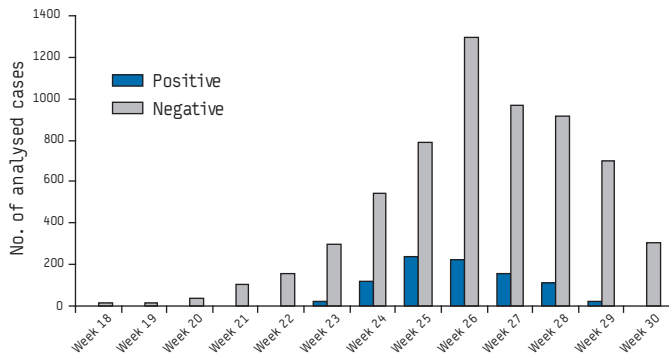
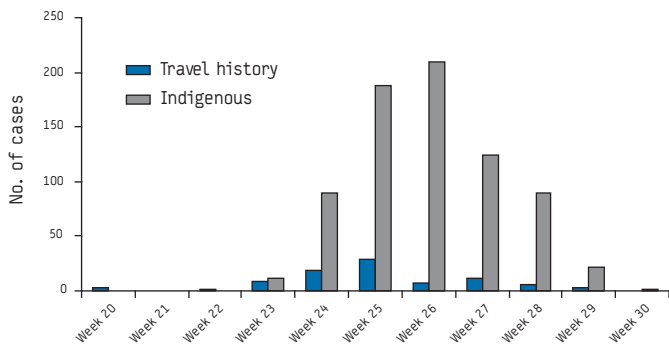


FIGURE 2

Number of laboratory-confirmed influenza A(H1N1)v infections by week of disease onset and travel history, Bolivia, 11 May-26 July 2009 (n=824*)



*for whom travel history was known

TABLE 1

Geographic distribution of influenza A(H1N1)v samples with known place of origin (n=7,018)

Department	Locality	Total	% Laboratory-confirmed for influenza A(H1N1)v
Santa Cruz	Santa Cruz	4,933	12.8
	Other	343	9.0
La Paz	La Paz/Alto	843	12.6
Beni	Trinidad	62	6.5
Chuquisaca	Sucre	60	10.0
Cochabamba	Cochabamba	351	20.2
	Other	153	3.9
Oruro	Oruro	67	17.9
	Other	6	0
Potosi	Potosi	41	24.4
	Other	19	10.5
Tarija	Tarija	92	6.5
	Other	48	14.6
Total		7,018	12.7%

15 June onwards, the number of cases increased greatly, mainly in Santa Cruz.

Between 5 May and 2 August 2009, CENETROP received 7,060 samples of suspected cases, of which 895 (12.7%) were confirmed by PCR as influenza A(H1N1)v virus. Thirteen patients (1.5%) died, two of them children under the age of five years, and six of them adults who suffered from chronic medical conditions (diabetes, Chagas disease, chronic respiratory disease) [1]. The temporal distribution of cases by week of onset of disease is presented in Figure 1. The average time between onset of symptoms and arrival of the samples at the CENETROP laboratory was 2.9 days. The weekly number of confirmed cases reached a peak between 22 June and 5 July (21.8% of cases), and decreased until the last week of July. From 1 August 2009, swabs were no longer systematically taken and sent to CENETROP.

Patients with recent history of travel to the US, Argentina, Brazil, Chile, Colombia, Cuba, Paraguay, Peru, Spain, Uruguay or Venezuela accounted for 9.9% of confirmed (n=89). The proportion of travel-related cases among all cases decreased after the end of June (week 26) (Figure 2).

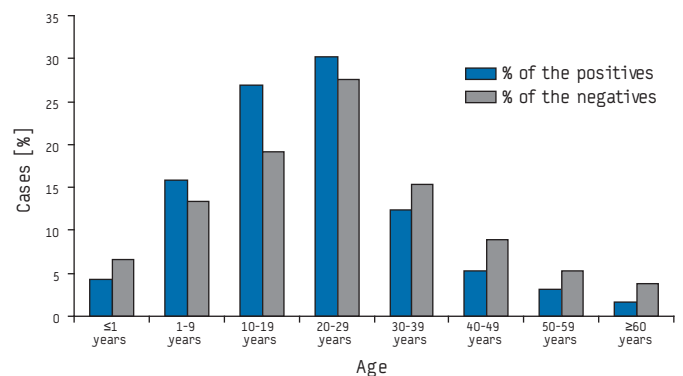
The majority of cases were recorded in the main cities of Bolivia like Santa Cruz (73.7%) and La Paz, Tarija and Cochabamba (Table 1). Other localities were either less affected or sent less samples to CENETROP. The proportion of laboratory-confirmed samples among suspected ones varied from one Department (Bolivia is divided into nine administrative Departments) to the other. By 2 August, cases had been reported in eight of the nine departments.

Of 7,060 specimens analysed, 3,462 were from men and 3,598 from women. The proportion of laboratory-confirmed cases was higher for men (13.6% male versus 11.7% female, P=0.017). The age ranged from one month to 80 years. The average age was 21.5±13.7 years, the median age was 20 years, and the age group most affected was the group of 10-29 year-olds (Figure 3). There was no difference in the mean age according to the sex (women: 21.9±13.6 years, men: 21.0±13.9 years, P<0,05).

The symptoms most frequently reported by confirmed influenza A(H1N1)v patients were fever (91.6%), cough (86.7%), nasal discharge (82,4) and headache (82,4 followed by sore throat,

FIGURE 3

Age distribution of suspected and laboratory-confirmed influenza A(H1N1)v cases, Bolivia, 5 May-2 August 2009 (n=7,060)



myalgia, and asthenia. Diarrhoea was rare as well as bronchitis and pneumonia. Symptoms that were found to be correlated with laboratory-confirmed samples are listed in Table 2 (P<0,01). Diarrhoea and pneumonia were negatively correlated. Nasal discharge and otitis were observed more frequently in women than in men (P<0,05). Fever and vomiting were observed more frequently in young people under the age of 15 years, while myalgia, headache, asthenia and short breath were observed more frequently in adults over the age of 15 years (P<0,05).

Discussion

By 25 May 2009, the new influenza A(H1N1)v virus had entered Bolivia from the US, Peru and Chile, one month after the first notification of the infection in Mexico, and two to three weeks after the neighbouring countries were affected [2-4]. Despite the fact that Bolivia continued to observe sporadic imported cases, mainly from Argentina (47/89), indigenously acquired infections predominated as a consequence of local transmission (90%). Indigenous cases in Bolivia had a rate of local transmission almost like the one observed in Peru (95.6 %) [2] and much higher than in Colombia (35.5 %) [3]. As soon as the new influenza virus arrived in the country, it spread rapidly in the major urban centres, particularly in Santa-Cruz. Geographical spread within rural Bolivia currently seems low, but unfortunately cannot really be estimated in this study, based on analyse of received suspected nasal swabs.

The distribution of cases by age and sex is similar to what is observed elsewhere [4-7], with young adults being mostly affected by the disease. However, in Bolivia men are slightly more affected than women, and the median age is at the higher end of the range observed worldwide. It is possible that the rapid spread of disease in Santa Cruz has enlarged the age range.

As of 2 August, CENETROP has confirmed only a small proportion of 12.7% influenza A(H1N1)v virus infections among the total of 7,060 samples analysed. Of the 81.7% of submitted

samples that matched perfectly the inclusion criteria, 13.8% were laboratory-confirmed). The remaining 18.3% analysed samples came from patients who had fever without respiratory symptoms (7.12% of those were confirmed) or respiratory symptoms without fever (8.2% of those were confirmed). Finally, six asymptomatic patients (tested as contacts) were confirmed to have influenza (H1N1)v virus infection. The low concordance between early clinical suspicion of influenza A(H1N1)v and laboratory confirmation may be partly due to the fact that other influenza viruses are currently circulating in Bolivia (apart from other virus such as dengue virus). Of 179 samples negative for influenza A(H1N1)v that were subsequently analysed for other respiratory viruses in La Paz, seven (3.9%) were positive for syncytial respiratory virus by indirect immunofluorescence test, 24(13.5%) were positive for seasonal influenza A by PCR, and 12(6.7%) were positive for influenza A by indirect immunofluorescence [1].

The low percentage of laboratory-confirmed samples also reflects the impact on healthcare services of the current H1N1 influenza pandemic. Between May and August 2009, an abundance of samples were sent to the national reference laboratory at CENETROP. It was partly a consequence of the high concern in the population, fed by the media in response to the increasing number of positive cases throughout the world. Symptoms are similar to those of seasonal influenza, and many people in Bolivia would not usually consult at healthcare facility for such symptoms. The volume of medical consultations has overwhelmed the CENETROP laboratory which succeeded in managing the extraordinary work load but experienced a shortage in reagents after only a few weeks. The drop in the epidemiological curve at the end of July is a reflection of this deficit in reagents, which are currently reserved for severe cases. At the same time, medical staff began to send fewer samples to CENETROP. Overall, this study also highlights the difficulty, with regard to local resources, of managing an epidemic surveillance system at a high level and for a long time.

TABLE 2

Clinical characteristics of patients with RT-PCR-positive and -negative result for influenza A(H1N1)v, Bolivia, 5 May-2 August 2009 (n=7,055*)

Symptoms	Total number with symptoms	% with symptoms		P value
		RT-PCR A(H1N1)v positives(n=895)	RT-PCR A(H1N1)v negatives(n=6,160)	
Asthenia	4,370	65.8	61.3	0.01
Bronchitis	1,144	19.4	15.7	0.005
Conjunctivitis	2,240	35.0	31.2	0.02
Cough	5,599	86.7	78.1	<0.001
Diarrhoea	964	10.6	14.1	0.004
Fever	6,078	91.6	85.2	<0.001
Headache	5,450	82.4	76.3	<0.001
Myalgia	4,812	74.2	67.2	<0.001
Nasal discharge	5,504	82.4	77.2	<0.001
Otitis	966	13.7	13.7	NS
Pharyngitis	5,183	77.9	72.7	0.001
Pneumonia	368	3.5	5.5	0.01
Vomiting	1,506	21.5	21.3	NS

NS: non-significant.

* for which information on symptoms was available.

Acknowledgements

We would like to express our gratitude to the personnel of the Immunology and Molecular Biology Laboratory of CENETROP for all their hard work during this pandemic period.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the National Minister of Health of Bolivia.

References

1. Ministerio de Salud y Deportes. Dirección General de Salud. Unidad de Epidemiología - Centro Nacional de Enlace, Bolivia. [Ministry of Health and Sports]. Boletín N° 35 Semana Epidemiológica 31 Agosto 12, 2009. [Spanish]. Available from: http://www.sns.gov.bo/documentos/epidemiologia/2009_8_13_1.pdf
2. World Health Organization. Human infection with new influenza A (H1N1) virus: clinical observation from Mexico and other affected countries, May 2009. *Wkly Epidemiol Rec.* 2009;84(21):185-9. Available from: <http://www.who.int/wer/2009/wer8421.pdf>
3. Munayco CV, Gomez J, Laguna-Torres VA, Koschel TJ, Fiestas V, Garcia J, et al. Epidemiological and transmissibility analysis of influenza A(H1N1)v in a southern hemisphere setting: Peru. *Euro Surveill* 2009;14(32):pii=19299. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19299>.
4. Castro-Jiménez MÁ, Castillo-Pabón JO, Rey-Benito GJ, Pulido-Domínguez PA, Barbosa-Ramírez J, Velandia-Rodríguez DA, et al. Epidemiologic analysis of the laboratory-confirmed cases of influenza A(H1N1)v in Colombia. *Euro Surveill.* 2009;14(30):pii=19284. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19284>
5. Ministerio de Salud, Chile. Informe situación de infección por nueva influenza A (H1N1) en Chile al 11 de junio de 2009. Status report of new influenza A(H1N1) in Chile as of June 11, 2009. [Spanish]. Available from: <http://www.redsalud.gov.cl/minsaludios/reporte12junio.pdf>
6. Health Protection Agency and Health Protection Scotland new influenza A(H1N1) investigation teams. Epidemiology of new influenza A(H1N1) in the United Kingdom, April – May 2009. *Euro Surveill.* 2009;14(19):pii=19213. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19213>
7. Ciblak MA, Albayrak N, Odabas Y, Basak Altas A, Kanturvardar M, Hasoksuz M et al. Cases of influenza A(H1N1)v reported in Turkey, May-July 2009. *Euro Surveill.* 2009;14(32):pii=19304. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19304>
8. World Health Organization . New influenza A (H1N1) virus: global epidemiological situation, June 2009. *Wkly Epidemiol Rec.* 2009;84(25):249-60. Available from: <http://www.who.int/wer/2009/wer8425/en/index.html>

SPORADIC CASES OF CHIKUNGUNYA, RÉUNION ISLAND, AUGUST 2009

E D'Ortenzio (ericdortenzio@gmail.com)¹, M Grandadam², E Balleydier¹, J S Dehecq³, M C Jaffar-Bandjee⁴, A Michault⁵, S F Andriamandimby⁶, J M Reynes⁶, L Filleul¹

1. Regional office of the French Institute for Public Health Surveillance, Institut de Veille Sanitaire, Réunion, France
2. National Reference Centre for Arboviruses, World Health Organization Collaborating Centre for Arboviruses, Institut Pasteur, Paris, France
3. Vector control team, Regional office for sanitary and social services (DRASS), Réunion, France
4. Microbiology Laboratory, Regional Hospital Centre of Saint-Denis, Réunion, France
5. Laboratory for Bacteriology, Parasitology, Virology and Hospital Hygiene, Regional Hospital Centre of Saint-Pierre, Réunion, France
6. Virology Unit, Institut Pasteur, Antananarivo, Madagascar

This article was published on 3 September 2009.

Citation style for this article: D'Ortenzio E, Grandadam M, Balleydier E, Dehecq JS, Jaffar-Bandjee MC, Michault A, Andriamandimby SF, Reynes JM, Filleul L. Sporadic cases of chikungunya, Réunion Island, August 2009. *Euro Surveill.* 2009;14(35):pii=19324. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19324>

On 28 August 2009, French authorities reported five cases of chikungunya fever on Réunion Island: three confirmed, one probable, and one suspected case under investigation. All three confirmed patients presented with an acute febrile syndrome, arthralgia, myalgia and cutaneous rash. All live in the same area on the western side of the island.

Introduction

In 2005-2006 a major epidemic of chikungunya virus (CHIKV) infections occurred on Réunion Island [1] and in the southwestern Indian Ocean region [2]. In Réunion, the cumulative attack rate was 36% [1] and corresponded to the seroprevalence rate of 38% that was measured at the end of the epidemic [3]. After December 2006, no new autochthonous confirmed case of CHIKV was detected on Réunion Island [4].

On the neighbouring island of Madagascar, chikungunya virus was responsible for a large outbreak in 2006 in Toamasina (Tamatave), a coastal town located 350 km northeast from the capital Antananarivo. Within 4,242 randomly selected patients over near 200 000 dengue like syndromes reported among representative residents, 67,5% were found positive for a recent Chikungunya infection [5]. Further outbreaks of chikungunya fever occurred in May 2006 in Mahajanga (northwest coast), in February 2007 in the Sava region (northeast coast), in March to June 2007 in Antsiranana (northern coast), with 20 (29 sampled), 10 (15 sampled) and 14 (28 sampled) confirmed cases, respectively [6]. Since March 2009, the sentinel surveillance network of the Malagasy Ministry of Health has reported sporadic confirmed cases in Toamasina [6]. In June 2009 viraemic cases imported from Madagascar (Toamasina) to continental France were documented [6].

Cases of chikungunya on Réunion Island in 2009

On 5 April 2009 a Malagasy patient travelled for a medical visit from Madagascar to Réunion where he developed symptoms typical of chikungunya fever. A blood sample on 10 April 2009

was positive for CHIKV by specific anti-CHIKV IgM and by real time RT-PCR [6,7].

An autochthonous confirmed case of chikungunya fever was reported to the regional office of the French Institute for Public Health Surveillance in Réunion (Cire Réunion-Mayotte, Institut de Veille Sanitaire) in August 2009 by the Pasteur Cerba laboratory. The Pasteur Cerba laboratory is a central laboratory that receives specimens (on average 3,500 specimens per month) from all over the country including the French overseas territories (West Indies, Guyana, Polynesia). This autochthonous confirmed case lives in Saint-Gilles-Les-Bains on the western side of the island. On 18 July 2009, she had presented with an acute febrile syndrome associated with arthralgia, myalgia, and a cutaneous rash. A blood sample, drawn on 24 July 2009 was found positive for specific anti-CHIKV IgM but negative for IgG and in the RT-PCR. The case was confirmed at the National Reference Centre for Arboviruses at the Institut Pasteur in Paris by detection of anti-CHIKV IgG in a second blood sample taken on 11 August 2009.

Two further autochthonous cases of CHIKV infection in people from the same town were diagnosed at two local hospitals. Both patients reported an acute febrile syndrome associated with arthralgia, myalgia, and cutaneous rash on 23 July and 3 August 2009, respectively. The first one was found positive for CHIKV by RT-PCR and the second by seroconversion demonstrated on paired sera. All results were confirmed by the National Reference Centre for Arboviruses at the Institut Pasteur in Paris.

None of these three confirmed cases of chikungunya virus infection reported a recent travel history off the island or a contact with persons with a travel history or having received a package from abroad.

Currently two other probable cases are being investigated: a tourist who reported an acute febrile syndrome associated with arthralgia and cutaneous rash on 4 August 2009 and had stayed in the same area as the confirmed cases and a permanent resident

of Saint-Paul, a neighbouring town of Saint-Gilles-Les-Bains who had reported a stay in Saint-Gilles-Les-Bains.

Sequence analysis is in progress at the National Reference Centre for Arboviruses at the Institut Pasteur in Paris to tentatively determine the origin of the chikungunya virus in order to establish whether the 2005-2006 Réunion strain has re-emerged or whether a new isolate has been introduced.

Conclusion

Epidemiological and biological investigation of these cases provides evidence for active transmission of chikungunya virus in Saint-Gilles-Les-Bains, a tourist location on Réunion Island. In response to this outbreak, control measures are being organised by the Cire Réunion-Mayotte and the Vector Control Team of Drass Réunion. Active mosquito control measures and information to the population on how to prevent mosquito bites have rapidly been implemented.

Entomologic investigation found low vector activity correlated to winter in the southern hemisphere. Nevertheless, mosquito density seems to be sufficient to support CHIKV transmission. The current austral winter may contribute to moderate the transmission, but special attention in the next weeks is needed. Reinforcement of epidemiological and entomological surveillance has been organised to prevent the risk of potential spread of the virus on the island. Medical staff on the island has been informed about the situation and recommendations on how to react to suspected cases have been issued to them.

Currently, health services in Réunion are under intense strain because of the current H1N1 influenza pandemic. However, despite the small number of cases of CHIKV infection, special attention should be focused on arbovirus activity to prevent, or at least minimise, the spread of the virus during next summer in the southern hemisphere starting in November. Physicians should be aware to sample patients for chikungunya infection when facing a patient presenting an influenza-like syndrome without respiratory symptoms. The Réunion-Continental France laboratory network, built up in 2005 to support local laboratories confronted with the emergence of Chikungunya virus, has been reactivated to reinforce diagnostic capabilities. Specific information of persons living in the area or visiting this island, focusing on individual mosquito bite prevention, should be intensified both locally and in northern hemisphere countries.

References

1. Renault P, Solet JL, Sissoko D, Balleydier E, Larrieu S, Filleul L, et al. A major epidemic of chikungunya virus infection on Réunion Island, France, 2005-2006. *Am J Trop Med Hyg.* 2007;77(4):727-31.
2. Staples JE, Breiman RF, Powers AM. Chikungunya fever: an epidemiological review of a re-emerging infectious disease. *Clin Infect Dis.* 2009;49(6):942-8.
3. Gérardin P, Guernier V, Perrau J, Fianu A, Le Roux K, Grivard P, et al. Estimating Chikungunya prevalence in La Réunion Island outbreak by serosurveys: two methods for two critical times of the epidemic. *BMC Infect Dis.* 2008;28:8:99.
4. Cire Réunion-Mayotte. *Épidémiologie du chikungunya à la Réunion – Bilan d'une année de surveillance – 19 avril 2007 – 18 avril 2008.* Institut de veille sanitaire, décembre 2008, 8 p. [Article in French]. Available from : <http://www.invs.sante.fr/regions/index.htm>.
5. Ratsitorahina M, Harisoa J, Ratovonjato J, Biacabe S, Reynes JM, Zeller H, et al. Outbreak of dengue and Chikungunya fevers, Toamasina, Madagascar, 2006. *Emerg Infect Dis.* 2008;14(7):1135-7. Available from: <http://www.cdc.gov/EID/content/14/7/1135.htm>
6. ProMED-mail archive no. 20090611.2156. Available from: http://www.promedmail.org/pls/otn/f?p=2400:1001:735112850628827:::F2400_P1001_BACK_PAGE,F2400_P1001_ARCHIVE_NUMBER,F2400_P1001_USE_ARCHIVE:1001,20090611.2156,Y
7. Cire Réunion-Mayotte. Chikungunya à Madagascar et en Asie du sud-est et suspicion de dengue à Maurice Point épidémiologie n°37 au 16/06/2009. Available from : <http://www.reunion.sante.gouv.fr/epidemiologie/PE-CHIK-DENGUE-17-06-09.pdf>

FINLAND INTRODUCES ROTAVIRUS VACCINE INTO THE NATIONAL VACCINATION PROGRAMME IN SEPTEMBER 2009

H Nohynek (hanna.nohynek@thl.fi)¹, H Salo¹, M Renko², T Leino¹

1. Department of Vaccines and Immune Protection, National Institute of Health and Welfare, Helsinki, Finland

2. Department of Paediatrics, University of Oulu, Finland

This article was published on 3 September 2009.

Citation style for this article: Nohynek H, Salo H, Renko M, Leino T. Finland introduces rotavirus vaccine into the national vaccination programme in September 2009. *Euro Surveill.* 2009;14(35):pii=19322. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19322>

Supported by an economic evaluation, rotavirus vaccine is introduced into the national immunisation schedule in Finland. The vaccination programme has been estimated to be reasonably cost-effective. Given at the age of two, three and five months, the vaccine is expected to prevent annually in Finland among children under the age of five years approximately 2,000 rotavirus diarrhoea episodes needing hospitalisation, and over 10,000 outpatient visits. The impact of the programme will be evaluated in 2011 by repeating the economic analysis and carefully monitoring adverse events.

Rotavirus causes epidemics every year during the months of winter and spring in northern Europe. Especially in young children, the infection manifests as acute gastroenteritis with high fever, vomiting and watery diarrhoea, with 10-20 stools per day, lasting for a total of three to eight days. The first rotavirus infection in a person is usually symptomatic, and can easily lead to severe dehydration. The typical clinical picture is usually observed in children between the ages of six months and two years. Almost all children are infected with rotavirus, either with symptoms or asymptomatic, before they are five years old. Rotavirus infection is easily transmitted, since a lot of virus is excreted in stools during diarrhoeal bouts.

As in Europe in general, serotypes G1 and G4 have been the dominant serotypes causing annual rotavirus diarrhoea epidemics during 1980s and 1990s in Finland [1,2]. In recent years, serotype G9 has gained importance and was the most common serotype found in 2005. Among the total 125 isolates serotyped from the Helsinki metropolitan area during the epidemic season in 2006-7, the G1P[8] was dominant (57%) followed by G9P[8] (29%). The G4P[8] serotype was found in only four isolates [3].

Presently there are two live rotavirus vaccines on the market, which differ in their antigenic composition and protective principle [3]. The RotaTeq vaccine is a live reassortant vaccine derived from human and bovine rotaviruses. For sufficient protection, three doses are needed. Rotarix is a live attenuated vaccine based on human rotaviruses (RIX4414). For sufficient protection, two doses are needed. The vaccine preparations contain different rotavirus serotypes: RotaTeq is composed of serotypes G1, G2, G3, G4 and P[8] and Rotarix of G1P[8].

In clinical trials, vaccine efficacy of either vaccine against severe rotavirus diarrhoea that requires rehydration therapy was over 90 %, and against any rotavirus diarrhoea 60–70 % (3). Although no

formal comparative efficacy analysis was performed, there is no scientific reason to believe that the protective efficacy of these two vaccines would be significantly different that could guide the choice of one vaccine over the other. Based on the trial outcome, the risk profiles of the two vaccines are also fairly similar.

In Finland, a new vaccine can be introduced to the national immunisation programme if it fulfils four key criteria. There needs to be a public health disease burden that is to be prevented, the vaccine needs to be safe and able to reduce the disease burden, it should not have any significant adverse events on the population level, and finally, the intervention should be reasonably cost-effective to justify the expense from the state budget [4].

Evaluation of the cost-effectiveness of rotavirus vaccination

In order to understand the burden of disease caused by rotavirus, we estimated the proportion of healthcare resource use attributable to rotavirus. We regressed [5,6] the weekly laboratory reports of gastrointestinal pathogens on the weekly infectious and non-infectious intestinal disease episodes (constructed from the hospital outpatient visits and inpatient hospitalisations) and weekly primary healthcare visits according to a model. According to this estimation of the burden of disease, approximately 11,100 children under five years of age annually need health care services due to rotavirus in Finland [7]. We estimated that rotavirus gastroenteritis annually leads to 2,400 episodes needing hospitalisation, 3,700 hospital outpatient visits and 9,000 visits to healthcare centres.

To investigate the potential cost-effectiveness of the vaccination programme, a cohort model was constructed to compare the costs and outcomes of the two rotavirus vaccines to a scenario without intervention [8]. A hypothetical birth cohort was followed over the first five years of life. The analysis was conducted from the perspectives of the health care provider and of society.

It was estimated that a rotavirus vaccination programme in Finland could prevent annually approximately 2,000 rotavirus diarrhoea episodes requiring hospitalisation and over 10,000 outpatient visits among children under the age of five years. The estimated annual costs to the healthcare provider of rotavirus infection among children under five years were EUR 4.2 million without vaccination. The cost per quality-adjusted life year (QALY) gained from the perspective of the healthcare provider was EUR 25,218 for Rotarix (assuming EUR 39.5 per dose) and EUR 45,199 for RotaTeq (assuming EUR 29.5 per dose). In the

probabilistic sensitivity analysis (healthcare payer perspective), the 95% confidence intervals for cost per QALY gained ranged from EUR 20,370 to EUR 30,498 for Rotarix and from EUR 38,177 to EUR 48,506 for Rotateq.

The Finnish National Institute of Health and Welfare (THL) and National Advisory Boards of Vaccination and Infectious Diseases who reviewed the analysis in 2007 agreed that the parameter values were based on good quality national data and that the assumptions chosen were conservative enough to give relevant guidance for national decision making [4]. Based on this analysis, the rotavirus vaccination programme appeared to be not cost-saving but reasonably cost-effective, especially if nosocomial infections and home-treated rotavirus cases were included. Thus, rotavirus vaccine was recommended to be included into the national programme – a recommendation which the Ministry of Social Affairs and Health as well as the Ministry of Finances agreed to in 2008.

Choosing the vaccine to be used

In Finland, the procurement of vaccines for the national programme is centralised. In the competitive bidding done in 2008, the only decisive factor was the price. The offer of RotaTeq manufactured by Sanofi Pasteur MSD was cheaper; at this price the programme was cost-saving. Finland has now agreed to include RotaTeq into the national programme for two years after which a new tender will be launched. Today, given the present price of Rotateq, the rotavirus vaccine programme is estimated to be cost saving both from the societal and health care provider perspective. Also, it is to be expected that the vaccine provides indirect protection to the society as a whole when transmission of rotavirus is reduced [9].

In Finland, the three doses of the vaccine will be given at the ages of two, three, and five months thus increasing by one the visits to a well-baby clinic for vaccination (the one at two months of age). As a precaution, the first dose is recommended to be given before the age of 12 weeks, but not earlier than six weeks. Also, the child should not be older than 26 weeks (i.e. 6.5 months) when the third dose is given. These age limits approved by the European Medicines Agency (EMA) are somewhat stricter than those recommended by the United States Food and Drug Administration (FDA), which has recently raised the upper limit of the third dose to the age of eight months. In addition, the Strategic Advisory Group of Experts (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO) have suggested that these limits be raised even more in resource-poor countries where the rotavirus disease burden is very high, and where it is important for rotavirus vaccine coverage to be as high as possible. In such countries the recommended upper limit is 15 weeks for the first dose and 36 weeks for the third dose [10].

Safety of the RotaTeq vaccine

The clinical safety of RotaTeq was proven in trials involving approximately 70,000 children in 12 countries. One third of these were Finnish children (11). By spring 2009, the manufacturer had sold approximately 22 million doses of RotaTeq. In those countries where the vaccine was introduced into the national programme (i.e. Australia, Austria, Luxembourg, and the United States), it has proved to be safe. In the US, the reported incidence of intussusception (1/25–50,000 first doses) did not differ from that expected, i.e. from the observed incidence before starting the vaccinations [12]. Cases of intussusception were reported somewhat more often after the first than after the second or third doses. Another cause for

concern has been Kawasaki disease. During the clinical trials the suspicion of an increased incidence of Kawasaki disease arose, although the difference between the vaccines and controls was not significant. After the introduction of the vaccine and careful monitoring, there has been no evidence that would point to an increased risk of Kawasaki disease among those vaccinated [12]. The most common expected adverse events are mild and transient gastrointestinal and respiratory symptoms [11]. After the first dose, less than 9 % of the vaccinees excrete the vaccine virus into stools. This is even more rare after receiving the second or third dose.

Monitoring the impact of rotavirus vaccination

Rotavirus vaccinations will be started in September 2009 in all the well-baby clinics in Finland, which cover approximately 99% of the Finnish cohort of newborns. For the time being, Finland does not have an operational vaccine registry. Thus, vaccine coverage, which traditionally has been high in the country, i.e. above 90% for most vaccines used in the national programme [13], will be monitored using the administrative method combined with periodic surveys of the vaccination status of a randomly chosen sample of 1,000 children. Adverse events associated with rotavirus vaccination will be monitored through the existing passive surveillance system, i.e. health care personnel will notify of any suspect case of adverse events following immunisation (AEFI) to THL. In addition, certain clinical manifestations like intussusception and Kawasaki disease will be actively monitored as part of the VAESCO project, a project for harmonising vaccine safety in Europe (www.vaesco.net). A systematic monitoring of the effectiveness of the rotavirus vaccination programme is planned for the year 2011 repeating the collection of morbidity and mortality data as done for the economic evaluation [7,8]. In addition, isolated rotavirus vaccine strains will be sero- and genotyped to understand the possible impact of vaccination on new reassortments and shifts in the proportions of the prevailing serotypes [2].

Details on the rotavirus vaccines used, vaccinating, adverse event monitoring and frequently asked questions can be found at the THL website both in Finnish and Swedish language (www.thl.fi).

References

1. Maunula L, von Bonsdorff CH. Rotavirus serotypes and electropherotypes in Finland from 1986 to 1990. *Arch Virol.* 1995;140(5):877-90.
2. Maunula L, von Bonsdorff CH. Frequent reassortments may explain the genetic heterogeneity of rotaviruses: Analysis of Finnish rotavirus strains. *J Virol.* 2002;76(23):11793-800
3. Vesikari T. Rotavirus vaccines. *Scand J Infect Dis.* 2008;40(9):691-5.
4. Nohynek H. The Finnish decision-making process to recommend a new vaccine: From vaccine research to vaccination policy. *Eur J Publ Health.* 2008;16(4):275-80.
5. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. *Vaccine.* 2007;25(20):3962-70. Epub 2007 Mar 15.
6. Jit M, Bilcke J, Mangen MJ, Salo H, Melliez H, Edmunds JW, et al. The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe. *Vaccine.* 2009 Aug 25. [Epub ahead of print]
7. Salo H, Ollgren J, Linna M, Sintonen H, Kilpi T. Economic evaluation of rotavirus vaccination in Finland [poster]. *Eur J Public Health.* 2007;17 Suppl 2:S3-36.
8. Kansanterveyslaitoksen asettaman lasten rotavirusrokotustyöryhmän selvitys. Kansanterveyslaitoksen julkaisu, 26.11.2007. (KTL Expert Group report on children's rotavirus vaccination). [Article in Finnish]. Available from: http://www.ktl.fi/attachments/suomi/julkaisuut/julkaisusarja_b/2007/2007b28.pdf
9. Pitzer VE, Viboud C, Simonsen L, Steiner C, Panozzo CA, Alonso WJ et al. Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. *Science.* 2009;325(5938):290-4.

10. World Health Organization. Anonymous. Meeting of the immunization Strategic Advisory Group of Experts, April 2009 – conclusions and recommendations. WHO Weekl Epidemiol Rec 2009;84:220-236
11. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(1):23-33.
12. Cortese MM, Parashar UD; Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children. Recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58(RR-2):1-25.
13. Leino T, Koskenniemi E, Saranpää PR, Strömberg N, Kilpi TM. Rokotuskattavuus edelleen huippuluokkaa. [Vaccine coverage still extremely high]. Suom Lääkäril 2007;62:739-743. [Finnish].

UNIVERSAL VARICELLA VACCINATION IN THE SICILIAN PAEDIATRIC POPULATION: RAPID UPTAKE OF THE VACCINATION PROGRAMME AND MORBIDITY TRENDS OVER FIVE YEARS

G Giammanco (giugiam@unict.it)¹, S Ciriminna², I Barberi³, L Titone⁴, M Lo Giudice⁵, L R Biasio⁶

1. Department of Hygiene, University of Catania, Catania, Italy

2. Regional Public Health Office, Palermo, Italy

3. Department of Paediatric Sciences, University of Messina, Messina, Italy

4. Department of Infectious Diseases, University of Palermo, Palermo, Italy

5. Family paediatrician, Palermo, Italy

6. Sanofi Pasteur MSD, Rome, Italy

This article was published on 3 September 2009.

Citation style for this article: Giammanco G, Ciriminna S, Barberi I, Titone L, Lo Giudice M, Biasio LR. Universal varicella vaccination in the Sicilian paediatric population: rapid uptake of the vaccination programme and morbidity trends over five years. *Euro Surveill.* 2009;14(35):pii=19321. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19321>

Following the licensure of the Oka/Merck varicella vaccine in Italy in January 2003, the Sicilian health authorities launched a universal vaccination programme in all nine Local Health Units. A two-cohort vaccination strategy was adopted to minimise the shift of the mean age of varicella occurrence to older age groups, with the goal of vaccinating with one dose at least 80% of children in their second year of life and 50% of susceptible adolescents in their 12th year of life. Two studies were implemented in parallel to closely monitor vaccination coverage as well as varicella incidence. Overall, the programme achieved its target, with 87.5% vaccine coverage for the birth cohort 2005 and 90.2% for adolescents born in 1995 and 1996. Varicella surveillance data obtained from a total of 28,188 children (0-14 years-old) monitored by family paediatricians showed a decline in incidence rates from 95.7 (95% confidence interval (CI): 72.2-126.8) for 1,000 person-years (PY) in 2004 to 9.0 (95% CI: 6.4-12.6) for 1,000 PY in 2007. In Europe, the only similar experience is the routine childhood varicella vaccination programme in Germany that started in 2004 with a single dose at the age of 11-14 months. The two-cohort universal vaccination programme implemented in Sicily, as well as the network for the surveillance study, can offer a model to other European countries that are considering introducing universal childhood varicella vaccination.

Introduction

Now that many vaccine preventable paediatric diseases have been eliminated or controlled, varicella remains one of the most common childhood diseases. Although varicella-zoster virus (VZV) infections are generally mild and self-limiting in the vast majority of children, complications such as secondary bacterial infections, pneumonia, encephalitis, cerebellar ataxia, transverse myelitis and death, can occur [1].

The incidence of varicella in Italy is believed to approximate the birth cohort, with over 5,300 annual estimated cases per 100,000 children under the age of 15 years [2], 3.5-5% of whom develop

complications such as upper respiratory tract and cutaneous infections [3]. The figures presented in this report illustrate the significant burden of the disease in Sicily both for parents and for health services [4] and support the launch of a universal vaccination programme. Following the licensure of the Oka/Merck varicella vaccine (Varivax®) in Italy in 2001 for use in healthy children, the Sicilian health authorities launched a two-cohort universal vaccination programme. The impact of varicella vaccination was monitored in two studies conducted in parallel, one focusing on vaccination coverage and the other on varicella incidence.

Methods

Coverage study

Sicily (5,015,297 inhabitants in the national census of 1 January 2006) is one of twenty Regions in Italy. Public health policies are established autonomously in the Regions, based on recommendations from the Italian National Health Service. Compulsory and recommended vaccinations are actively offered free of charge to all Sicilian children against diphtheria, tetanus, poliomyelitis, hepatitis B, pertussis, *Haemophilus influenzae* type b, measles, mumps, and rubella. In Italy, childhood vaccinations are mostly performed in Vaccination Centres (VCs). Sicily counts 386 VCs that are part of Health Districts (HDs), themselves part of Local Health Units (LHUs).

Vaccination programme

Universal varicella vaccination was added to the standard childhood vaccination programme in January 2003 and was actively offered free of charge to all children in their second year of life (at about 15 months of age) and to all susceptible adolescents in their 12th year of age, at the time of the measles, mumps and rubella (MMR) vaccination in order to improve parents compliance. Although two vaccines were available, only Varivax® was licensed for universal vaccination at the time and thus selected for the programme. Once the parents consented to the vaccination, varicella vaccine was administered on the same occasion as MMR

vaccine, injected in the counter lateral arm. Following existing recommendations at the start of the programme, one dose of varicella vaccine was administered to every participating child and adolescent.

Public health physicians carried out most of the vaccinations, although paediatricians were the key contacts for counselling and in some cases vaccinated the children themselves. In addition, ad hoc information campaigns in secondary school were performed and susceptible adolescents could also be vaccinated at their own school surgery. Varicella vaccine was also offered free of charge to the siblings of all vaccinated children and to household contacts of varicella cases.

The vaccination target was set at $\geq 80\%$ coverage for children in their second year of life and $\geq 50\%$ for susceptible adolescents. Vaccination coverage was analysed overall, by age group and by birth cohort.

Collection and recording of data

Demographic and vaccination data were collected by VCs and reported monthly to HDs. Data was entered in a protected internet database with varying levels of access, connecting HDs, LHUs and the Regional Public Health Office (RPHO), each of these entities having a different level of access for data entry, data monitoring and analysis. For the few vaccinations performed by family paediatricians (FPs) or other structures, the vaccination data was communicated to the public health system for entry into the database. Quality control of the database was monitored by an external agency through quarterly visits and audits.

Target population for data analysis

The target population for data analyses for the period 2003-2007 included:

all children aged 12-23 months (100% of the resident population in this age group),

all susceptible adolescents aged 11-12 years (18% of the resident population in this age group).

Susceptibility to varicella was based on self-reported negative history for the disease. Although there are limitations associated with parental reporting (e.g. under- or overestimation of disease occurrence), these limitations are usually accepted in observational epidemiological surveillance studies.

The denominator for coverage rate was calculated using resident population numbers according to the National Institute of Statistics (ISTAT, data as of 1 January 2006) and prevalence of VZV, extrapolated using known Italian VZV seroprevalence data by age range [5].

Surveillance study

Varicella surveillance was performed through a sentinel network of randomly selected FPs in order to describe age-specific varicella incidence rates among children 0-14 years after the introduction of the universal vaccination programme, as well as age-specific related complications. FPs offer a unique surveillance opportunity since every child in Italy is registered with an FP from birth until the age of 14 years. Thus, each FP has a precise paediatric population under their care (between 800 and 1,000 children) and their public health duty includes routine control visits that are perfect opportunities for offering vaccination, for disease control and surveillance. Of the 844 FPs operating in Sicily, 30

were randomly selected to participate in the study. The number of FPs from each LHU was balanced by resident population and geographical location (urban versus rural) with at least one FP from each of the nine LHUs. Computations of incident cases and person-year (PY) computation were recorded prospectively from March 2005 and retrospectively (based on physicians records) for the period from January 2003 to February 2005. This could result in some degree of underreporting for the retrospective period, although it is noteworthy that most of the physicians participating in the study had already been involved in active infectious diseases surveillance before the start of the study.

All children registered with the 30 sentinel FPs were proposed participation into the study. Informed parental consent was

TABLE

Number of children vaccinated against varicella, by birth cohort, Sicily, 2003-2007

Birth cohort	1995-1996	1997-2004	2005
Vaccinated children	8,839	152,308	35,123
Resident children*	108,958	410,652	50,202
Susceptible children**	19,613	nd	50,202

nd: not done.

*National Institute of Statistics data (ISTAT) data as of 1 January 2006.

**Estimated based on published seroprevalence data [5].

FIGURE 1

Coverage rates for varicella vaccination of children, by birth cohort (2001-2005), Sicily

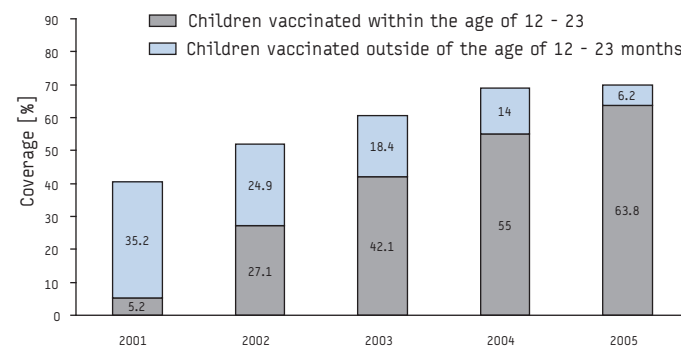
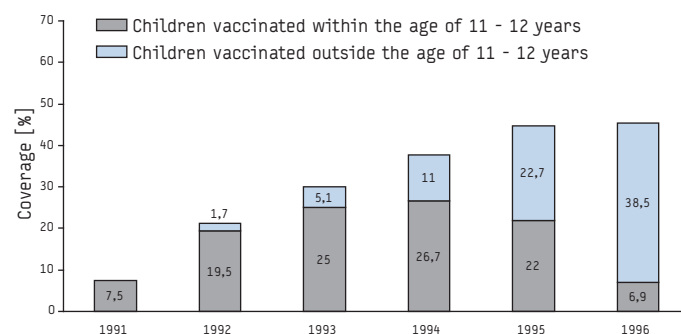


FIGURE 2

Coverage rates for varicella vaccination of adolescents, by birth cohort (1991-1996), Sicily



requested. The at-risk population (denominator) included all children susceptible to varicella who were followed by participating FPs. The PY contribution of each child followed up was calculated using information from the FPs' records. This was done for the active surveillance period of the study (2005 to 2007), as well as for the years 2003 and 2004 using information in the FPs' records

FIGURE 3
Overall coverage rates of varicella vaccination in children 12-23 months, by Local Health Unit, Sicily, 2003-2007

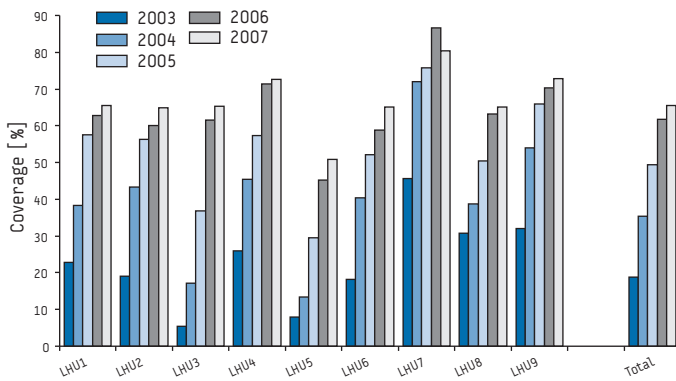


FIGURE 4
Annual varicella incidence rates per age group, sentinel FP network, Sicily, 2003-2007

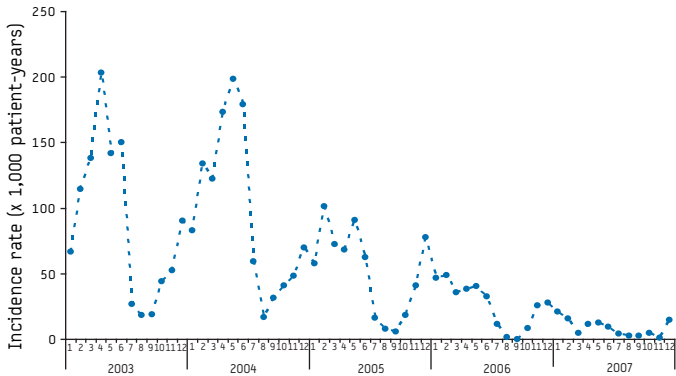
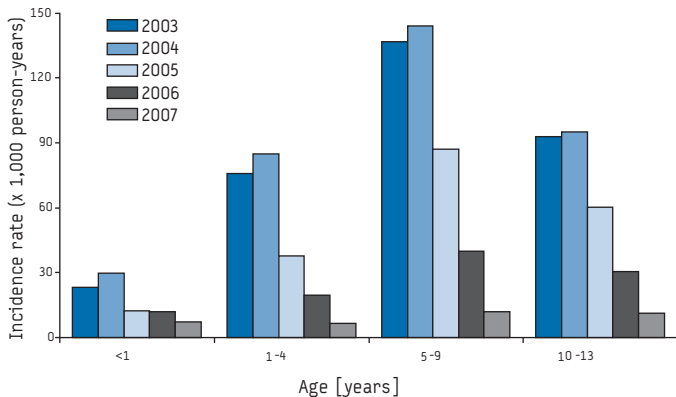


FIGURE 5
Annual varicella incidence rates per age group, sentinel FP network, Sicily, 2003-2007



to obtain 'historical' rates for the period between the introduction of the vaccine in Sicily (2003) and the implementation of the study (2005).

Results

A total of 225,642 children vaccinated during the study period (1 January 2003 to 31 December 2007) were taken into consideration for the analysis, as presented in the Table.

The coverage rate for children born in 2005 was 70.0% (Figure 1), while that of susceptible adolescents born in 1995 and 1996 was 45.1% (Figure 2).

The overall coverage rate for 2007 was 65.5% in children 12-23 months (range 50.9-80.5%), as shown in Figure 3, and 12.1% in adolescents 11-12 years of age (range 5.1-40.9%).

Varicella surveillance data were obtained from a total of 28,188 children at the age of 0-14 years (the 86.7% of the registered children for whom informed parental consent was obtained). Of those, 21,568 susceptible children were taken into account for the calculation of varicella incidence. The varicella incidence rates per month in 0-14 year-old children are presented in Figure 4.

Annual incidence rates declined from 95.7 (95% confidence interval (CI): 72.2-126.8) for 1,000 PY in 2004 to 9.0 (95% CI: 6.4-12.6) for 1,000 PY in 2007. The incidence of varicella declined in all age groups (Figure 5).

A total of 22 cases of breakthrough varicella (occurring more than six weeks after vaccination) were reported. Ten cases occurred in 1-4 year-old children, nine cases in the age group of 5-9 year-olds and three cases in 10-13 year-old children. No case required hospitalisation. In addition, seven herpes zoster cases were reported among vaccinated children: three in 1-4 year-old children, three cases in 5-9 year-olds and one case in the age group of 10-13 year-olds.

Discussion

Varicella vaccination is not yet routine in Europe despite the availability of VZV vaccines in at least 14 European countries [6]. In general, selected high-risk groups, such as healthcare workers, susceptible adults, and immunocompromised patients are targeted for vaccination. Although the epidemiology of varicella in Europe is similar to that observed in the prevaccine era in the United States, Germany remains the only country that has incorporated the VZV vaccine nationwide in the routine immunisation schedule as a single dose at the age of 11-14 months, starting from July 2004 [7].

Sicily was the first Italian region to introduce universal varicella vaccination in its childhood vaccination programme in 2003 and to date, only three other Italian regions have a similar programme for varicella. The model adopted by the Sicilian health authorities took into account the peculiarities of the age-specific varicella seroprevalence in Italy. Indeed, the reproduction numbers and herd immunity thresholds can have a profound impact on susceptibility patterns and disease transmission and thus have important implications for the design and implementation of varicella vaccination programmes in a given country [6]. Standardised serological surveillance established for eight-vaccine preventable diseases [8,9] showed striking variations in the rate of VZV transmission in different European countries. While seroprevalence

for varicella at the age of five years was high in some countries (97% in the Netherlands, 86% in Israel, 81% in Belgium), but very low in Italy, with only 38% of children seropositive for VZV antibodies [5]. Within Italy, however, VZV is circulating more intensely in the southern part of the country and affects people at an earlier age [4]. No clear explanations can be given for the relatively low seroprevalence of varicella antibodies across all age groups in the Italian population. Nevertheless, these data provide a good rationale for varicella vaccination in early childhood and adolescence in a population relatively less well protected by natural immunity compared to other European countries.

The programme Sicily was taken up rapidly, with increasing coverage rates in both cohorts over time. Although significant differences were initially observed between LHUs, the figures became more uniform over the years. The average coverage rates were 65.5% for children in their second year of life and 12.1% for adolescents at the age of 11-12 years. A steady uptake of the programme was observed between 2003 and 2007, and the programme's target was achieved, with 87.5% coverage for the birth cohort 2005 and 90.2% for adolescents born in 1995-1996. The introduction of the combined MMR-VZV vaccine is expected to modify the acceptance of varicella vaccination and could further increase coverage rates [10] in view of the MMR vaccination rates of up to 85% currently attained in all Sicilian LHUs.

Vaccination of young children before the peak age of varicella prevalence can have a significant impact on the incidence of the disease, as already demonstrated in the United States (US), where universal childhood vaccination was introduced in 1995. In Sicily, the main targeted cohort (children at the age of 15 months) was selected based on the fact that infection in Sicily occurs at an earlier age compared to the rest of the country. After the launch of the varicella vaccination programme, a steady decrease in varicella incidence was observed, reaching 9.0 for 1,000 PY during the last year of observation (2007), a number well below the national estimate of 70 for 1,000 PY. So far, this strategy has proven very effective and breakthrough disease has been rare (only 22 cases reported in the surveyed population). Low levels of circulating VZV in early childhood warrant better protection of susceptible adults and adolescents and can limit the potential shift of the disease towards older age that is generally put forward as a risk of universal varicella vaccination in childhood. The possible need for booster doses in adolescents and adults cannot be excluded, although the two-dose vaccination regimen currently proposed for all ages seems to lower the risk of breakthrough varicella in vaccinated children considerably. Good coverage rates in susceptible adolescents will be an additional barrier against the shift of the disease to older age. Clearly, the dynamics of disease epidemiology after the start of the vaccination programme will need further assessment and one key element will be the observed incidence of breakthrough disease.

Another potential risk that has limited the uptake of varicella vaccination in Europe is the possible increase in the incidence of herpes zoster. Our data show a very low number of herpes zoster cases in the surveyed population. Unfortunately, virological data were not available for these latter cases, although virological typing (differentiating between the Oka/Merck vaccine strain and the wildtype virus) had been made available to participating physicians for a number of complications or breakthrough cases. Longer follow-up is required, as well as more consistent data on the background rates of herpes zoster in the general paediatric population.

Overall, long-term surveillance is needed to evaluate the effectiveness of the programme over time, and the progressive introduction of the second dose of varicella vaccine in early childhood, as already recommended in the US [11], will have to be closely monitored. Nevertheless, very good results have already been obtained in the five years of universal varicella vaccination with one dose, as shown by the very low incidence of the disease in all age groups in 2007, including those not targeted by the vaccination programme. Close collaboration between public health services and family paediatricians also proved effective.

The two-cohort universal vaccination programme implemented in Sicily, as well as the network for the surveillance study, can offer a model to other European countries that are considering introducing universal childhood varicella vaccination.

Acknowledgements

Special thanks to F Blangiardi, G Canzoneri, G Casella, N Casuccio, M Cuccia, G Ferrera, B Gucciardi, F Iacono, E Monteleone, V Pinella, S Sammarco and G Stella, as members of the Hygienists Group; to M Alessi, C Algozino, A Alongi, P Aurnia, G Avarello, G Bottaro, A Cavaliere, P De Luca, S Di Francesco, M Di Stefano, MG Fiamingo, F Gaipa, A Galletta, F Gambuzza, A Gennaro, L Grasso, R La Paglia, G Leone, A Lo Cascio, P Montalbano, MP Muccioli, S Patania, V Prestia, R Rizzari, F Russo, A Siragusa, S Speciale, A Tummarello, C Vitale and C Zinna as members of the Family Paediatricians Group; and to P Dang and E Perinetti (Sanofi Pasteur MSD).

Conflict of interest statement:

LR Biasio is Medical and Development Director of Sanofi Pasteur MSD.

References

1. Liese JG, Grote V, Rosenfeld E, Fischer R, Belohradsky BH, v Kries R, et al. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *Pediatr Infect Dis J*. 2008;27(2):119-24.
2. Ciofi degli Atti ML, Rota MC, Mandolini D, Bella A, Gabutti G, Crovari P, et al. Assessment of varicella underreporting in Italy. *Epidemiol Infect*. 2002;128(3):479-84.
3. Rentier B, Gershon AA, European Working Group on Varicella. Consensus: varicella vaccination of healthy children – a challenge for Europe. *Pediatr Infect Dis J*. 2004;23(5):379-89.
4. Fornaro P, Gandini F, Marin M, Pedrazzi C, Piccoli P, Tognetti T, et al. Epidemiology and cost analysis of varicella in Italy: results of a sentinel study in the pediatric practice. *Italian Sentinel Group on Pediatric Infectious Diseases*. *Pediatr Infect Dis J*. 1999;18(5):414-19.
5. Nardone A, de Ory F, Carton M, Cohen D, van Damme P, Davidkin I, et al. The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. *Vaccine*. 2007;25(45):7866-72.
6. Pinot de Moira A, Nardone A. Varicella zoster virus vaccination policies and surveillance strategies in Europe. *Euro Surveill*. 2005;10(1):pii=511. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=511>
7. Rasch G, Hellenbrand W. Germany adds varicella vaccine to the national vaccination programme. *Euro Surveill*. 2004;9(31):pii=2511. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2511>
8. Osborne K, Weinberg J, Miller E. The European Sero-Epidemiology Network. *Euro Surveill*. 1997;2(4):pii=167. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=167>
9. Nardone A, Miller E. Serological surveillance of rubella in Europe: European Sero-Epidemiology Network (ESEN2). *Euro Surveill*. 2004;9(4):pii=456. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=456>
10. Bernstein HH, Eves K, Campbell K, Black SB, Twigg JD, Reisinger KS, et al. Comparison of the safety and immunogenicity of a refrigerator-stable versus a frozen formulation of ProQuad (measles, mumps, rubella, and varicella virus vaccine live). *Pediatrics* 2007;119(6):e1299-305.
11. Marin M, Güris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1-40.