Eurosurveillance

Volume 14, Issue 5 - 05 January 2009

Rapid communications

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Mumps outbreak on the island of Anglesey, North Wales, December 2008-January 2009

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Twenty-three cases of clinical mumps in young people have been reported in North Wales over a five-week period since late December 2008. All cases have social links, and most of them have received two doses of mumps-containing vaccine.

Since 27 December 2008, the North Wales Health Protection Team of the National Public Health Service for Wales has been notified of 23 cases of clinical mumps. The onset dates are shown in the Figure. The age range was 9-37 years with a median of 15-16 years, and similar numbers of males and females were affected. The cases are all linked via family or social groups.

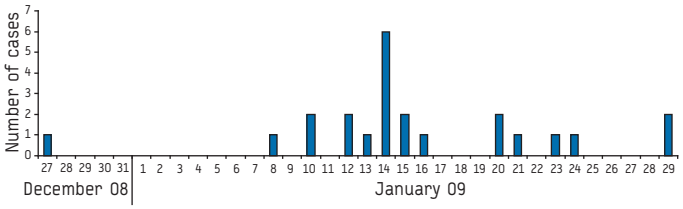
Epidemiological investigation

The first case reported on 27 December was a student in Manchester where, as confirmed by the Health Protection Unit, a number of mumps cases have occurred among students in recent weeks. They received an increase in notifications in the first week of December 2008 which peaked in the second week of December, and it is plausible that the student was infected at this time. Transmission from this case probably occurred at a Young Farmers party held on Anglesey on the 27 December 2008. Members of two local Young Farmers groups were invited, comprising around 50 young people aged 13 to 27 years.

An unusual feature of this outbreak is that 20 of the cases had received two doses of the measles, mumps, rubella (MMR) vaccine and two cases had had one dose. The only unvaccinated case was a 37 year-old patient who was too old to have been offered MMR as a child. Most cases appear to be mild, with no reports to date of orchitis or other complications. MMR vaccine was introduced into the childhood vaccination programme of the United Kingdom (UK) in 1988. The mumps strain currently used in the MMR vaccine is Jeryl Lynn. However, some of the older cases (over 17 years-old) in this outbreak will have received MMR vaccine containing the Urabe strain which was used in the UK from 1988 to 1992.

Figure

Epidemic curve, mumps cluster on Anglesey, North Wales, December 2008 – January 2009 (n=23)



Laboratory investigation

One case was admitted to the district general hospital where blood for serology was taken. This was reported as negative for IgM against mumps virus, but positive for IgG with no evidence of recent infection. This sample was taken the day after onset of symptoms, and would have been too early to capture an IgM response. A convalescent sample has been requested.

Another case, who is a healthcare worker, had paired sera taken by the Occupational Health Department, which showed a rising titre of mumps antibodies and was therefore confirmed as recent mumps infection by the regional virology laboratory.

Salivary swab samples of the remaining 21 clinical cases have been submitted to the reference laboratory at the Health Protection Agency Centre for Infections (CfI) at Colindale. The results for three cases have been received to date and are as follows:

Case 1.
The samples were IgM-negative and IgG-positive (very high titre), possibly indicating infection. A repeat salivary antibody test has been requested to ascertain whether IgM titres have subsequently risen.

Case 2.
The samples were IgM-negative and IgG-positive, although the titre was not particularly high.. This is consistent with past immunisation, but does not allow comfirmation of recent mumps infection. The patient's general practitioner notes that it was a very mild case of mumps.

Case 3.
The samples tested IgM-positive and IgG-positive (very high titre). Recent mumps infection is confirmed.

Two recent cases have been swabbed within 48 hours of onset, and their samples will be tested by PCR at the CfI reference laboratory.

Discussion and conclusion

Salivary swabs are usually submitted two weeks after notification of clinical mumps. In this outbreak blood samples have been taken in individual cases because of special circumstances. The

laboratory results to date indicate that this is a genuine outbreak of mumps, although the timing of some of the samples may not have been optimal for capturing the antibody response.

This outbreak is different form the one described in Austria in 2008, where 49.1% of the young people affected had not been vaccinated [1]. However, in the Netherlands, a number of fully vaccinated individuals were affected as part of an outbreak in a predominantly unvaccinated community in 2008 [2].

Uptake of MMR vaccination has historically been high in Anglesey, and the majority of cases in the outbreak had received two doses. The lack of cases among unvaccinated individuals may reflect the high uptake of vaccine, and an investigation is ongoing to determine coverage rates for the birth cohorts involved. Current isolates from mumps cases in the UK have been identified as genotype G. Further tests are required in order to confirm that this is also the genotype for this outbreak.

The mumps component of the MMR vaccine does not provide the same high levels of protection as the measles and rubella components. One dose protects around 65% (62%-85%) of those who receive it [3]. A second dose raises the effectiveness to around 85%. This still leaves one in six recipients of two MMR doses vulnerable to mumps. This primary vaccine failure may be the explanation for this outbreak, but the contribution of waning immunity, secondary vaccine failure, must also be considered.

Infection control measures

Letters have been sent to the school many of the cases attend, advising that all children should ensure that they have received two doses of MMR vaccine. Letters have also been sent to general practitioners in the area alerting them to the fact that cases of mumps are occurring despite complete vaccination status, and preparing them for requests for MMR vaccination.

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This article was published on 5 February 2009.

Citation style for this article: Roberts C, Porter-Jones G, Crocker J, Hart J. Mumps outbreak on the island of Anglesey, North Wales, December 2008-January 2009. Euro Surveill. 2009;14(5):pii=19109. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19109

Increase in invasive group A streptococcal infections in England, Wales and Northern Ireland, 2008-2009

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Increases in invasive and non-invasive group A streptococcal diseases are currently being seen in the United Kingdom. National enhanced surveillance is being launched to examine the clinical presentations, risk factors, outcome and clustering patterns of cases to further inform public health management strategies.

Following the increases in the number of scarlet fever cases identified across England during the 2007-8 season, further increases are being seen during the current 2008-9 season, accompanied by increases in invasive group A streptococcal *(Streptococcus pyogenes)* infections [1,2]. Although group A streptococcal infections typically increase at this time of year, the rises seen currently are above the seasonally expected.

Scarlet fever

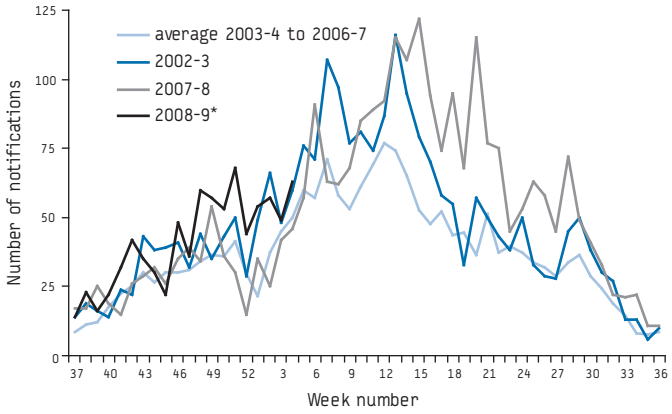
In the United Kingdom (UK), statutory notifications of scarlet fever, based on clinical symptoms consistent with scarlet fever, are submitted by diagnosing clinicians to the local public health officials. A total of 222 notifications of scarlet fever were made during the last four weeks of 2008 by clinicians across England, compared to 134-141 notifications for the same period in 2004 to 2007, and 153 notifications for 2003, the last peak year for scarlet fever (Figure 1). Numbers of notifications were elevated relative to the period between 2003 and 2007 in all nine regions of England except the South West and Yorkshire and the Humber. Notifications for the first four weeks of 2009 showed a continuation of the high level of activity, with 223 notifications compared to 143-180 for 2004-2008 and 223 for 2003.

Invasive group A streptococcal infection

Cases of invasive group A streptococcal (iGAS) infection, defined through the isolation of group A streptococci from normally sterile sites, are identified through national routine laboratory surveillance and isolate referral to the national reference laboratory. Routine surveillance data identified 151 cases of iGAS in December 2008, with a further 98 reports made so far for January 2009, compared to 80-127 for December in the years 2003 to 2007 (Figure 2).

Figure 1

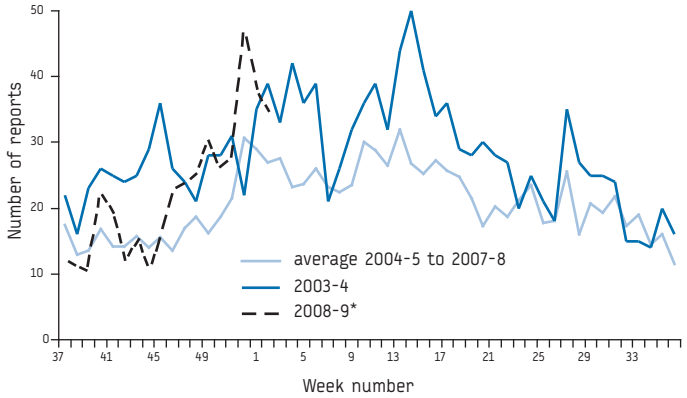
Scarlet fever notifications, England 2002-3 to 2008-9



* data available up to week 4, 2009

Figure 2

Weekly reports of invasive group A streptococcal infections, England, Wales and Northern Ireland 2002-3 to 2008-9



* reports received by 2 February 2009 up to week 2, 2009 (further reports expected)

Increases above the total seen in December 2003, the last peak season for invasive disease, have been seen in three of nine regions in England and Northern Ireland so far, whilst data for Wales remain within the seasonally expected range. Given delays inherent within routine laboratory reporting, further reports for 2008 can be expected. Overall, 2% (2/97) of iGAS isolates from December 2008 were reported as erythromycin-resistant. Age- and sex-specific rates of iGAS infection show highest rates in the elderly and infants (Figure 3).

iGAS isolates referred to the national reference laboratory from hospitals in England showed a substantial increase in December 2008 (n=143) compared to the same period in 2007 (n=86). The most common *emm*/M-types identified in December 2008 were *emm*/M1 (25% of all iGAS isolates), *emm*/M3 (25%), *emm*/M89 (9%) and *emm*/R28 (9%). Of the 100 GAS isolates received and typed so far for 2009, there has been a significant increase in *emm*/M3, with 50% of isolates typed belonging to this *emm* type.

Discussion

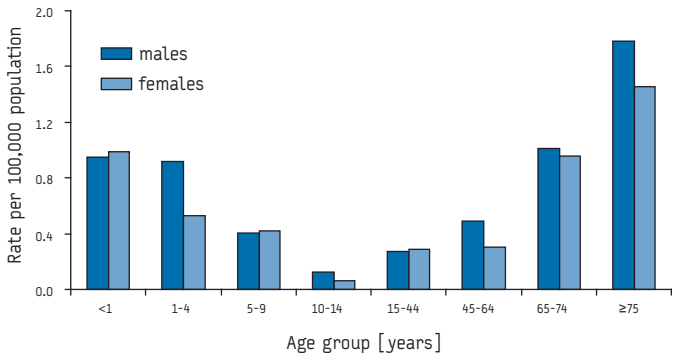
Periodic upsurges in iGAS have been reported in many countries across Europe and North America since the 1980s [3], with Finland the latest country to report an increase in iGAS from 2006 onwards [4,5]. The reasons behind these increases are poorly understood. Analysis of scarlet fever notifications in England over the last century suggest cyclical incidence patterns, with resurgences occurring on average every four years [6]. The last peak season for scarlet fever was 2002-3, although notifications were also high for 2003-4. A recent project started in the UK to examine the potential value of using syndromic indicators of superficial manifestations of GAS infection in forecasting rises in invasive disease, found that clinically diagnosed scarlet fever mirrored the pattern of iGAS [7], and as such the current increases in invasive disease may be attributable to a natural cycle in disease incidence.

The potential remains for changes in virulence of circulating strains or for increased incidence in particular risk groups, as seen in the UK during the early 2000s [8]. It is also possible that the significant influenza activity in the UK this winter may be contributing directly or indirectly by increasing transmission of GAS and/or rendering individuals with influenza more susceptible to secondary infection with iGAS [9]. Analysis of isolates submitted to the national reference laboratory has not identified any unusual types circulating this season, although an increase in *emm*3 is currently being seen. Further typing results are awaited to confirm this trend, which would be of concern given its association with a higher case fatality rate than most other *emm* types [10].

As a result of the current rise in iGAS notifications, national enhanced surveillance is being introduced in order to gain additional information on clinical presentations, risk factors, outcome and clustering. Alerts have been issued to regional health protection staff and consultant microbiologists, and a template letter outlining the current situation and reminding clinicians of possible early signs and symptoms of iGAS has been made available for cascade to hospital emergency departments and primary care services.

FIGURE 3

Age- and sex-specific rates of invasive group A streptococcal infection*, England, Wales and Northern Ireland, December 2008-January 2009



* reports received by 2 February 2009 (futher reports expected)

Aknowledgements

We thank the local and regional health protection staff and microbiologists for their rapid provision of information concerning incident cases, and Ruth Blackburn for her assistance in developing the national enhanced surveillance questionnaire.

The additional members of national incident management team were: Alexandra Baker, Paul Davison, Gareth Hughes, Isabel Oliver, Mark Reacher, Christopher Williams.

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This article was published on 5 February 2009.

Citation style for this article: Lamagni TL, Efstratiou A, Dennis J, Nair P, Kearney J, George R, on behalf of the national incident management team. Increase in invasive group A streptococcal infections in England, Wales and Northern Ireland, 2008-9. Euro Surveill. 2009;14(5):pii=19110. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19110

Increased number of dengue cases in Swedish travellers to Thailand

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Between 2004 and 2008, around 30-60 cases of dengue fever in travellers were reported annually in Sweden. Over 75% of cases in 2005-2008 were infected when travelling to Southeast Asia, most if them in Thailand, one of the Swedes' most popular holiday destinations. Since 2007, we have observed a 55% increase in the number of dengue fever cases reported per month, with 17 cases reported in January 2009 alone.

The global incidence of dengue fever has increased over the past few years, and there are frequent reports of large outbreaks in Asia and Latin America [1]. It is estimated that 50-100 million people are infected world-wide each year and that approximately 500,000 are hospitalised for treatment [2]. Dengue virus infection is one of the most common causes of fever in travellers to countries in the Caribbean, Central America and Southeast Asia [3].

Globally, there has been a marked increase of dengue and countries like Singapore, Malaysia, Thailand, Vietnam, Indonesia and India have all reported increased frequencies of infection [4]. Thailand experienced a major outbreak of dengue fever during the spring and summer of 2008. By August 2008 the total number of reported cases was 43 911 with 46 deaths nationwide. A possible factor behind last year's epidemic in Thailand was the fact that the virus serotype DEN-2 was found to dominate, whereas recent years have seen mostly DEN-1 [5].

Trends in Swedish travellers

Dengue fever is a notifiable disease in Sweden, and the cases reported here are laboratory-confirmed cases that were reported to the Swedish Institute for Infectious Disease Control.

A total of 100 cases were reported among Swedish travellers in the period November 2007-January 2009 (Figure 1), with a monthly average of 6.7 cases. Of these 100 cases, 52 originated in Thailand. The number of cases reported in January 2009 alone was 17, with 13 (76%) infected in Thailand

The cases presented with fever and influenza-like symptoms upon return from travel abroad. Patients were referred to infectious disease clinics, where the diagnosis was made following laboratory confirmation at the Swedish Institute for Infectious Disease Control. There has been no report of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) among Swedish travellers.

Swedish data on dengue virus infections have been available since 2004, and there has been an insignificant rise in the number of annual reported cases since then (Figure 2).

Figure 1

Reported cases of dengue fever in Sweden, November 2007–January 2009 (n=100)

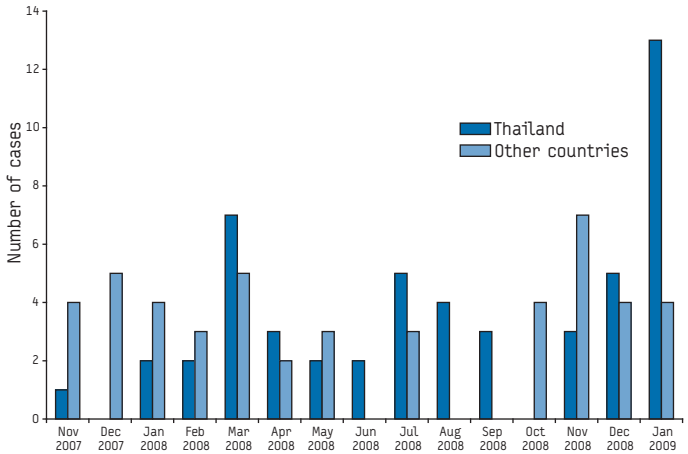
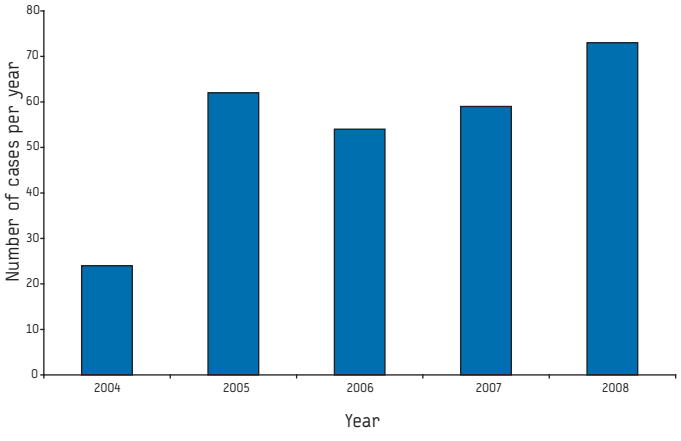


Figure 2

Annual number of dengue fever cases reported in Sweden, 2004-2008



Discussion

The underlying causes behind the seemingly increasing global trends of dengue infection are complex and not fully elucidated. A number of possible contributing factors have been suggested:

- Demographic changes including rapid urbanisation with large populations living in peri-urban slums in poor sanitary conditions, which provide favourable breeding conditions for the Aedes mosquito vector and promote dengue transmission;
- Increased international travel;
- Failing health systems with decreased access to public health services;
- Climate change, particularly change in rainfall [8];
- Failing vector control programmes;
- Increased attention to dengue fever (World Health Organization programmes, the Bill and Melinda Gates Foundation and others), leading to more accurate reporting and data.

Around 350,000 Swedes visited Thailand in 2007 (personal communication: Swedish aviation authority). The increase in dengue fever cases reported here is based on too small a number to draw any significant conclusions, but available international data suggests that the incidence of dengue fever has indeed increased in Thailand as well as globally, and the trend seen amongst Swedish travellers may be indicative of a changing risk.

The above has not led to changes in travel recommendations to Swedish travellers, and there are no restrictions on travel to endemic areas, as the overall risk of contracting a dengue virus infection is still deemed relatively low for the ordinary tourist. However, adequate precautionary measures including bednets, mosquito repellents and appropriate clothing should be encouraged in order to avoid exposure to mosquito bites. People who have had the infection once and are worried about the potential increased risk to develop DHF/DSS when infected a second time should be advised to consult an infectious disease/travel medicine clinic prior to departure to get advice. There are no general recommendations for this group to abstain from travel to areas where dengue virus is endemic.

Future considerations

Dengue virus does not occur naturally in the geographical area of the European Union (EU), and current conditions do not seem to be conducive to endemic transmission in the region. However, this may change. It is thus important to closely monitor the development of dengue epidemiology world-wide as well as within the EU. The outbreak of chikungunya fever in Ravenna in 2007 showed that the presence of a competent vector can enable spread under the right conditions [7]. Studies have shown that case fatality rates of DHF/DSS are higher among the elderly and people with underlying complicating disease such as diabetes and cardiovascular disease [8]. This may call for extra caution as this is also a growing group of travellers.

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This article was published on 5 February 2009.

Citation style for this article: Heddini A, Janzon R, Linde A. Increased number of dengue cases in Swedish travellers to Thailand. Euro Surveill. 2009;14(5):pii=19111. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19111

Use of oseltamivir in 12 European countries between 2002 and 2007 – lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses

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Variable levels of oseltamivir resistance among seasonal influenza A(H1N1) isolates have been reported in Europe during the 2007-8 northern Hemisphere influenza season. It has been questioned whether oseltamivir use could have driven the emergence and predominance of resistant viruses. This study aimed at describing the levels of use of oseltamivir in 12 European Union (EU) Member States and European Economic Area (EEA)/European Free Trade Area (EFTA) countries. The data were converted into prescription rates and compared with the national proportions of resistant influenza A(H1N1) viruses through regression analysis. Overall use of oseltamivir in European countries between 2002 and 2007 was low compared to e.g. the use in Japan. High variability between the countries and over time was observed. In eight of the 12 countries, there was a peak of prescriptions in 2005, coinciding with concerns about a perceived threat from an influenza pandemic which might have lead to personal stockpiling. Ecological comparison between national levels of use of oseltamivir in 2007 and the proportions of A(H1N1) viruses that were resistant to oseltamivir showed no statistical association. In conclusion, our results do not support the hypothesis that the emergence and persistence of these viruses in 2007-8 was related to the levels of use of oseltamivir in Europe. Further investigation is needed to elucidate the reasons for different level of use between the countries.

Introduction

Annual epidemics of human seasonal influenza are associated with a substantial burden of morbidity and mortality, which cumulates in certain groups of the population such as older people and those with chronic medical conditions [1-3]. Annual vaccination remains the mainstay of influenza prevention, and antiviral medications, including the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, and M2 protein inhibitors (the adamantanes amantadine and rimantadine) play an auxiliary role in the prevention or treatment of influenza infection. They can be especially helpful in controlling outbreaks in nursing homes, in individuals who cannot be immunised or in situations in which vaccine has not been given or in which vaccination is not optimally effective due to a poor match between the vaccine strain and the circulating strains [4-9].

NAIs, especially the oral drug oseltamivir, became increasingly important after a sudden increase in adamantane resistance among seasonal influenza A viruses between 2004 and 2006 [5,10,11]. NAIs have also been preferred in recommendations to amantadine (the most commonly used adamantane) since they show lower levels of adverse neurotoxic reactions [12]. Before the 2007-8 influenza season, resistance to the NAIs among transmitting seasonal influenza A viruses was extremely rare in Europe and elsewhere [13-15] and higher proportions of resistance had been reported only in children: up to 18% of children infected with influenza A(H3N2) and treated with oseltamivir shed virus resistant to oseltamivir [16-17]. However, NAI-resistant viruses detected before 2007-8 showed in most cases a poor ability to transmit from human to human.

This situation changed abruptly during the 2007-8 northern Hemisphere influenza season when influenza A(H1N1) virus isolates highly resistant to oseltamivir were detected as part of surveillance in the Europe through the networks of the European Influenza Surveillance Scheme (EISS)/European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) [13,18]. Laboratory analyses showed that up to 67.4% of all influenza A(H1N1) viruses isolated from specimens collected between November 2007 and April 2008 in Europe either carried the mutation H274Y which is associated with high levels of oseltamivir resistance or tested positively in the IC50 phenotypic examination for oseltamivir resistance (Figure 1) [19]. This was the first indication that influenza A(H1N1) virus resistant to oseltamivir could readily transmit between humans.

The question arises whether current levels of oseltamivir use in European countries could have been associated with the emergence and sustained transmission of resistant influenza A(H1N1) viruses. The aim of the study was thus to describe, using all available data (including data from prescription surveys and databases), oseltamivir usage at population level in several EU Member States and EEA/EFTA countries and to determine if there was any correlation between the level of use and the observed proportions of A(H1N1) viruses that were resistant.

Methods

We used several sources of information on oseltamivir prescriptions as a proxy measure for oseltamivir utilisation in EU Member States and EEA/EFTA countries.

Information on oseltamivir use from a prescription survey

We used data from a continuing survey of a panel of office-based physicians in EU Member States and EEA/EFTA countries from databases maintained by Intercontinental Marketing Services (IMS) Health, an independent commercial company providing information on the use of pharmaceuticals. IMS Health attempts to achieve a high level of representativeness of their panels for the population of all physicians in the involved countries. Participating physicians are being surveyed for two consecutive workdays per quarter of a year and provide information on each patient encounter during this period. The manufacturer of oseltamivir, F.Hoffmann-La Roche Ltd., provided the European Centre for Disease Control and Prevention (ECDC) with the data from IMS Health on the numbers of oseltamivir prescriptions in Austria, Belgium, Finland, France, Germany and Greece for the years 2002 to 2007. We then converted these data into prescription rates (number of prescriptions per 1,000 inhabitants per year) using Eurostat population data [20]. Four other countries monitored by IMS Health, the Netherlands, Portugal, Switzerland and the United Kingdom (UK), had only negligible prescription levels for oseltamivir.

Information on oseltamivir use from population prescription databases

In Denmark and Norway, data on the number of patients having used oseltamivir at least once each year between 2002 and 2007 and between 2004 and 2007, respectively, were extracted from national, publicly available databases on redeemed prescriptions [21,22]. These numbers of prescriptions were converted into rates of redeemed prescriptions per 1,000 inhabitants per year. In both countries, data included corporate prescriptions, i.e. medicines purchased by business organisations for their employees. The data did not include any supply of antiviral medications to countries for national or corporate stockpiles.

Quarterly prescription information

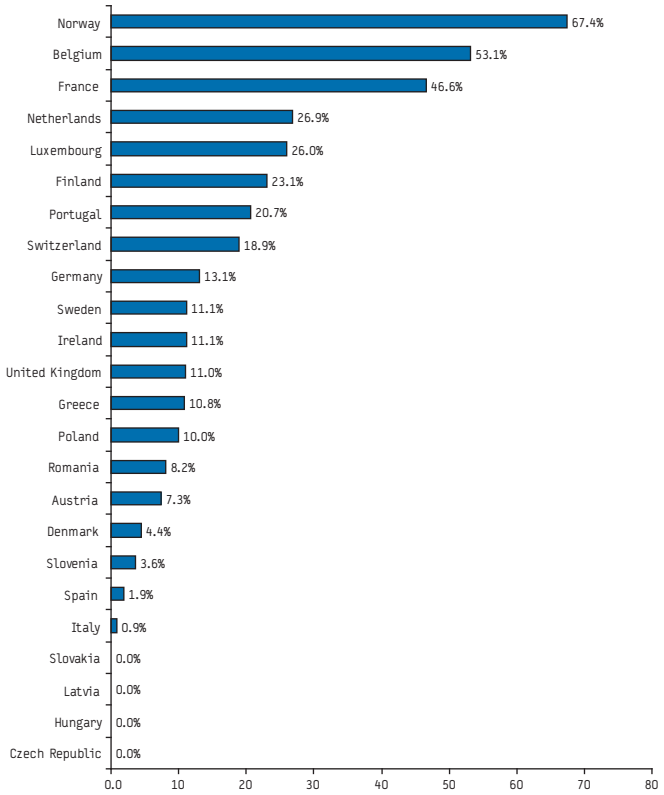
The initial analysis consisted in computing annual figures for oseltamivir prescriptions per 1,000 inhabitants. To examine trends in oseltamivir use over time in more detail, we also obtained quarterly prescription numbers and converted them into prescription rates. Quarterly data were available for eight countries: Austria, Belgium, Finland, Germany, Greece, the Netherlands, Portugal, Switzerland, and the UK.

Investigation of the relationship between oseltamivir use and levels of resistance

Linear regression analysis was performed to determine whether there was any relationship between the use of oseltamivir and the levels of oseltamivir resistance. Proportions of oseltamivir resistance during the 2007-8 influenza season among all A(H1N1) tested strains expressed on the web sites of ECDC, EISS and the World Health Organization (WHO) were regressed on the levels of

Figure 1

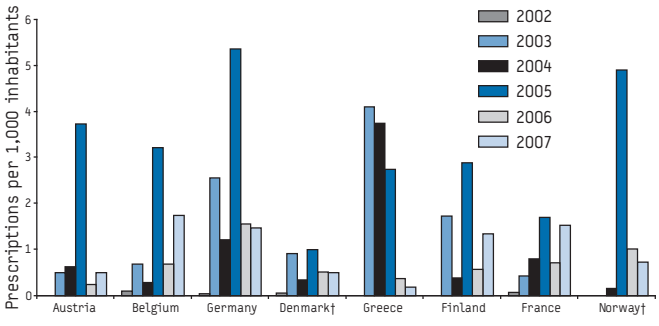
National proportions of antiviral resistance in A(H1N1) influenza viruses for EU/EEA Member States, 2007-8



Data (available as of 6 August 2008) were provided by European Influenza Surveillance Scheme www.eiss.org/index.cgi and the VIRGIL Project www.virgil-net.org.
Countries with fewer than 10 test results (Bulgaria, Estonia) are not shown in the graph.
EU/EEA/EFTA countries in the EISS network for which no test results were available: Cyprus, Lithuania, Malta.
EU: European Union; EEA: European Economic Area EFTA: European Free Trade Area; EISS: European Influenza Surveillance Scheme; VIRGIL: European Surveillance Network for Vigilance against Viral Resistance.

Figure 2

Prescriptions of oseltamivir per 1,000 inhabitants in eight European countries*, 2002-2007



* Data only include patient prescriptions. They do not include stockpiles at national/regional level or by hospitals/institutions. Data for Denmark and Norway include corporate prescriptions.
Netherlands, Portugal, UK and Switzerland: data not presented due to 'negligible' number of prescriptions.
† Denmark and Norway: the data are based on the number of patients, which may slightly underestimate the number of prescriptions.
Source: IMS Health data provided by F. Hoffmann – La Roche Ltd., Basel except for: Denmark;,data provided by Danish Medicines Agency, and Norway: data provided by Norwegian Institute of Public Health.

oseltamivir use in the countries in 2007. STATA (STATA/SE 10 for Windows, STATA Corporation) was used for statistical analyses.

Results

Annual oseltamivir prescription rates

As shown in Figure 2, the overall prescription rates for oseltamivir remained under six prescriptions/1,000 inhabitants/year in the eight EU Member States for which such data was availabe. This is low compared to those reported, for example, in Japan where the reported prescription rate in 2005 was 70.9/1,000 inhabitants/year [23].

After a substantial peak in prescriptions in 2005, when three countries exceeded three prescriptions/1,000 inhabitants/year (Austria, Belgium and Norway) and one country exceeded five prescriptions/1,000 inhabitants/year (Germany), the use of oseltamivir decreased to under two prescriptions/1,000 inhabitants/year in 2006 and 2007 in all included countries. However, the trends from 2006 to 2007 differed: an increase occurred in Austria, Belgium, Finland and France, a small decrease in Germany, Greece and Norway, and the rates remained stable in Denmark.

In the most recent year with available data (2007), we observed a substantial variation in oseltamivir prescription rates in EU Member States, with an almost tenfold differences in those countries with any significant use of oseltamivir. The highest rates were seen in Belgium and the lowest in Greece. Countries with negligible use that are not shown in the figure are the Netherlands, Portugal, Switzerland and the UK. Greece exhibited a different prescription pattern with high use in 2003 and 2004.

In summary, our analysis showed low prescription rates of oseltamivir with substantial variation between analysed countries and over time.

Quarterly oseltamivir prescription rates

Figure 3 shows a more detailed comparison of oseltamivir prescription rates in eight countries for which data were available at the level of periods of three months.

It was noticeable that the peak of oseltamivir use observed in 2005 in Austria, Belgium, Finland and Germany (Figure 2) concentrated mostly during the first quarter of that year.

No correlation of prescription data and resistance development

We have analysed oseltamivir resistance in 2007-8 because a sharp increase in resistance was observed during that season. We regressed it against oseltamivir use in 2007 assuming this was a good proxy for oseltamivir use in 2008. However, regression analysis for twelve countries (Figure 4) did not show any statistical association between the levels of oseltamivir resistance during the influenza season 2007-8 and oseltamivir prescriptions in 2007 ($R2 = 0.02$).

Discussion

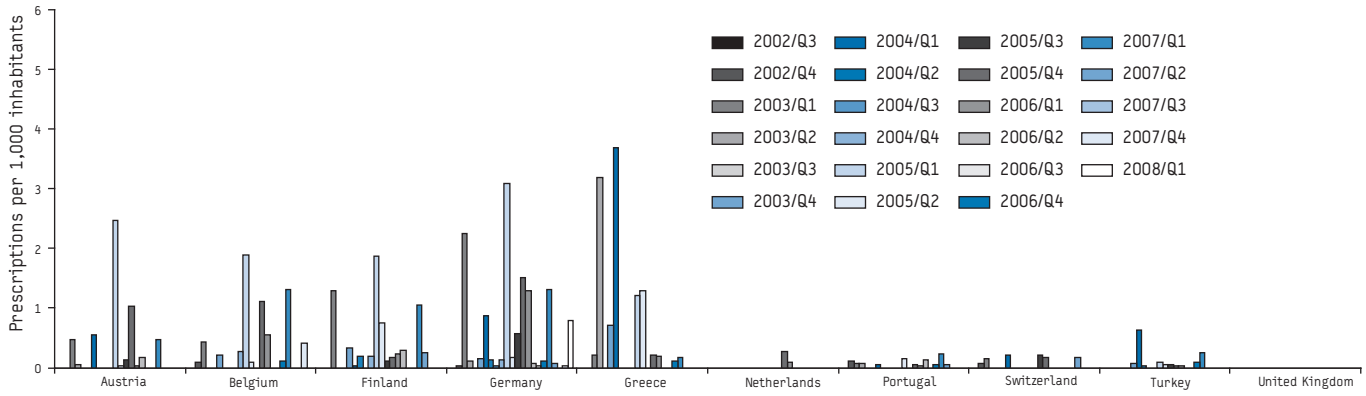
We found overall low levels of oseltamivir use in EU Member States in the period between 2002 and 2007, compared to the use of oseltamivir in Japan, a country with the world's highest per capita use of oseltamivir (70.9/1,000 inhabitants/year), but relatively low levels (3%) of oseltamivir resistance during the 2007-8 season [23,24].

There was a common peak in prescriptions in 2005 in eight countries. One possible explanation for this phenomenon is the concern over 'bird flu' influenza A(H5N1) in 2005 when spread of these viruses from Asia towards Europe received considerable attention in the media. Many of these prescriptions to individuals and families may therefore have gone to form a source of medication for the future ("personal stockpiling"). A similar spike of influenza antiviral medication sales, was observed in October 2005 in New York [25] and, in general, in the autumn and winter of 2005 accross the United States [26]. It did not coincide with influenza activity itself, but rather with the beginning media coverage of avian influenza A (H5N1) and the potential for an influenza pandemic [23].

It is more difficult to explain the observation that most of the oseltamivir use in EU Member States in 2005 concentrated in the first quarter of the year. Influenza activity during the season 2004-5

Figure 3

Prescriptions of oseltamivir per 1,000 inhabitants in eight European countries*, 2002-2007, by quarter of a year



Source: IMS Health data provided by F. Hoffmann – La Roche Ltd., Basel except for: Denmark;,data provided by Danish Medicines Agency, and Norway: data provided by Norwegian Institute of Public Health.

only partially explains this peak. Although the media paid some attention in early 2005 to ongoing outbreaks of avian influenza among poultry in Indonesia, Thailand, and Vietnam and possibly also in Cambodia and Lao People's Democratic Republic, it was the outbreaks of avian influenza in Turkey, Romania, Croatia and the UK in October 2005 which spiked most of the media reports that year [26]. At the time there were public statements in many countries about national antiviral stockpiles being purchased by governments [28,29].

It should be noted that some countries had significant levels of prescribing even before 2005, which could be an indication for therapeutic or prophylactic application by physicians. The contrasting prescription pattern in Greece with high use in 2003 and 2004, may represent the seasonal influenza activity pattern in that country with the highest activity in February-April 2003, and then from December 2003 to the first months of 2004.

We also found a substantial variation in prescription rates between the analysed countries, which is hard to justify on any scientific grounds. Reasons may be differences in national guidelines, clinical practice patterns, marketing strategies or insurance companies' reimbursement [30]. Among the countries with negligible use of anti-influenza drugs, the UK and the Netherlands have medical guidelines on when antiviral medications are indicated that restrict their widespread use [4,12,31], while in Switzerland, most insurance companies do not reimburse the use of antivirals (D. Koch, personal communication). Exploring this phenomenon in more detail would warrant a separate study and would be justified because the wide variations in the use of antivirals for influenza does at present not reflect observed patterns of influenza-like illness/influenza and cannot be seen as having a scientific basis.

Although the analyses had to be restricted to ecological analyses, these preliminary data do not point towards any correlation between a higher prevalence of resistance and higher rates of antiviral use. Hence, it seems very unlikely that oseltamivir use has driven the rise and persistence of 'fit' oseltamivir-resistant influenza viruses A(H1N1) in Europe in the 2007-8 season. The H274Y point mutation, which confers oseltamivir resistance is most likely a random event, and potential factors influencing its occurrence are not known [32].

Our study had several limitations, apart from being restricted to an ecological level of analysis. Firstly, we obtained information on antiviral medication prescriptions which do not necessarily represent all medications consumed. Indeed, it is possible that some of the purchased medications were not consumed but stored in "private stockpiles". This seems especially likely for the antivirals acquired in the peak year of 2005. Secondly, the IMS Health data are based on a sample of physicians who may not necessarily be representative for all physicians in the analysed countries. Thirdly, data were only available for a limited number of EU Member States and EEA/EFTA countries, and the situation could be quite different in the countries that we could not study. Moreover, for several countries we only had data on oseltamivir resistance for the first quarter of 2008.

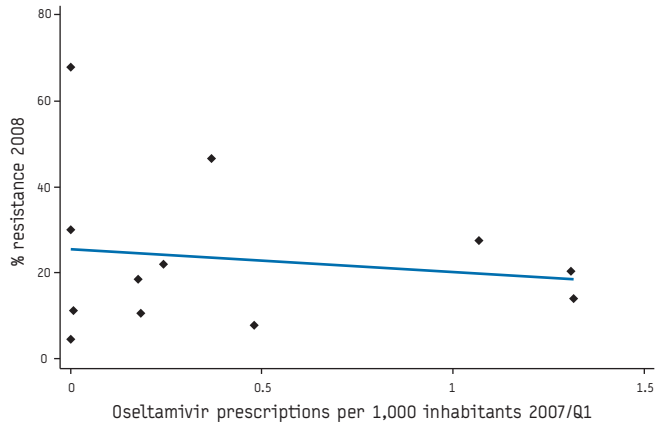
Conclusion

While the precise relationship between oseltamivir use and resistance of influenza A(H1N1) to oseltamivir remains uncertain, the available data do not suggest a link between the rapid rise in the proportion of the resistant A(H1N1) and the use of oseltamivir in Europe.

The use of influenza antiviral medication in EU Member States should be closely monitored in the future. More studies are needed to assess how the influenza prescription rates reflect the actual use of the medication by patients, in order to explore the potential causes of the large variation in the number of prescriptions in EU Member States and EEA/EFTA countries. In addition, a scientific discussion is needed about what are the right indicators for use of these drugs. Virological studies are needed to better understand the mechanism behind the development of oseltamivir resistance among A(H1N1) seasonal influenza viruses, and to monitor the possible emergence and spread among other influenza viruses. Epidemiological studies are needed to understand the determinants of resistance development, in order to be able to design targeted interventions and to assess the impact on transmission and clinical outcome.

Figure 4

Regression of the proportion of resistant strains on the number of prescriptions of oseltamivir per 1,000 inhabitants in European countries



Source as in Figure 3.

Aknowledgements

We wish to thank David Reddy and James Smith (F.Hoffmann-La Roche Ltd) for making available the data on oseltamivir use in the analysed countries.

ECDC would like to thank all countries, virologists, clinicians and others for contributing data. Funding for the VIRGIL project comes from the European Union FP6 Research Programme http://ec.europa.eu/research/health/influenza/proj13_en.html and EISS is supported by ECDC. Laboratories in EISS contribute to the Global Influenza Surveillance Network managed by WHO.

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This article was published on 5 February 2009.

Citation style for this article: Kramarz P, Monnet D, Nicoll A, Yilmaz C, Ciancio B. Use of oseltamivir in 12 European countries between 2002 and 2007 – lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses . Euro Surveill. 2009;14(5):pii=19112. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19112

EpiSouth: a network for communicable disease control in the Mediterranean region and the Balkans

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The countries around the Mediterranean Sea share epidemiological characteristics and public health problems. In 2006 the EpiSouth Project was started as a framework for collaboration for communicable diseases surveillance and training in the Mediterranean Basin. As of December 2008, 26 countries from southern Europe, the Balkans, North Africa and the Middle-East are members of EpiSouth and several international organisations and institutions collaborate: the European Commission (EC), the European Centre for Disease Prevention and Control (ECDC), the Italian Ministry of Work, Health and Social Policies and the World Health Organization (WHO). The project is coordinated by the Italian national public health institute and three work packages (WPs) *Cross-border epidemic intelligence, vaccine preventable diseases and migrants* and *Cross-border emerging zoonoses* are operated by the national institutes of France, Bulgaria and Greece. These WPs constitute technical pillars on which the project develops. *Networking* and *Training* are WPs dedicated to capacity building and are run by the Padua Teaching Hospital (Italy) and the Spanish national public health institute. A steering committee guides EpiSouth's activities while all countries collaborate through WP steering teams and focal points. A number of outcomes have been accomplished and documents with results are available from the EpiSouth website which hosts a public website and a restricted area for direct sharing of information among the participants. Five electronic bulletins were published, two trainings for 63 participants performed, national epidemic intelligence systems were evaluated, a preliminary survey on vaccine-preventable diseases and migrants performed, and a list of priorities for emerging zoonoses in the Mediterranean area was selected. Overall the network succeeded in creating cohesion, mutual trust and concrete collaboration on cross-border public health issues in a geographical area that is not addressed as a whole by any other initiative or organisation.

Background

Infectious diseases are threats to human health that can rapidly spread across geographical regions and borders. Today, a number of them are preventable through effective and safe vaccines however, the majority are still prevented and controlled through a comprehensive approach, in which surveillance plays a crucial role. In order to initiate appropriate public heath action, early detection of cases, dissemination of information, and cross-border, harmonic and prompt response are crucial. The countries of the Mediterranean region have common sea borders in the ecosystem of the Mediterranean Sea and share public health problems. To address these common problems, in 2004, experts from Bulgaria, Greece, France and Italy designed a co-operative initiative covering the Mediterranean region and the Balkans, similar to that developed by the EpiNorth Project for the Baltic Region [1]. Spain soon joined the initiative and on occasion of the *Year of the Mediterranean*, in 2005, the project called EpiSouth was proposed to the countries in this area and to the European Commission (EC) for funding. EpiSouth was officially launched on 1 October 2006 and receives funding until 30 September 2009. The general objective of the project is to create a framework for collaboration on epidemiological issues to improve communicable diseases surveillance and communication and provide training for public health experts in the participating countries.

Methods

To enhance communicable disease control capacity in the Mediterranean region and the Balkans priority areas for activities were identified. Work in these areas is conducted through specific work packages (WP) and EpiSouth is focussing on the WPs *Cross-border epidemic intelligence, vaccine preventable diseases and migrants* and *Cross-border emerging zoonoses* which are expected

to produce, among others, strategic documents and guidelines aimed at supporting the EpiSouth countries in setting standard operating procedures and in dealing with emerging health threats. Training modules on field/applied epidemiology intend to strengthen the capacities in the areas mentioned above.

A project steering committee identifies priorities, guides and advises the project coordinating structure. It is composed of the WP leaders plus observing representatives of EC Directorate-General for Health and Consumer Protection (DG Sanco), the European Centre for Disease Prevention and Control (ECDC), the Italian Ministry of Work, Health and Social Policies, the World Health Organization (WHO) and its Regional Office for Europe, Regional Office for the Eastern Mediterranean, and Lyon Office. All WHO entities provide input to the WPs' activities.

To enhance work in the WPs, steering teams (STs) were created. They consist of eight to nine experts, including the WP leader and representatives from European Union (EU) and non-EU countries that expressed interest in the respective WP. Finally, the network is constituted by one or two focal points (FP) formally appointed by each country. They interact with the relevant officers in their respective countries/organisations, with the other FPs of the network and with the project coordinator. FPs are expected to carry out, or promote and facilitate, all activities in the WPs requiring the countries' active involvement such as filling in questionnaires for assessment and evaluation, data and alerts sharing, contribution to documents and articles. According to their needs and interests countries can participate in the activities of one up to all WPs.

Results and achievements

Participants

Starting with nine EU countries, Italy, Spain, France, Bulgaria, Greece, Cyprus, Malta, Romania and Slovenia, EpiSouth has rapidly grown. As of December 2008, 26 countries (see figure) have appointed 63 country FPs, 29 from EU-countries and 34 from non-EU countries. Furthermore, seven experts represent collaborating institutions (see table) A directory of public health institutions participating in the network provides useful information on their respective mission, structure, role and activities in the field of infectious diseases prevention and control is available from the projects website [2]. The progress towards the network's building and development, was assessed through questionnaires distributed among the participants during the two annual meetings in Rome and Athens [3].

Cross-border epidemic intelligence

Consensus among EpiSouth partners was reached for the working definitions of *epidemic intelligence:* monitoring of health events occurring outside EpiSouth catchment area but with a possibility to affect EpiSouth countries and for *cross-border issues:* monitoring of health events occurring within the EpiSouth area for early warning and information sharing. Needs and expectations of participating countries towards this critical domain were assessed in a questionnaire that was elaborated by the ST members and distributed to all partners in November 2007. A report based on the outcomes was published on the public portal of the project's website [4]. It shows a common understanding of the perceived importance posed by emerging health threats throughout the EpiSouth catchment area. However, some differences were observed mainly related to historical structures of the surveillance systems (e.g. availability of adequate resources) and countries specificities (e.g. geographical location, history etc.). Although the number of returned questionnaires is not exhaustive, the analysis provided a solid base for elaborating EpiSouth international epidemic intelligence criteria both in terms of geographic coverage and type of health events potentially concerned.

Regarding regional cross-border issues, the assessment showed that most of the countries apply either national or international guidelines to report potential cross-border outbreaks. Concerning the implementation of a data platform exchange, half of the responding countries foresaw possible difficulties or restrictions to sharing information, particularly sharing of genuinely sensitive data.

Based on the needs and expectations identified in the survey, a pilot electronic EpiSouth Weekly Epi Bulletin (e-WEB) was elaborated and it is shared within the network since March 2008. Starting from summer 2008 a specific section of the bulletin is reporting events occurring in the EpiSouth area. In addition, direct exchange of information was initiated between the WP6 team and EpiSouth countries to add details or clarify information on health events occurring especially at cross-border level. The access-restricted area on the website is going to be used as platform to allow confidential and rapid exchange of information and alerts from and restricted to the partners in the EpiSouth network. Thematic notes on specific diseases or events were produced on an ad hoc basis, one of them in collaboration with WHO [5].

Vaccine-preventable diseases and migrants

A provisional survey has been carried out among the seven WP steering team countries to collect the following set of information: type and size of migrant populations in the countries; immunisation programmes; assessment of vaccination coverage; availability of programmes ensuring high vaccination coverage of migrants; surveillance of vaccine-preventable diseases (VPD) in migrants. The results were internally shared in February 2008 and have guided the expanded multi-country on-line assessment among all 26 countries of EpiSouth network.

In February 2008 a workshop was held in Sofia, organised by ECDC and WHO-EURO in collaboration with EpiSouth and the EU surveillance network for vaccine-preventable diseases (EUVAC.NET), with the aim of improving the immunisation coverage in hard-to-reach target groups, particularly Roma communities in eastern Europe, by providing participating countries with technical guidance on using communication and information in this respect.

Figure

Countries participating in the EpiSouth network as of December 2008 (n=26).

Special attention was paid to improving measles vaccination coverage in migrant population in these countries.

Cross-border emerging zoonoses

A dedicated questionnaire was developed for the selection of the priority zoonoses in the Episouth region.

The data, collected from 21 EpiSouth countries and analysed with specific criteria, have led to the formulation of the EpiSouth list of priority zoonotic diseases that includes: brucellosis, leishmaniasis, campylobacteriosis, rabies, West Nile virus infection [6]. The zoonoses selected cover at least two pathogens of public health importance for each participating country as well as a wide spectrum of diseases. These priority zoonoses are the basis for strengthening surveillance by describing the epidemiological situation in the area and for enhancing, among others, the collaboration and communication between human and veterinarian public health officials within each country and among countries of the EpiSouth network.

Training

The training modules programmes are based on results from a training needs assessment conducted in July 2007, through a questionnaire submitted to decision-makers/epidemiologists in all the countries of the network [7]. This assessment showed that participating institutions tend to be understaffed at central level and lack trained professionals. Furthermore, it revealed that in most of the responding countries, less than 25% of personnel in surveillance had received training in the past two years and that priority topics for training were quantitative risk assessment, modelling to understand dispersion of environmental risks and

Table

Countries, Organisations and institutions participating in the EpiSouth network as of December 2008.

Country or Organisation, location	Institution
ALBANIA - Tirana	Institute of Public Health
ALGERIA - Alger	National Institute of Public Health
BOSNIA and HERZEGOVINA - Sarajevo, Banja Luka, Mostar	Public Health Institute, Banja Luka, Republica Srpska Ministry of Health of Federation of Bosnia and Herzegovina, Mostar Ministry of Civil Affairs, Sarajevo
BULGARIA - Sofia	National Center of Infectious and Parasitic Diseases - NCIPD
CROATIA - Zagreb	Croatian National Institute of Public Health
CYPRUS - Nicosia	Ministry of Health
EGYPT - Cairo	Ministry of Health and Population
FORMER YUGOSLAV REPUBLIC OF MACEDONIA - Skopje	Institute for Health Protection and Clinic of Infectious Diseases
FRANCE - Saint Maurice Cedex	French Institute for Public Health Surveillance – InVS
GREECE - Athens	Hellenic Center for Diseases Control and Prevention – HCDCP
ISRAEL - Jerusalem	Israel Center for Disease Control Tel Hashomer and Ministry of Health Jerusalem
ITALY - Rome, Padua	Italian National Institute of Health – ISS, Rome Padua Teaching Hospital, Padua
JORDAN, Amman	Ministry of Health
KOSOVO (UNSCR 1244) - Pristina	National Institute of Public Health
LEBANON - Beirut	Ministry of Public Health
MALTA - Msida	Ministry of Social Policy
MONTENEGRO - Podgorica	Institute of Public Health
MOROCCO - Rabat	Ministry of Health and National Institute of Hygiene
PALESTINE - Ramallah	Ministry of Health
ROMANIA - Bucharest	Institute of Public Health - IPH/ISPB
SERBIA - Belgrade	Institute of Public Health of Serbia
SLOVENIA - Ljubljana	Institute for Public Health of the Republic of Slovenia - NIPH/IVZ-RS
SPAIN - Madrid	Health Institute Carlos III
SYRIA - Damascus	Ministry of Health
TUNISIA - Tunis	Ministry of Health
TURKEY - Ankara	Ministry of Health & Refik Saydam Hygiene Center
European Commission - Luxembourg	Directorate-General for Health and Consumer Protection (DG Sanco)
European Community agency - Stockholm	European Centre for Disease Prevention and Control (ECDC)
ITALY - Rome	Ministry for Work, Health and Social Policies
WHO - Lyon	World Health Organization Headquarters, Lyon office - WHO HQ/LYO
WHO - Copenhagen	World Health Organization Regional Office for Europe - WHO EURO
WHO - Cairo	World Health Organization Regional Office for Eastern Mediterranean - WHO EMRO

infectious diseases dynamics, epidemic intelligence and advanced data analysis.

So far, two training modules were conducted in September 2007 and June 2008, with the participation of 33 and 30 experts from 18 countries and 20 countries respectively, with 60% of participants from non-EU countries. Both training modules were anticipated by a workshop session were participants reported and shared experiences concerning the training topics.

The EpiSouth website and data dissemination

The EpiSouth website, launched in March 2007, contains a public portal devoted to the dissemination of information and results generated by EpiSouth and an access-restricted network working area to support the work of the project participants by enabling direct sharing and discussion of information [2]. Through the public website relevant guidelines, documents, and policies on topics of interest for the project as well as links to useful national and international organisations are made available. The official language of EpiSouth, and thus the website, is English. However, documents in French or Arabic, both languages spoken in more than one fourth of participating countries, are posted on the public web site without translation.

During the second year of activities (October 2007-September 2008), there were 9,079 unique visitors accounting for 14,895 visits on the public area of the website. Both the number of visitors and the number of visits have increased since the launch of the website (first year of activities: monthly average number of visitors and visits 173 and 399 respectively; second year of activities: 757 and 1,241). Furthermore, in 2008, the access-restricted network working area was accessed at least once by 64 (79%) of the 81 authorised users. A total of 150 documents were uploaded, a monthly average of 12.5 documents compared with 9.0 documents in the first year of activities.

In September 2007 the first issue of the EpiSouth electronic bulletin summarising the latest information presented in the website, was released and sent to 500 recipients. Further issues were published in January, May, July and November 2008, the latest of which was sent to 592 recipients in 51 countries, an increase of almost 20% in recipients compared to the first issue [8].

Conclusions

EpiSouth has been successfully positioned in the international context through a wide range of communication activities and networking at meetings and conferences. It has attracted many different countries in the Mediterranean region and the Balkans (26 countries participate) as well as distinguished international partners. The network has contributed to building mutual trust and understanding which are an important basis for creating stability and collaboration in case of a public health emergency. Some of the challenges that lie ahead are related to project timelines and targets and to the sustainability of the project beyond 2009. So far however, there has been a growing capacity to network among the EpiSouth countries. The progressive acquaintance with the networking tools made available via the EpiSouth website and the enthusiastic collaboration in the context of the WP steering teams are indicators for an increasing sense of ownership among participants. In this respect it is necessary to consider that this project is peculiar. It covers a geographical area, the Mediterranean Basin and the Balkans, which as a whole is neither addressed by any EU network nor by WHO, as it encompasses both EU and non-EU countries and countries belonging to three different WHO regional offices. In this framework, efforts need to be performed to critically define all activities with the aim of enhancing work done by other institutions by filling gaps and avoiding overlapping or duplication of work. The EU, ECDC and WHO participation in the project steering committee is actually helping this process.

The EpiSouth network is in line with the EU neighbourhood policy and the Euro-Mediterranean partnership which identifies networks as tools for cooperation and integration with neighbouring countries. Well beyond the duration of the EpiSouth project, EpiSouth could effectively act as a bridge among countries that are epidemiologically linked but jurisdictionally separated.

Aknowledgements

We acknowledge the contribution to the project development of M. Ciotti (ECDC), P. Nabeth (WHO-HQ/LYO), N. Emirouglu and D. Mercer (WHO-EURO), J. Jabbour and J. Majour (WHO-EMRO) who have actively participated in the project's meetings and steering committee meetings as members of the network and as observers of the steering committee. We are also grateful to Flavia Riccardo for her contribution to the drafting of this article.

The project receives funds from the EU Public Health Programme (EC-DG Sanco) and the Italian Ministry of Work, Health and Social Policies (through the EpiMed Project). In addition, the financial support of EC EuropeAid and DG Enlargement (through the TAIEX facility) has made the participation of non-EU Countries to the 1st and 2nd EpiSouth Project Meetings possible.

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This article was published on 5 February 2009.

Citation style for this article: Dente MG, Fabiani M, Gnesotto R, Putoto G, Montagna C, Simon-Soria F, Martin de Pando C, Barboza P, Ait-Belghiti F, Kojouharova M, Vladimirova N, Vorou R, Mellou K, Thinus G, Declich S, for the EpiSouth Network . EpiSouth: a network for communicable disease control in the Mediterranean region and the Balkans. Euro Surveill. 2009;14(5):pii=19113. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19113