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2010-2011 influenza seasonal vaccine, preliminary mid-season effectiveness estimates: reason for concern, confounding or are we following the right track?

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During the last 10 years there have been major advances in influenza surveillance, vaccine production and methods to determine vaccine effectiveness (VE), influenza diagnosis by real-time polymerase chain reaction (PCR), and influenza virology. Most of these have been fostered by the threat of a possible pandemic and the planning efforts devoted to minimising its impact.

The Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network, funded by the European Centre for Disease Prevention and Control (ECDC), has made a substantial contribution to these efforts. Among other activities, it has endorsed,case–control test-negative studies focused on providing VE estimates for specific laboratory-confirmed influenza outcomes, especially medically attended influenza-like illness (ILI) [1-3]. As a result of this initiative, I-MOVE associates have published preliminary mid-season estimates of the VE of the 2010/11 influenza seasonal trivalent vaccine to prevent cases of medically attended ILI laboratory-confirmed for influenza [4,5]: two additional preliminary reports are published in this week's issue of *Eurosurveillance* [6,7].

The present influenza season, which is now coming to an end, has been characterised predominantly (70–80%) by influenza A/California/07/2009(H1N1)-like isolates. There has also been a smaller but notable proportion (15–24%) of B/Brisbane/60/2008 (Victoria lineage) isolates in the season thus far, but in week 9 of 2011, they accounted for 80% of virus isolates [8],Both virus types are included in the trivalent seasonal vaccines now used in Europe [8,9]. Thus, the currently circulating influenza A(H1N1)2009 virus and the currently used vaccine are similar but not identical to the virus circulating in the autumn 2009 pandemic wave [7,10] and the monovalent adjuvanted vaccines used then [4,5,7].

Perhaps not surprisingly, the published VE estimates for the current seasonal vaccine [4-7] were lower that those published for the pandemic vaccine used in 2009/10 [3,11-13]. They were, however, so low that when the usual confounding factors are taken into account, the estimates are compatible with a hypothesis of no effect. This raises the question of whether the lower adjusted VE of the 2010/2011 trivalent influenza vaccine is a real phenomenon or whether it is due to confounding, mismeasurement or other unknown factors. Some of the recent studies have mentioned the possible role of antigenic drift and differing study populations [4,6,7]. Although these possible explanations are intuitive and plausible – and no doubt partially explain the situation – there are some other issues that also merit discussion. Moreover one needs to keep in mind that the VE of the non-adjuvanted vaccines in the pre-pandemic area was lower than that of the adjuvanted monovalent pandemic vaccine.

From the data presented in these studies, we can build a scenario in which older age, the presence of risk factors and previous vaccination in the study population were highly correlated with being vaccinated with the 2010/2011 seasonal influenza vaccine. However, the data do not show that this was linked with a differential risk of acute respiratory infection due to influenza.

It should also be remembered that negative controls were negative for influenza, but may have had other infections. Influenza viruses are one of several groups of respiratory viruses that affect us at the same time of the year and at any age. Some of the test-negative controls probably went to their physicians with symptoms such as fever, cough, malaise and dyspnoea resulting from episodes of undetected respiratory syncytial virus (RSV), rhinovirus, coronavirus, metapneumovirus, or other unidentified viral infections that could not possibly be affected by influenza vaccination, but could be affected by the same underlying factors that increase the risk of becoming an influenza case.

If the analysis is adjusted for factors associated with influenza vaccination rather than for vaccination itself, the vaccine effect will be diluted and disappear, as can be seen when comparing the crude and adjusted effects reported. The test-negative approach can be

considered as a variant of a case–case comparison study [14], where recruitment has been prospective and within a short period, and where the most plausible factor associated with not being a true influenza case is having received influenza vaccination. For this reason any adjustment for factors correlated to vaccination must be dealt with caution [14,15]. The non-adjusted estimates might be a more plausible estimate of vaccine effectiveness than the adjusted results.

Even the crude VE estimates would still be confounded to the null because the study design was based purely on laboratory results. The negative controls were a mixed population of people most of whom were positive for viruses other than influenza, possibly including some false influenza-negatives and some people with non-infectious ailments. Therefore, a case–case approach comparing influenza-positive patients with those positive for other respiratory viruses (see [14,15]), with incidence sampling of both groups in periods of similar risk for influenza, would provide more realistic and convincing estimates of the influenza vaccination effect.

The authors also state that this year's study population was different from that of the previous year [4,6,7]. Vaccination recommendations differed, at least with respect to age, so age was a direct correlate of vaccination. Moreover, the population as a whole has had a wider exposure to influenza A(H1N1)2009 virus now than just a year ago [16]. Nevertheless, it is difficult to understand how this can explain the low VE results, unless this situation had an effect on the virus itself.

Another important element is therefore the influenza virus itself. Some of the recent reports on its evolution are reassuring and clearly state that the circulating viruses are well matched to the vaccine strains [7,10,17], while others propose that vaccination and previous exposure lead to immunological pressure that has driven virus evolution [7,10,17,18] in ways that could explain, at least in part, the observed differences between the highly effective monovalent pandemic vaccine and the lower effectiveness attributable to this year's seasonal trivalent vaccine. In fact, the reported observations point to a certain degree of mismatch between the circulating influenza A(H1N1)2009 strains and the corresponding vaccine component. The available results for the influenza B strain, however, point to a reasonable VE.

In conclusion, the four preliminary mid-season studies discussed provide timely and useful information. However, it is clear that we need a better understanding of the true impact of other respiratory viruses. To this end, we need to establish active, comprehensive and continuous surveillance systems that take advantage of the advances in diagnostic tools such as multiplex real-time PCR, which will allow us to conduct more focused case–case comparison VE studies. We need, without any doubt, better influenza vaccines, in terms of viral spectrum, and effectiveness, and we cannot forget the important seasonal impact that RSV, rhinovirus, coronavirus, parainfluenza or metapneumovirus infections have in all age groups. And last but not least, comprehensive and meticulous immunological and virological surveillance must be accompanied by timely communication and publication of observations, results and their interpretation.

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Effectiveness of the 2010/11 seasonal trivalent influenza vaccine in Spain: preliminary results of a case–control study

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We present preliminary results of a case–control study to estimate influenza vaccine effectiveness in Spain, from week 50 of 2010 to week 6 of 2011. The adjusted effectiveness of the vaccine in preventing laboratory-confirmed influenza due to any type of influenza virus was 50% (95% CI: –6 to 77%) for the trivalent seasonal vaccine and 72% (95% CI: 7 to 92%) for both trivalent seasonal and monovalent pandemic vaccines, suggesting a protective effect of seasonal vaccination lower than that reported for the previous season.

Background

After the 2009 influenza A(H1N1) pandemic, the World Health Organization (WHO) in February 2010 recommended the trivalent influenza vaccine for the northern hemisphere for the 2010/11 influenza season. The vaccine included the pandemic strain A/California/07/2009 (H1 subtype), the A/Perth/16/2009 (H3 subtype) and the B/Brisbane 60/2008 viruses. The influenza A(H1) strain is the same as that used in the monovalent 2009/10 pandemic vaccine, which showed good effectiveness in preventing influenza A(H1N1)2009 infection in the 2009/10 season [1,2].

In Spain, influenza vaccination is offered free of charge each year to people in high-risk groups. In the 2010/11 season, it was recommended to persons over six months old with chronic conditions, elderly people aged over 60 years (65 years in some regions), healthcare workers and caregivers. The vaccination campaign lasted between September and November 2010 and several vaccine brands were used [3]. The monovalent pandemic vaccine was only offered in the 2009/10 season: the vaccine brands were mainly adjuvanted, except those used for pregnant women, for whom a non-adjuvanted vaccine was recommended. The pandemic vaccine was also not recommended for elderly people aged over 64 years without underlying diseases.

Since the 2008/09 influenza season, Spain has been participating in the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network, established by the European Centre for Disease Prevention and Control (ECDC) [4]. Various study designs were tested: the test-negative case–control design proved suitable for such studies in Spain [5,6]. One of the objectives of this network is to provide early intraseasonal estimates of influenza vaccine effectiveness. The importance of having such estimates early in the season was highlighted during 2009/10, when intraseasonal estimates were needed in order to evaluate the impact of vaccination with the monovalent pandemic influenza vaccine [7].

The study presented here aims at providing an intraseasonal estimate of the seasonal trivalent vaccine 2010/11 effectiveness in preventing laboratory-confirmed influenza in Spain, in order to guide public health policies.

Methods

We conducted an observational case–control study (cycEVA) using the test-negative design described previously for the study of influenza vaccine effectiveness in elderly people [5]. Our study was carried out between week 50 of 2010 (12–18 December 2010) – when the influenza-like illness (ILI) threshold was first passed in the participating regions – and week 6 of 2011 (6–12 February 2011). Of the 17 regions of the Spanish Influenza Sentinel Surveillance System, eight participated in the study. In these eight regions, 246 of 325 (76%) sentinel general practitioners (GPs) and paediatricians agreed to take part in the study, covering a population of 313,734 inhabitants, representing 2.1% of the total population in these regions [8]. Of the 246 GPs and paediatricians, 159 (65%) recruited at least one patient in the study.

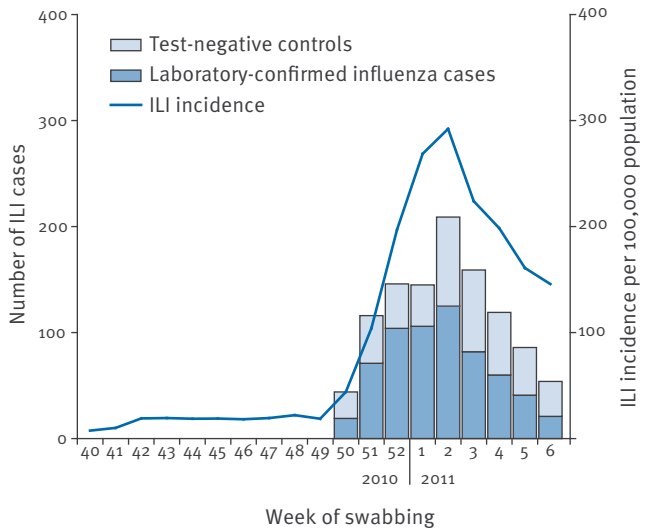
Each week, participating GPs and paediatricians systematically swabbed the first two patients presenting with ILI according to the European Union case definition [8]. A case of confirmed influenza was defined as an ILI patient with laboratory confirmation of influenza virus infection. Three outcomes were used in the study: infection with any type of influenza virus, influenza A(H1N1)2009 virus and influenza A(H3) or influenza B viruses. The controls were ILI patients whose laboratory results were negative for any influenza strain.

Data collection

Using a standardised questionnaire, participating GPs and paediatricians collected the following data for the recruited patients: age, sex, clinical symptoms, date of symptom onset, date of swabbing, vaccination status for 2010/11 seasonal influenza vaccine, influenza vaccination status for the previous season (seasonal and pandemic vaccines), laboratory result, chronic conditions, pregnancy, morbid obesity (defined as body mass index greater than 40), smoker status (current versus previous or non-smoker), functional status, any hospitalisation for chronic conditions in the previous year and the number of outpatient visits for any reason in the previous year. The patients were defined as having a chronic condition if they had any of the following: diabetes mellitus, cardiovascular disease, chronic pulmonary disease, renal disease, hepatic disease, congenital or acquired immunodeficiency, and chronic treatment with acetylsalicylic acid (in children). Poor functional status was defined as needing help for walking or bathing. Individuals were considered vaccinated if they had received the seasonal influenza vaccine 14 days or more before the date of symptom onset. Vaccinated individuals whose date of vaccination was missing (n=7) were considered vaccinated if the date of onset was two weeks after the end of the vaccination campaign.

Figure 1

Laboratory-confirmed influenza cases (n=629) and test-negative controls (n=449) among ILI patients by week of swabbing, cycEVA study, week 50 (2010)–week 6 (2011) and weekly ILI incidence, week 40 (2010)–week 6 (2011), Spain



ILI: influenza-like illness.

Source: cycEVA study and Spanish Influenza Surveillance System, National Centre of Epidemiology, Institute of Health Carlos III, Spain.

Data analysis

We restricted all analyses to patients with an interval between symptom onset and swabbing of less than eight days. Logistic regression was used to calculate the crude and adjusted odds ratios (ORs) and their corresponding 95% CIs. Vaccine effectiveness was calculated as (1–OR) multiplied by 100. All variables collected in the study were checked for possible confounding: we included in the regression model those that changed the crude OR by >10%. Thus, the final model included age group (0–4, 5–14, 15–44, 45–64 and ≥65 years), week of swabbing and previous vaccination status (seasonal or pandemic vaccine, according to the analysis performed).

We first carried out the analysis with all eligible patients, as some previously healthy people might have been vaccinated in an occupational setting or in private clinics. Then we restricted the analysis to those eligible for vaccination (people in high-risk groups) [3]). To check the effect of being vaccinated with both vaccines when using influenza A(H1N1)2009 virus infection as the outcome, we also carried out the analysis using a categorical variable for vaccination (unvaccinated, vaccinated with only seasonal trivalent vaccine 2010/11, only monovalent 2009/10 pandemic vaccine and both vaccines) [10]. We conducted all statistical analyses using STATA/IC 11.

The surveillance-affiliated laboratories or the National Centre of Microbiology (WHO National Influenza Centre-Madrid) confirmed influenza infection using real-time polymerase chain reaction (PCR). A number of laboratory-confirmed cases were genetically studied by sequencing the viral haemagglutinin gene. Phylogenetic analysis was carried out in order to characterise the specific strains of influenza A and B viruses.

The cycEVA study was included as part of influenza surveillance activities in Spain: therefore no ethical approval was needed for the study. No personal data were collected and patients gave verbal informed consent to be swabbed.

Results

From the beginning of the 2010/11 season in Spain, influenza A(H1N1)2009 virus has been predominant, with an increasing contribution of influenza B virus after the week 2 of 2011 when the peak of influenza activity was registered [11]. A similar viral circulation pattern and influenza activity evolution has been observed in the eight cycEVA regions. The incidence of ILI peaked in week 2 of 2011 (294 ILI cases per 100,000 population in the participating regions) (Figure 1). The

highest incidence was recorded in children under 15 years, with a maximum weekly incidence of 543 and 533 ILI cases per 100,000 population in the age group 5–14 years and 0–4 years, respectively. During the study period, the proportion of influenza virus-positive samples increased from 40.3% in week 50 of 2010 to 64.3% in the epidemic peak and then decreased to 48.4% in week 06 of 2011 [11].

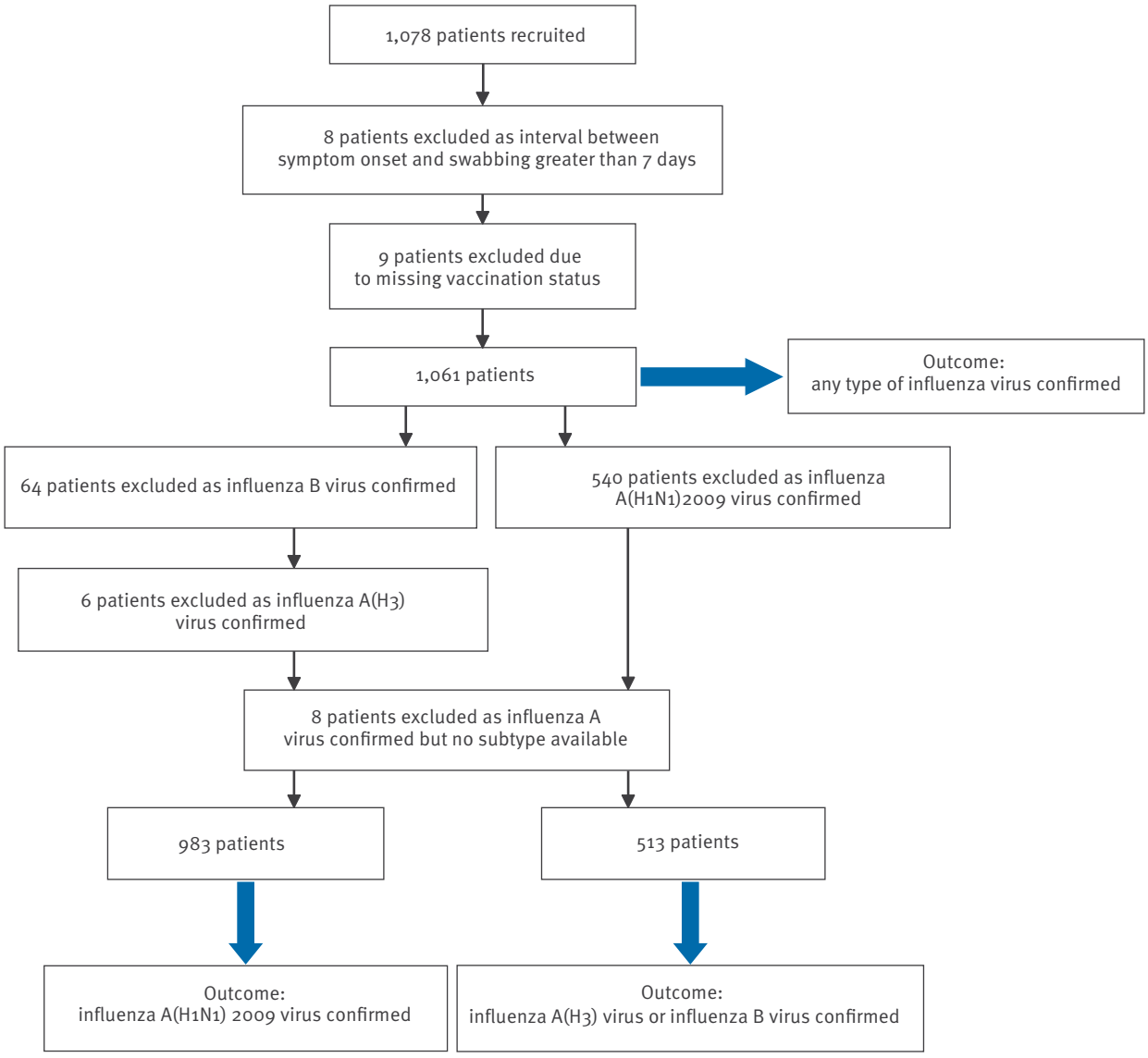
A total of 1,078 patients were recruited. Of these, 1,061 (98%), comprising 618 cases and 443 controls, were included in the analysis where the outcome was laboratory confirmation of any type of influenza virus. For the analysis in which influenza A(H1N1)2009 infection was the outcome, we included 983 patients: 540 were laboratory-confirmed cases. When influenza A(H3) virus or influenza B virus infection was the outcome, 513 patients were included: six were laboratory-confirmed cases of influenza A(H3) infection and 64 were laboratory-confirmed cases of influenza B infection (Figure 2).

The number of patients recruited in the study peaked in week 2 of 2011 and decreased thereafter during the study period, following the weekly ILI incidence in the eight participating regions (Figure 1).

Laboratory-confirmed influenza cases and test-negative controls did not differ regarding the covariates collected, except for age group and eligibility for vaccination (Table 1). Among cases, 53.9% belonged to the age group 15–44 years compared with 47.6% of controls, and 3.6% of cases belonged to the age group ≥65 years compared with 8.6% of controls. A higher proportion of patients were eligible for vaccination among controls (11.5%) than among cases (7.9%).

Figure 2

Flowchart of data exclusion and analysis outcomes, cycEVA study, Spain, week 50 (2010)–week 6 (2011)



Estimates of the effectiveness of the seasonal trivalent influenza vaccine 2010/2011

The crude effectiveness of the vaccine in preventing influenza caused by any type of influenza virus was 65% (95% CI: 41–79%). Adjusting for age group, monovalent pandemic vaccination, previous seasonal vaccination in 2009/10 and week of swabbing, the effectiveness was 50% (95% CI:–6 to 77%). In the group eligible for vaccination (n=91), the adjusted vaccine effectiveness was 66% (95% CI: –1 to 89%).

In the analysis with influenza A(H1N1)2009 virus infection as the outcome, the crude vaccine effectiveness was 66% (95% CI:41–81%) and the adjusted

Table 1

Characteristics of influenza cases with any type of influenza virus (n=618) and test-negative controls (n=443), cycEVA study, Spain, week 50 (2010)–week 6 (2011)

Characteristic	Cases[a] No./total no. (%)[b]	Controls[a] No./total no. (%)[b]	P value[c]
Vaccination status			
Vaccinated with trivalent 2010/11 seasonal vaccine	26/618 (4.2)	49/443 (11.1)	<0.0001
Vaccinated with monovalent 2009/10 pandemic vaccine	12/594 (2.0)	24/398 (6.0)	0.001
Age group (years)			
0–4	44/618 (7.1)	32/443 (7.2)	0.007
5–14	101/618 (16.3)	80/443 (18.1)	
15–44	332/618 (53.9)	211/443 (47.6)	
45–64	118/618 (19.1)	82/443 (18.5)	
≥65	22/618 (3.6)	38/443 (8.6)	
Male	300/618 (48.6)	204/443 (46.0)	0.422
Any chronic condition	67/450 (14.9)	61/330 (18.5)	0.180
Pregnancy	1/255 (0.4)	5/217 (2.3)	0.065
Obesity[d]	4/475 (0.8)	3/349 (0.9)	0.978
Any hospitalisation for chronic conditions in the previous year	4/611 (0.6)	8/431 (1.9)	0.073
Number of visits to a GP in the previous year			
None	164/610 (26.9)	96/432 (22.2)	0.107
1–4	256/610 (42.0)	178/432 (41.2)	
>4	190/610 (31.2)	158/432 (36.6)	
Smoking	47/532 (8.8)	38/366 (10.4)	0.436
Poor functional status	2/571 (0.3)	4/393 (1.0)	0.195
Eligible for vaccination	49/618 (7.9)	51/443 (11.5)	0.049

GP: general practitioner.

[a] Cases and controls recruited with an interval between symptom onset and swabbing of less than eight days.

[b] Unless otherwise indicated.

[c] Chi-square test or Fisher's exact test, when appropriate.

[d] Defined as body mass index greater than 40.

Table 2

Intraseasonal estimates of trivalent 2010/11 seasonal influenza vaccine and monovalent 2009/10 pandemic vaccine in preventing influenza A(H1N1) 2009 infection, Spain, week 50 (2010)–week 6 (2011)

Patients	Vaccination status	Number of cases	Number of controls	Crude vaccine effectiveness, as percentage (95% CI)	Adjusted vaccine effectiveness[a], as percentage (95% CI)
All[b]	Unvaccinated	494	344	Reference	Reference
	Seasonal 2010/11 vaccine only	18	30	58 (24 to 77)	52 (6 to 75)
	Pandemic 2009/10 vaccine only	5	9	61 (–16 to 87)	67 (–5 to 90)
	Seasonal and pandemic vaccines	4	15	82 (44 to 94)	72 (7 to 92)
Eligible for vaccination[c]	Unvaccinated	27	20	Reference	Reference
	Seasonal 2010/11 vaccine only	9	17	61 (–6 to 86)	52 (–53 to 85)
	Pandemic 2009/10 vaccine only	2	0	ND	ND
	Seasonal and pandemic vaccines	3	10	78 (9 to 95)	83 (15 to 97)

CI: confidence interval; ND: not determined.

[a] Adjusted for age group and week of swabbing.

[b] Includes 521 cases and 398 controls.

[c] Includes 41 cases and 47 controls.

effectiveness estimate, taking into account age group, monovalent pandemic vaccination and week of swabbing, was 49% (95% CI: 3–73%). For those eligible for seasonal vaccination (n=88), the adjusted vaccine effectiveness was 63% (95%CI: –15 to 88%).

Crude vaccine effectiveness in preventing influenza A(H3) virus or influenza B virus infection was 51% (95% CI: –40 to 88%), which increased when adjusted for age group, previous seasonal vaccination in 2009/10 and week of swabbing to 84% (95% CI:16–97%). For those eligible for vaccination, the adjusted vaccine effectiveness was 90% (95% CI: –80 to 100%).

In the analysis with the four-level vaccination variable in preventing influenza A(H1N1)2009 infection, in patients who received 2010/11 seasonal trivalent vaccine only, the vaccine effectiveness, adjusted for age group and week of swabbing, was 52% (95% CI: 6–75%) (Table 2). For patients receiving both seasonal trivalent and monovalent pandemic vaccines, the adjusted vaccine effectiveness was 72% (95% CI: 7–92%). In the analysis including patients eligible for vaccination, the adjusted effectiveness when vaccinated with both vaccines was (83%; 95% CI: 15–97%). Point estimates for patients vaccinated only with the pandemic vaccine were higher than for the patients vaccinated only with the 2010/11 seasonal vaccine, but the difference was not statistically significant (Table 2).

Laboratory findings

A total of 56 specimens were sent for genetic characterisation of the virus. In 40 specimens, there was sufficient PCR-amplified product for sequencing of the viral haemagglutinin gene: 33 were influenza A(H1N1)2009, one was influenza A(H3) and six were influenza B viruses. Phylogenetic analysis of the 33 A(H1N1)2009 sequences showed a genetic similarity to the influenza virus of the pandemic vaccine since neither specific mutations 94N, 125D and 250A defining the A/Christchurch/16/2010 clade, nor 128P, 199A and 295V defining the A/Hong Kong/2213/2010 clade were found. Nevertheless, three of the 33 sequenced viruses showed other amino acid changes compared with the vaccine strain. The six influenza B viruses were similar to the vaccine strain. Specific mutations 53N, 94H, 230V and 280A, defining the clade A/Hong Kong 2121/2010 were identified for the patient with influenza A(H3) virus.

Discussion

Our results suggest a protective effect of the seasonal trivalent vaccine in preventing influenza due to infection of any type of influenza virus, including influenza A(H1N1)2009 virus and influenza A(H3) or influenza B viruses. Similar results were obtained when we restricted the analysis to those eligible for vaccination. These are preliminary results and should be interpreted with caution, taking into consideration the sample size.

However, the effectiveness of the trivalent seasonal vaccine in preventing influenza A(H1N1)2009 infection in both analyses (49% and 52%) is lower than that reported for the monovalent pandemic vaccine in the 2009/10 season in the same study population, which reached 75% (unpublished data). Several factors might have contributed to this finding. Firstly, the monovalent pandemic vaccine used in the 2009/10 season was adjuvanted (with the exception of that used for pregnant women), while the current seasonal trivalent vaccine used in all participating regions is non-adjuvanted. Secondly, the monovalent pandemic vaccine was not recommended for elderly people aged over 64 years without underlying diseases, resulting in a vaccinated population that was younger and more immunocompetent. Last, but not least, the lower effectiveness of the seasonal vaccine might suggest that there may have been some genetic changes in the influenza A(H1N1)2009 virus. Most influenza A(H1) viruses circulating in Spain remained closely related genetically to the vaccine virus; however, there have been observed some amino acid changes in the haemagglutinin gene of a small proportion of studied strains that could be reasonably be attributable to genetic drift, since these mutations are different from those defining new clades observed in September 2010 [12]. Notably, the only influenza A(H3) virus characterised in our study falls within a subgroup represented by the influenza A/Hong Kong/2121/2010 virus.

We also observed a higher protective effect in preventing infection due to influenza A(H1N1)2009 virus in patients who had received both seasonal trivalent and monovalent pandemic vaccines, consistent with other early reports [10,13].This might suggest a type of cumulative protection, which should be confirmed by immunological studies, and highlights the need for routine annual influenza vaccination for people in the recommended groups.

In the same analysis, we also found that the monovalent pandemic vaccine had a higher point estimate than that for the seasonal vaccine, but this difference was not statistically significant due to the low number who were vaccinated. These findings might be related again to the type of the vaccine used (adjuvanted versus non-adjuvanted) or to the population targeted for vaccination.

Interestingly, we found a good protective effect of the seasonal trivalent vaccine against influenza A(H3) and influenza B viruses, although this effect was higher than that reported in another study [10]. This is consistent with the good match between the vaccine and circulating influenza B strain. The difference in the estimates could be related to different confounding factors that the effectiveness calculations were adjusted for.

This is the third season in which we have used the test-negative case–control design in the cycEVA study. The experience of the two previous seasons [1,5] was

reflected in increased participation of GPs and paediatricians, compliance with the protocol and completeness of data collection (less than 10% data were missing for important variables). The introduction of systematic swabbing for ILI patients might have reduced the selection bias toward vaccinated patients, which is known to occur in surveillance-based studies [14].

In conclusion, the cycEVA study was able to provide an early intraseasonal estimate of the effectiveness of the seasonal vaccine nine weeks since the epidemic started. It suggests a protective effect of the vaccine against all types of influenza viruses. This effect was also seen in the group eligible for vaccination; however, the effect was lower than that reported in the previous season [1]. It also demonstrates that intraseasonal vaccine effectiveness estimates are possible by conducting observational studies, with an acceptable additional effort, within the framework of a well-organized influenza surveillance system meeting the criteria of the European Influenza Surveillance Network.

The cycEVA study is ongoing in Spain and ILI cases are still being recruited while sporadic circulation of influenza viruses is registered in the participating regions. Therefore we expect that at the end of the season the sample size will allow more precise estimates of vaccine effectiveness and will enable us to control for other confounding factors known to influence vaccine effectiveness. In addition, the I-MOVE multicentre study, pooling data from eight European countries including Spain, will be able to present even more precise estimates.

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Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case–control study

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We present early estimates (up to week 4 of 2011) of the 2010/11 seasonal influenza vaccine effectiveness in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza. Practitioners from seven European sentinel networks systematically swabbed ILI patients. We included patients meeting the European Union ILI case definition and swabbed less than eight days after symptom onset. Laboratory-confirmed influenza cases were compared with negative controls. The adjusted vaccine effectiveness was 42.3% (95% CI: –7.3 to 69.0%), suggesting moderate protection of the seasonal vaccine.

Background

The Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network was established in 2007 by the European Centre for Disease Prevention and Control (ECDC) to monitor seasonal and pandemic influenza vaccine effectiveness [1-3]. In the 2010/11 season, to estimate the effectiveness of the seasonal vaccine in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza we undertook a multicentre case–control study based on sentinel practitioner surveillance networks from eight study sites (France, Hungary, Ireland, Italy, Romania, Poland, Portugal and Spain). We report the preliminary results from seven study sites (data from France are not included in this preliminary analysis as data collection is ongoing).

Data collection and analysis

We used similar methods to those used in the first two seasons of I-MOVE [1,3]. The studies were conducted within the context of the existing European Influenza Surveillance Network (EISN) [4].

The study population consisted of patients consulting a participating practitioner for ILI within eight days after symptom onset. Practitioners systematically selected ILI patients to swab.

A case of confirmed influenza was an ILI patient (defined according to the European Union case definition [5]) who was swabbed and tested positive for influenza using real-time polymerase chain reaction (PCR) or culture. Controls were ILI patients who were swabbed and tested negative for any influenza virus.

Individuals were considered vaccinated if they had received a dose of the seasonal vaccine more than 14 days before the date of onset of ILI symptoms. Participating sentinel practitioners interviewed ILI patients to collect information on ILI signs and symptoms, date of onset of symptoms, current vaccination status (including date of vaccination), prior seasonal and pandemic influenza vaccination status and a list of potential confounding factors: age, sex, presence of chronic condition(s), severity of chronic disease(s) using the number of hospitalisations for the chronic disease(s) in the previous 12 months as a proxy, smoking history (non-smoker, past, current smoker), number of practitioner visits in the previous 12 months. We included in the study patients recruited up to the end of week 4 of 2011, meeting the European ILI case definition with onset of symptoms more than 14 days after the start of national 2010/11 influenza vaccination campaigns. In each study, we excluded controls with symptom onset in the weeks before the week of symptom onset of the first confirmed influenza case of the season and individuals with missing information on laboratory results. In addition, for effectiveness of the vaccine in preventing influenza A(H1N1)2009 virus infection, we excluded any individual positive for other influenza virus types and excluded controls with symptom onset in the weeks before the week of symptom onset of the first case of influenza A(H1N1)2009 virus infection recruited in the 2010/11 season.

We estimated the pooled seasonal influenza vaccine effectiveness as one minus the odds ratio (OR) (expressed as a percentage) using a one-stage method with the study site as fixed effect in the model. To estimate adjusted vaccine effectiveness, we used logistic regression models including all potential confounding factors.

We first conducted the analysis excluding all individuals with at least one missing value (complete case analysis). We then estimated missing data for vaccination status and covariates using the multiple multivariate imputation by chained equations procedure in Stata [6]. We used missing at random assumptions. We used all predictors together to impute the missing values and independently analysed 20 copies of the data using 30 cycles of regression.

Estimates of seasonal influenza vaccine effectiveness

A total of 585 practitioners agreed to participate in the study; 352 of them (60%) recruited at least one ILI patient (Table 1). After excluding 71 individuals with missing information on laboratory results, a total of 1,671 ILI patients were included in the analysis: 846 cases and 825 controls (Figure 1). Among the cases, 649 (76.7%) were positive for influenza A(H1N1)2009 virus, nine (1.1%) for influenza A(H3N2) virus, 15 (1.8%) were positive for influenza A virus that could not be subtyped and 173 (20.5%) were positive for influenza B virus.

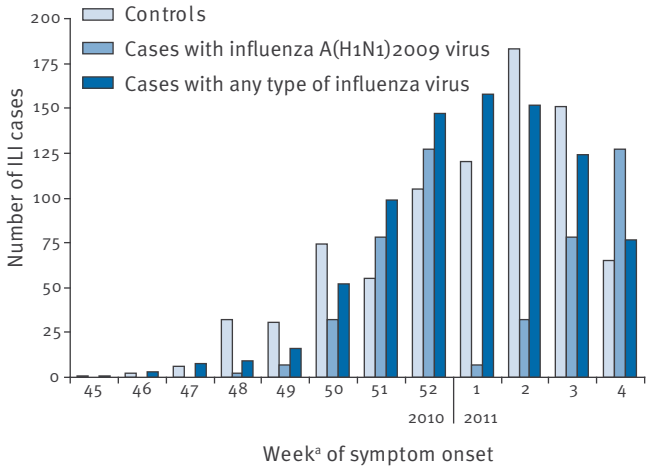
Among 1,658 individuals with information on vaccination status and vaccination date for seasonal vaccination in 2010/11, 116 (7.0%) were vaccinated (ranging from 2.2% in Poland and Ireland to 19.9% in Italy).

The median age was lower in cases (29 years, standard deviation (SD): 18 years) than in controls (34 years, SD: 21 years) (Table 2). The delay between onset of symptoms and swabbing was slightly shorter in cases (mean: 1.8 days, range: 0–7 days) than in controls (mean: 1.9 days, range: 0–7 days).The proportion of individuals presenting with fever, malaise, headache, myalgia or cough was higher among cases than among controls (Table 2). Compared with cases, a higher proportion of controls had diabetes, heart disease or were hospitalised at least once for their chronic disease in the previous 12 months. A higher proportion of controls were current or past smokers, vaccinated with the 2009/10 seasonal influenza vaccine, and vaccinated with the 2009/10 pandemic influenza vaccine. The median number of practitioner visits in the previous 12 months was two for cases (ranging from 0 to 26) and three for controls (ranging from 0 to 60) (Table 2).

A total of 34 cases were vaccinated with the 2010/11 seasonal vaccine. In two of the seven studies there

Figure

Influenza A(H1N1)2009 cases (n=649), all influenza cases (n=846) and influenza-negative controls (n=825) recruited by week of symptom onset, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)



ILI: influenza-like illness.

[a] International Organization for Standardization (ISO) definition of a week.

Table 1

Practitioners' participation, influenza-like illness (ILI) patients recruited by case–control status, vaccination status and study site, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Study site	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI patient[a]	Number of ILI patients[a] recruited by practitioners	Inclusion period for the study	Number of ILI patients included in the study positive for any influenza virus[c]		Number of ILI patients included in the study negative for any influenza virus[c]	
				ISO week number (year)[b]	Total	Vaccinated	Total	Vaccinated
Hungary	98	64	242	50 (2010)–4 (2011)	47	1	195	11
Ireland	22	17	160	48 (2010)–4 (2011)	84	0	54	3
Italy	38	31	220	48 (2010)–4 (2011)	40	7	126	26
Poland	34	16	46	48 (2010)–4 (2011)	24	0	21	1
Portugal	58	30	186	45 (2010)–4 (2011)	117	5	69	11
Romania	89	40	69	52 (2010)–4 (2011)	32	2	37	5
Spain	246	154	819	49 (2010)–4 (2011)	498	19	314	25
Total	**585**	**352**	**1,742**	–	**842**	**34**	**816**	**82**

ISO : International Organization for Standardization.

[a] ILI patients meeting the European Union case definition, swabbed less than eight days after onset of symptoms within the study period.

[b] From 15 days after the start of the seasonal influenza vaccination campaign to the week of symptom onset of the last case recruited. Controls with an onset of symptoms in the weeks before the first case were excluded.

[c] ILI patients in the study after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

were no vaccinated individuals among the recruited cases.

In the pooled complete case analysis the adjusted vaccine effectiveness was 35.1% (95% CI: −23.0 to 65.8) in preventing influenza caused by all types of influenza viruses and 34.9% (95% CI: −37.5 to 69.2%) in preventing influenza A(H1N1)2009 virus infection (Table 3).

In the pooled analysis with imputed data, the adjusted vaccine effectiveness against all influenza strains was 42.3% (95% CI: −7.3 to 69.0%), and 44.1% (95% CI: −14.3 to 72.7%) against influenza A(H1N1)2009 virus (Table 3).

Discussion

Our early pooled estimates suggest that the 2010/11 seasonal vaccine conferred moderate protection against medically attended laboratory-confirmed influenza. These results should be interpreted with caution, however, for reasons including low vaccine coverage and potential biases due to the test-negative design, confounding factors, missing values and small sample size due to the early estimation in the season. Those biases have been described elsewhere in detail [3,7].

Our estimates of the 2010/11 seasonal vaccine effectiveness apply to the study period (until the end of week 4 of 2011). They are based on data from seven European study sites sharing the same protocol and definition of variables. The pooled point estimates of vaccine effectiveness were between 35% (adjusted) and 61% (crude).

Table 2

Characteristics of influenza cases (n=846) and test-negative controls (n=825) included, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Characteristic	Influenza cases No./total no. (%)[a]	Test-negative controls No./total no. (%)[a]	P value
Median age	29 years	34 years	< 0.001[b]
Age group (years)			
0–4	49/845 (5.8)	57/825 (6.9)	< 0.001[c]
5–14	146/845 (17.3)	88/825 (10.7)	
15–64	621/845 (73.5)	591/825 (71.6)	
≥65	29/845 (3.4)	89/825 (10.8)	
Female	443/844 (52.5)	433/825 (52.5)	1.000[c]
Symptoms			
Fever	818/845 (96.8)	763/819 (93.2)	0.001[c]
Malaise	791/846 (93.5)	745/822 (90.6)	0.037[c]
Headache	653/830 (78.7)	596/809 (73.7)	0.020[c]
Myalgia	683/827 (82.6)	626/806 (77.7)	0.013[c]
Cough	797/846 (94.2)	686/818 (83.9)	<0.001[c]
Number of days between symptom onset and swabbing			
0	49/846 (5.8)	39/825 (4.7)	0.327[c]
1	376/846 (44.4)	352/825 (42.7)	
2	247/846 (29.2)	242/825 (29.3)	
3	108/846 (12.8)	105/825 (12.7)	
≥4	66/846 (7.8)	87/825 (10.5)	
Seasonal vaccination, 2010/11	34/842 (4.0)	82/816 (10.0)	<0.001[c]
Pandemic vaccination, 2009/10	53/826 (6.4)	88/784 (11.2)	0.001[c]
Seasonal vaccination, 2009/10	58/825 (7.0)	109/780 (14.0)	<0.001[c]
Diabetes	15/741 (2.0)	38/774 (4.9)	0.003[c]
Heart disease	24/ 740 (3.2)	84/774 (10.9)	<0.001[c]
Smoker status			
Current	88/822(10.7)	123/786 (15.6)	<0.001[c]
Former	52/822 (6.3)	79/786 (10.1)	
Never	682/822 (83.0)	584/786 (74.3)	
Median number of GP visits in the previous 12 months	2	3	0.005[b]
Any hospitalisation in the previous 12 months for chronic diseases	1/846 (1.1)	23/823 (2.6)	0.026[c]

GP: general practitioner.

[a] Unless otherwise indicated.

[b] Non-parametric test of the median.

[c] Two-sided Fisher's exact test.

We adjusted for most of the confounding factors described in the literature (see, for example, [7]). The adjusted vaccine effectiveness was lower than the crude vaccine effectiveness (absolute differences ranging from 16.2% to 24.7%), suggesting some positive confounding. The main confounders identified were seasonal influenza vaccination in the previous season and age group.

This is the third season the I-MOVE programme has estimated influenza vaccine effectiveness using laboratory-confirmed outcomes. Compared with the I-MOVE estimates of last season, the 2010/11 seasonal vaccine seems to have a lower effectiveness against influenza A(H1N1)2009 virus infection than the monovalent pandemic vaccine of 2009/10 [3]. This may be explained by antigenic drift, by a different distribution of adjuvanted versus non-adjuvanted vaccines in some study sites [8] or by a different study population. The ILI cases included in the 2009/10 I-MOVE multicentre case–control study were younger (mean age: 12 years for cases and 24 for controls) than those included in this 2010/11 early analysis.

The pooled early estimates are similar to those observed in the United Kingdom [9], the Navarre region in Spain [8] and the cycEVA study in Spain [10]. Later in the season, the larger sample size per country will allow us to conduct precise pooled and stratified analyses and to further explore the difference in effectiveness of the seasonal vaccine with that of the 2009/10 pandemic vaccine. In addition, the use of validation subsets in France, in which we collect more accurate and additional information in a subsample of the ILI patients, will enable to base our estimates on data from eight countries.

I-MOVE is a unique network in Europe able to measure seasonal and pandemic vaccine effectiveness. The early estimates presented here suggest that the seasonal vaccine has a lower effectiveness than that observed with the monovalent pandemic vaccine [3].

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Table 3

Pooled crude and adjusted 2010/11 seasonal vaccine effectiveness, by type of outcome and type of analysis, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Outcome	Crude vs adjusted	Complete vs imputed data analysis	Number of ILI cases included	Vaccine effectiveness	
				%	95% CI
Infection with any influenza virus	Crude[a]	Complete case analysis[b]	1,390	56.9	32.2 to 72.6
		Imputed data[c]	1,671	58.5	35.7 to 73.2
	Adjusted model[d]	Complete case analysis[b]	1,390	35.1	−23.0 to 65.8
		Imputed data[c]	1,671	42.3	−7.3 to 69.0
Infection with influenza A(H1N1)2009 virus	Crude[a]	Complete case analysis[b]	1,158	59.6	32.6 to 75.8
		Imputed data[c]	1,407	60.5	35.3 to 75.8
	Adjusted model[d]	Complete case analysis[b]	1,158	34.9	−37.5 to 69.2
		Imputed data[c]	1,407	44.1	−14.3 to 72.7

ILI: influenza-like illness.

[a] Study site included in the model as fixed effect.

[b] Excluding individuals with missing values.

[c] Missing data imputed using imputation by chained equations.

[d] Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, visits to a general practitioner in previous 12 months (0–1, 2–4 and ≥5 visits) and week of symptom onset.

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Emergence of four cases of KPC-2 and KPC-3-carrying *Klebsiella pneumoniae* introduced to Switzerland, 2009–10

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We report four epidemiologically unrelated cases of KPC-carrying *Klebsiella pneumoniae* identified in Switzerland between May 2009 and November 2010. Three cases were transferred from Italy (two KPC-3, one KPC-2) and one from Greece (KPC-2). Resistance to colistin and doxycycline emerged in one KPC-3–carrying *K. pneumoniae* strain during therapy. These results demonstrate ongoing dissemination of KPC throughout Europe. Rapid and reliable identification of KPC and implementation of control measures is essential to limit spread.

Introduction

Carbapenems are first-line drugs for severe infections caused by *Enterobacteriaceae* expressing extended-spectrum beta-lactamases (ESBLs). The emergence of carbapenemase-producing *Enterobacteriaceae* in the past years is of great concern [1]. After the characterisation of the first *Klebsiella pneumoniae* isolate producing carbapenemase of the KPC type in 1996 in the United States [2], the KPC-producing bacteria spread worldwide. Poirel et al. reported the first KPC-2 *K. pneumoniae* isolate in Switzerland imported from Sicily (Italy) in 2010 [3]. Here, we report four additional imported cases of KPC-carrying *K. pneumoniae* detected in Switzerland.

Materials and methods

The four KPC-suspected strains were collected from different Swiss hospitals and were sent to our laboratory in Basel for confirmation. We performed conventional susceptibility testing using an automated micro-dilution test system (Micronaut-S, MERLIN Diagnostika mbH).Determination of minimum inhibitory concentrations (MIC) was performed with Etest stripes (bioMérieux). Results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [4], except for doxycycline which was interpreted according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) [5].

For phenotypic identification of KPC-producing isolates, both double disc synergy test and modified Hodge test were applied [1] . KPC-specific PCR and direct sequencing of the region encompassing the main part of the bla_{KPC} gene (ca. 820 nucleotides, sequenced in both directions) was performed according to Bradford et al. [6]. The KPC type was identified by the BLAST programme from the National Center for Biotechnology Information Web site (http://www.ncbi.nlm.nih.gov/BLAST).

Clinical data were available for two patients and were collected by full chart review.

Results

Four cases of KPC-carrying *K. pneumoniae* were detected in Switzerland between May 2009 and November 2010, two of type KPC-2 and two of type KPC-3. All patients were between 50 and 70 years-old and had been transferred from abroad, three from Italy and one from Greece. Two patients were colonised and two were infected with KPC-producing *K. pneumoniae* (Table 1).

The antimicrobial susceptibility profiles of the four *K. pneumoniae* isolates are listed in Table 2. Double disc synergy test as well as the modified Hodge test showed positive results for KPC-production in all four cases.

Case 1

The patient in their 50s lived in Greece and travelled to Switzerland in September 2009. The person was colonised in the urine, inguinal and perineum with

K. pneumoniae bla_{KPC-2}. No further clinical data were available for this patient.

Case 2

The patient was in their 60s and hospitalised in Italy due to upper gastro-intestinal problems, and underwent diagnostic endoscopy. The clinical history did not mention any antibiotic treatment. In May 2010 the patient was transferred to Switzerland. On hospital admission a constricted bile duct was stented endoscopically. Because the patient developed fever during the initial empiric antibiotic therapy with piperacillin/tazobactam, the therapy was changed to meropenem. During treatment with meropenem the patient developed bloodstream infection with *K. pneumoniae*. The isolate was resistant or intermediately resistant to all

Table 1

Main characteristics of four cases of KPC-producing *K. pneumoniae* detected in Switzerland, May 2009 and November 2010

	Case 1	Case 2	Case 3	Case 4
Age group (years)	50-59	60-69	40-49	60-69
Date of KPC detection	September 2009	July 2010	September 2010	November 2010
Infected/colonised with *K. pneumoniae*	Colonised	Infected	Infected	Colonised
Transferred from	Greece	Italy[a]	Italy[a]	Italy[a]
Hospitalised in Switzerland	Eastern part	North-western part	Western part	North-eastern part
bla_{KPC} gene	bla_{KPC-2}	bla_{KPC-3}	bla_{KPC-2}	bla_{KPC-3}

KPC: *Klebsiella pneumoniae* carbapenemase.

[a] The three patients were transferred from three different regions in Italy: Apulia, Liguria and Sicily

Table 2

Antimicrobial susceptibility profiles of the four *Klebsiella pneumoniae* first isolates carrying bla_{KPC-2} or bla_{KPC-3}, Switzerland, May 2009 and November 2010

Antibiotic	Case 1 bla_{KPC-2}	Case 2 bla_{KPC-3}	Case 3 bla_{KPC-2}	Case 4 bla_{KPC-3}
Ampicillin	R	R	R	R
Amoxicillin/clavulanate	R	R	R	R
Piperacillin/tazobactam	R	R	R	R
Cefuroxime	R	R	R	R
Ceftazidime	R	R	R	R
Ceftriaxone	R	R	R	R
Cefepime	R	R	R	R
Aztreonam	R	R	R	R
Imipenem	R (>32)	R (>32)	R (16)	R (>32)
Meropenem	R (>32)	R (>32)	R (12)	R (>32)
Ertapenem	R (>32)	R (>32)	R (16)	R (>32)
Trimethoprim/sulfamethoxazole	R	R	R	R
Nitrofurantoin	R	R	ND	R
Norfloxacin	R	R	ND	R
Ciprofloxacin	R (>32)	R (>32)	R (>32)	R (>32)
Levofloxacin	R	R	ND	R
Gentamicin	S (1)	S (2)	S (2)	I (4)
Tobramycin	ND	I	R	ND
Amikacin	S	S	R	ND
Netilmicin	R	R	R	ND
Colistin	R (4)	S (0.25)[a] R (16)[b]	S (0.25)	S (0.5)
Doxycycline	S (4)	S (4)[a] R (16)[b]	I (8)	I (8)
Tigecycline	S (1)	I (2)	S (1)	I (2)
Fosfomycin	S (32)	R (128)	S (32)	R (128)

I: intermediate; ND: no data; R: resistant; S: susceptible.
Minimum inhibitory concentration in mg/L is given in parentheses.

[a] Before antimicrobial treatment.

[b] After antimicrobial treatment.

antibiotics tested (see Table 2) except gentamicin, colistin, and doxycycline. KPC-specific PCR was performed detecting bla_{KPC-3}. The antibiotic therapy was adapted to intravenous colistin and gentamicin. Repeated stenosis of the intra-ductal stent and suspicion of cholangiocarcinoma provided evidence for a Whipple operation with pancreaticogastrostomy. After the operation the patient developed acute arterial bleeding and had to be surgically revised. Shortly after the second operation he had relapsing bloodstream infection with *K. pneumoniae* which were newly resistant to colistin. Colistin treatment was stopped and doxycycline and later fosfomycin were added to gentamicin. Fosfomycin was given because routine testing revealed an intermediate result. The patient died from multiorgan failure caused by an uncontrolled infection complicated by intra-abdominal bleeding. A bronchoalveolar lavage specimen taken one day before death was positive for *K. pneumoniae*, now also resistant to doxycycline.

Case 3

The patient in their 40s was injured in July 2009 in Italy. The person was treated initially with an external fixation for a pelvic fracture in a primary care hospital in Italy and referred to the University Hospital of Berne for secondary care. The surgeon noted a pin track infection and performed a wound excision. Perioperatively, as well as at discharge, no signs of infection were present. In September 2010 the patient was readmitted because of a pelvic abscess, which was drained and osteosynthesis material was removed. Empiric therapy included amoxicillin/clavulanate, but cultures of the abscess revealed a *K. pneumoniae* isolate resistant to all antibiotics tested except gentamicin, colistin, tigecycline and fosfomycin (Table 2).

Antibiotic treatment was switched to tigecycline and gentamicin, followed by a second and third surgical debridement. After two weeks gentamicin was discontinued because of ototoxicity and therapy with tigecycline for a chronic osteomyelitis was continued for three months. To the best of our knowledge the patient was cured with this antibiotic course.

Case 4

The patient was in their 60s and hospitalised in an intensive care unit in Italy for one month because of a cerebral vascular insult, before being transferred to Switzerland. This patient was colonised in the upper respiratory tract and on the subclavian catheter with *K. pneumoniae* that contained the bla_{KPC-3} gene.

Infection control measures

Cases 2 and 3 were isolated immediately after detection of KPC-producing *K. pneumoniae* by contact isolation [5,6], which involved stay in a single-patient room, use of gloves and gowns by medical personnel during physical contact, and use of masks by medical personnel when exposure to respiratory secretions was expected. Secondary spread was investigated by active surveillance. This included screening of all patients sharing the same room as the index patient for ESBL or KPC by testing stool samples and, if applicable, samples from wounds, drainages, etc. None of these patients was found to be positive for KPC-carrying *Enterobacteriaceae*. Patients who stayed in the same room as the index patient and who were already discharged from hospital were tagged in the hospital administration system to be screened at the next admission. Infection control measures taken around Cases 1 and 4 could not be made available during this study.

Discussion and conclusions

The global dissemination of KPC-producing *K. pneumoniae* is of great concern to public health services worldwide [9]. The first outbreak outside the United States was documented in Israel in 2004 [10]. Several reports of outbreaks and sporadic cases of KPC-producing *K. pneumoniae* in Italy and Greece have been described and indicated rapid spread within these two countries [11-15]. On the epidemiological scale for spread of KPC-carrying *K. pneumoniae* defined by Grundmann et al. [1] Greece was determined in November 2010 as 'endemic' and Italy as a country with 'interregional spread'. The first case of a KPC-2-producing *K. pneumoniae* in Switzerland was described in 2010 from a patient transferred from Sicily [3].

We document four further cases of KPC-carrying *K. pneumoniae* introduced to Switzerland, three from Italy and one from Greece. Three patients have been discharged from hospital in a stable state of health, one patient died from uncontrolled infection complicated by arterial intraabdominal bleeding. In one case the KPC-3 carrying *K. pneumoniae* strain developed resistance to colistin and doxycycline despite combined antibiotic treatment.

Phenotypic and molecular tests for KPC detection were concordant and confirmed carbapenemase production in all strains by conventional susceptibility testing. As shown in Table 2, the antibiotic susceptibility patterns of the four independent isolates were similar.

In this study, we confirm continuous dissemination of KPC-producing isolates from Greece and Italy to Switzerland. The fact that the three patients transferred from Italy had been hospitalised in three different geographic regions in Italy, Apulia, Liguria and Sicily, is a further indication for a wider dissemination of these isolates. We found no evidence for local spread within the Swiss hospitals where the four reported cases were treated, but sporadic cases are thought to precede endemicity, a likely scenario for resistance markers encoded on plasmids [9]. The worldwide spread of KPC-carrying *K. pneumoniae* is worrying, since this species is a main source for hospital-acquired infections in critically ill patients and well known for its ability to transfer resistance determinants. Due to the high mobility of KPC genes we anticipate that KPC-mediated resistance will be a prominent mechanism of multidrug

resistance in Gram-negative bacilli in the near future. As antimicrobial treatment options are dramatically restricted, rapid and reliable identification of KPC is mandatory to generate concepts to limit spread.

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Escherichia coli and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009

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Based on data collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the former EARSS, the present study describes the trends in antimicrobial susceptibility patterns and occurrence of invasive infections caused by *Escherichia coli* and *Staphylococcus aureus* in the period from 2002 to 2009. Antimicrobial susceptibility results from 198 laboratories in 22 European countries reporting continuously on these two microorganisms during the entire study period were included in the analysis. The number of bloodstream infections caused by *E. coli* increased remarkably by 71% during the study period, while bloodstream infections caused by *S. aureus* increased by 34%. At the same time, an alarming increase of antimicrobial resistance in *E. coli* was observed, whereas for *S. aureus* the proportion of meticillin resistant isolates decreased. The observed trend suggests an increasing burden of disease caused by *E. coli*. The reduction in the proportion of meticillin-resistant *S. aureus* and the lesser increase in *S. aureus* infections, compared with *E. coli*, may reflect the success of infection control measures at hospital level in several European countries.

Introduction

Escherichia coli and *Staphylococcus aureus* are the main causes of bloodstream infections (BSIs) in humans. The antimicrobial resistance of *E. coli* causing BSI is increasing alarmingly across Europe, while meticillin-resistant *S. aureus* (MRSA) is decreasing in several countries [1]. The antimicrobial susceptibility of these microorganisms and other selected bacterial pathogens causing invasive infections has been monitored for a decade by the European Antimicrobial Resistance Surveillance System (EARSS) [1]. Coordination and administration of the EARSS project, previously conducted by the Dutch National Institute of Public Health and the Environment (RIVM), was transferred to the European Centre for Disease Prevention and Control (ECDC) on 1 January 2010, and the network was renamed European Antimicrobial Resistance Surveillance Network (EARS-Net). The first data collection by EARS-Net (antimicrobial susceptibility data referring to 2009) took place during June and July 2010.

Whereas detailed analysis and trends at the national level are available in the EARSS and EARS-Net reports [1,2], the present study describes the trends in susceptibility patterns and number of invasive infections caused by *E. coli* and *S. aureus* in Europe from 2002 to 2009, based on data from laboratories reporting continuously during this period.

Methods

Data for *E. coli* and *S. aureus* BSIs were extracted from the EARSS/EARS-Net database for a convenience sample of laboratories reporting susceptibility results continuously during the period from 2002 to 2009 for aminopenicillin, fluoroquinolones, third generation cephalosporins and aminoglycosides in *E. coli* and for oxacillin in *S. aureus* [3]. Countries in which no laboratory participated for the entire period or that had only a small data set (less than 20 isolates per microorganism per year) were not included in the analysis. Only

the first isolate per patient, microorganism and year was included as a representative sample. Sampling and processing of isolates was done in agreement with the EARSS manual 2005 [3]. Resistance (R category of S, I, R) was defined by the guidelines in use in the reporting countries.

The number of BSIs caused by *E. coli* and *S. aureus* and the proportions of third-generation cephalosporin-resistant *E. coli* and of MRSA were recorded for each year from 2002 to 2009. To assess the patterns of combined resistance of *E. coli*, the following antimicrobial classes were analysed: aminopenicillins (ampicillin and amoxicillin), aminoglycosides (gentamicin, tobramycin and amikacin), third-generation cephalosporins (ceftriaxone, cefotaxime and ceftazidime) and fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin). Resistance to a class was defined as resistance (R category) to at least one agent in the class. The significance of the temporal linear trends for resistance proportions was evaluated by the Cochran–Armitage test for trend.

Results

A total of 198 laboratories in 22 countries continuously reported data from 2002 to 2009. The number of laboratories per country ranged between one (Iceland and Malta) and 33 (Czech Republic), while the mean number of *E. coli* and *S. aureus* isolates reported yearly per country ranged from 96 to 1,973 and from 56 to 1,290, respectively (Table).

Considering the whole group of selected laboratories, the reported number of *E. coli* BSIs increased by 71% from 10,688 in 2002 to 18,240 in 2009 (Figure 1); most of the rise (38% of 71%) in *E. coli* BSIs was due to isolates resistant to two or more antimicrobials. During the same period, *S. aureus* BSIs showed a 34% increase from 7,855 to 10,503 (Figure 1). In the period from 2002 to 2009, if only *E.coli* susceptible to aminopenicillins, third-generation cephalosporins, fluoroquinolones and aminoglycosides are considered, the number of BSIs increased by 39%. Similarly, the BSIs caused by meticillin-susceptible *S. aureus* showed an increase of 37%.

In the period from 2002 to 2009, the proportion among all *E. coli* of *E. coli* resistant to third-generation cephalosporins increased significantly from 1.7% to 8% ($p<0.001$) and the proportion of MRSA decreased from 21.5% to 19.7% ($p<0.001$) (Figure 2). Similar trends of resistance proportions as observed for aggregated data of all 198 laboratories were also observed at country level in 18 of 22 countries for *E. coli*, and in seven of 22 countries for *S. aureus*.

Table

Mean annual number of *Escherichia coli* and *Staphylococcus aureus* isolates per country reported by laboratories (n=198) reporting continuously to EARSS/EARS-Net, 2002–09

Country	Number of laboratories	Number of *Escherichia coli* isolates	Number of *Staphylococcus aureus* isolates
		Mean per year (2002–09)	Mean per year (2002–09)
Austria	10	802	630
Belgium	9	646	343
Bulgaria	7	96	82
Czech Republic	33	1,837	1,290
Estonia	5	142	125
Finland	5	849	381
France	12	1,583	1,018
Germany	2	156	121
Greece	22	829	472
Hungary	14	446	526
Iceland	1	97	56
Ireland	15	1,086	961
Italy	3	237	166
Luxembourg	4	176	80
Malta	1	104	96
Netherlands	4	291	238
Norway	7	975	467
Portugal	8	559	574
Slovenia	9	572	321
Spain	19	1,973	835
Sweden	3	578	331
United Kingdom	5	641	373

EARSS: European Antimicrobial Resistance Surveillance System; EARS-Net: European Antimicrobial Resistance Surveillance Network.

Combined resistance in *E. coli* (defined as resistance to two, three or four antimicrobial classes reported to EARS-Net) showed a significant increase (p<0.001) (Figure 3) whereas single resistance diminished from 37.1% in 2002 to 35.8% in 2009 (p<0.001). The proportion of *E. coli* isolates susceptible to all four antimicrobial classes decreased from 51.4% in 2002 to 41.7% in 2009 (p<0.001).

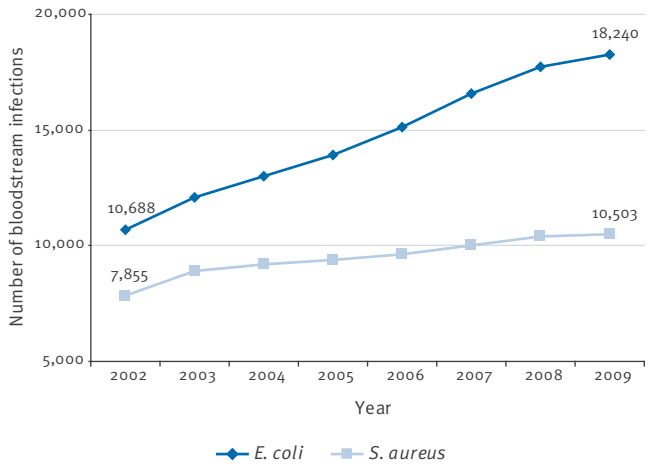
Discussion

The increase in antimicrobial resistance in *E. coli* between 2002 and 2009 was evident both in the observed increase of combined resistance and in the reduction of full susceptibility to the antimicrobials included in the analysis. In the same time period and considering the same data source, a significant decrease of meticillin resistance was observed for *S. aureus*. For this species, the number of BSIs increased less (+34%) than for *E. coli* BSI (+71%). Consistently, increasing resistance in *E. coli* and combined resistance of invasive and non-invasive isolates was reported by several European countries [4-8]. At the same time, the proportion of MRSA showed a significant decrease in many European countries [1,2]. The numbers of BSIs caused by MRSA, as reported by the mandatory surveillance system in England, decreased by 56% between 2004 and 2008 [9], and in France a significant decrease in the occurrence of MRSA was reported in 2008 [10]. A similar reduction in the rate of healthcare-associated invasive MRSA infections was observed in the general population in the United States [11].

The sampling approach selected for this study is likely to eliminate a large part of the possible temporal variation in the size of the catchment population behind the numbers. Based on the available surveillance data, it provides the best possible evidence of the increasing burden of disease caused by *E. coli* and *S. aureus* bacteraemia in the European Union. Nevertheless, if the population covered by the participating laboratories became larger during the study period, this may have contributed to the observed increase. Likewise, the sample approach includes laboratories without taking into account the size of the country, and therefore does not allow detailed analysis at national level. The disparity in the BSI trends for *E. coli* and *S. aureus* could partly be explained by ascertainment bias leading to higher reporting of *E. coli* infections. This could be caused by an increase of empirical treatment failures triggering delayed diagnostic procedures (blood culture). A similar upward trend in the number of reported cases of *E. coli* BSIs has been observed by

Figure 1

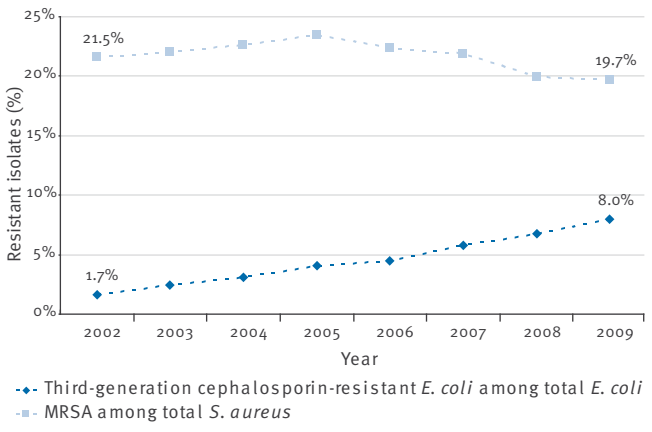
Annual number of bloodstream infections caused by *Escherichia coli* and *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARSS: European Antimicrobial Resistance Surveillance System; EARS-Net: European Antimicrobial Resistance Surveillance Network.

Figure 2

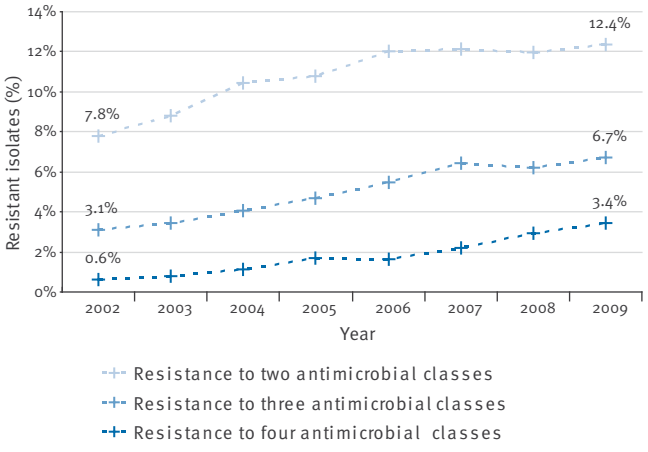
Proportion of third-generation cephalosporin-resistant *Escherichia coli* and of meticillin-resistant *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARS-Net: European Antimicrobial Resistance Surveillance Network; EARSS: European Antimicrobial Resistance Surveillance System.

Figure 3

Combined resistance of *Escherichia coli* to aminopenicillins, third-generation cephalosporins, fluoroquinolones and aminoglycosides, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARSS/EARS-Net: European Antimicrobial Resistance Surveillance Network; EARSS: European Antimicrobial Resistance Surveillance System.

the national voluntary surveillance scheme in England, Wales, and Northern Ireland between 2005 and 2009. The increase (37%) in BSIs caused by *E. coli* observed by this surveillance system is larger than the increase in all BSIs reported during that time period [12].

Despite the study limitations, the observed trends regarding resistance to third-generation cephalosporins and combined resistance in *E. coli* deserve further consideration. According to the results, it appears that the emergence and spread of combined resistance during the study period was the main factor that influences the decline in antimicrobial susceptibility in *E. coli*. From 2002 to 2009, a relative increase of combined resistance with a concurrent reduction of the proportion of single resistance was observed. The resistance pattern with the largest relative growth in the period from 2002 to 2009 was resistance to all four antimicrobial classes under surveillance: the frequency of this pattern increased more than fivefold from 0.6% to 3.4%. This trend suggests that within the subpopulation of resistant isolates, there was a continuous relative growth of combined resistance, possibly caused by the addition of resistance traits to strains that were already resistant to at least one of the considered antimicrobial classes. This trend may be explained by the spread of multidrug-resistant plasmids which also contain genes for the extended-spectrum beta-lactamase (ESBL) production [13-16].

Resistance trends were monitored using interpretations: susceptible, intermediate or resistant (SIR) [3], since the actual minimum inhibitory concentrations (MIC) were not systematically available from participating laboratories. Reporting MICs rather than SIR interpretations based on clinical breakpoints would improve the dynamic monitoring of subtle, incremental changes in antimicrobial susceptibility. Moreover, the interpretation using SIR categories reported to EARS-Net is based on breakpoints defined in the participating countries' guidelines over time. Nevertheless, for the combinations of microorganisms and antimicrobials included in this study, the variation in the proportion of resistance caused by using different guidelines is very limited (unpublished data).

Conclusion

This is a serious concern since, if the increasing trend of antimicrobial resistance and the spread of ESBL are not contained, the use of carbapenems will increase favouring the emergence of carbapenemase producing enterobacteria. This has been already observed for *Klebsiealla pneumoniae* in Greece, Israel and Cyprus [1,2].

At the same time, *S. aureus* showed a relatively smaller increase in the number of reported BSIs, but a significant decrease in the proportion of MRSA overall in the countries participating in EARSS/EARS-Net. This could be the result of public health efforts targeted at the containment of MRSA in several European countries.* Although an overall decreasing trend for MRSA is evident in Europe, not all countries contribute to this result. Efforts to reduce the occurrence of MRSA should remain a priority irrespective of decreasing trends.

In this context, coordinated international surveillance is particularly important in order to obtain accurate knowledge of the occurrence and spread of antimicrobial resistance and to plan public health interventions.

*** Authors' correction:**
At the request of the authors, the following correction was made on 18 March 2011: The sentence 'This could be the result of public health efforts targeted at the containment of MRSA in several European countries.' was changed to 'This could be the result of public health efforts targeted at the containment of MRSA in several European countries.'

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Letter to the editor. Group A streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England

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To the editor: We read with great interest the recent article about invasive Group A *Streptococcus* (GAS) infections associated with influenza B in England by Scaber et al. [1]. Indeed, since 2002 the Clinical Microbiology Laboratory of University Hospitals in Marseille, France, has implemented a tool for the weekly surveillance of microbiological data (called EPIMIC), which consists in a simple warning program using Microsoft Excel software. Both the numbers of samples received and of pathogens diagnosed are compared to historical data as soon as they are entered. Any significant increase beyond the critical threshold, defined by the mean of historical data plus two standard deviations (SDs), generates a signal allowing to detect abnormal and seasonal events in infectious diseases [2].

Recently, we have been alerted by an abnormal increase of invasive Group A *Streptococcus* (GAS) infections detected at the Point Of Care Laboratories of two main Marseille University hospitals (Timone and North hospitals), using rapid antigen detection (RAD) tests on throat swabs. In these two sites and during the three past years (2008-2010), the mean weekly number of GAS detection was six and four, respectively. Between 15 January, and 15 February, 143 RAD tests for GAS infections were positive in patients consulting at the emergency wards, including 98 at La Timone (69%) and 44 at Hospital Nord (31%). These patients had a mean age of 8.6 years (median, 5 years). At the beginning of February 2011, the number of positive GAS was higher than the critical threshold in both sites (mean +2 SDs), being about three times higher compared to the mean value. The number of samples to be tested also increased about the critical threshold.

When this alert was transmitted to the pediatricians working at the emergency wards of both hospitals, they reported to have examined an unusual number of children presenting with both influenza-like symptoms, in the context of seasonal influenza outbreak in France, and pharyngitis with GAS RAD positive testing.

At the same time, Scaber et al. reported their series of cases of invasive GAS co-infection with influenza B [1]. Therefore, we investigated retrospectively the association of GAS detection using the RAD test with influenza virus detection by the rapid influenza diagnostic test (RIDT) and real-time RT-PCR assays (rtRT-PCR) in naso-pharyngeal specimens [3]. From 1 January to 28 February, a total of 227 samples tested positive for GAS, and influenza tests were requested by clinicians in 74 of them. A total of 23 co-infections with influenza virus were identified (31%), including 15 with influenza B virus, six with influenza A (not subtyped) and two with influenza A(H1N1)2009. We also investigated the number of invasive GAS by checking the number of GAS positive blood cultures. From January 2007 through February 2011, 30 GAS positive blood cultures were identified in our laboratory, including 10 between 1 October, 2010 and 28 February, 2011 ($p<0.05$; Fisher and Yates tests, considering the number of blood culture samples received at the laboratories). As it can be considered that our laboratories cover a population of 600,000 persons living in Marseille and the surroundings, the incidence of invasive GAS in the last five months could be estimated at 1.6 per 100,000 population.

We provide here microbiological evidence of concurrent influenza viral infection in almost a third of children with GAS infections. It was a remarkable finding that over half of the 23 samples testing positive for influenza were influenza B. The high proportion of confirmed influenza B in our series, even if in a small sample size, is striking, regarding the potential morbidity and mortality associated with influenza B virus in the context of co-infection with invasive GAS, as recently reported [1].

Our warning and investigation resulted from the implementation of a surveillance tool to detect abnormal events in infectious disease. This method of surveillance may lead to other surprising discoveries.

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