

Rapid communications

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Rapid communications

OSELTAMIVIR ADHERENCE AND SIDE EFFECTS AMONG CHILDREN IN THREE LONDON SCHOOLS AFFECTED BY INFLUENZA A(H1N1)v, MAY 2009 – AN INTERNET-BASED CROSS-SECTIONAL SURVEY

A Kitching (Aileen.Kitchings@hpa.org.uk)^{1,2}, A Roche³, S Balasegaram⁴, R Heathcock⁵, H Maguire³

1. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

2. Health Protection Agency (HPA), London Region Epidemiology Unit, London, United Kingdom

3. Health Protection Agency, South West London Health Protection Unit (HPU), London, United Kingdom

4. Health Protection Agency, North East and North Central London HPU, London, United Kingdom

5. Health Protection Agency, South East London HPU, London, United Kingdom

This report describes the results of a cross-sectional anonymised online survey on adherence to, and side effects from oseltamivir when offered for prophylaxis, among pupils from one primary and two secondary schools with confirmed cases of influenza A(H1N1)v in London in April-May 2009. Of 103 respondents (response rate 40%), 95 were estimated to have been offered oseltamivir for prophylaxis, of whom 85 (89%) actually took any. Less than half (48%) of primary schoolchildren completed a full course, compared to three-quarters (76%) of secondary schoolchildren. More than half (53%) of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. Gastrointestinal symptoms were reported by 40% of children and 18% reported a mild neuropsychiatric side effect. The results confirmed anecdotal evidence of poor adherence, provided timely information with which to assist decision-making, and formed part of the body of growing evidence that contributed to policy changes to restrict widespread use of prophylaxis for school contacts of confirmed cases of influenza A(H1N1)v.

Background

During April-May 2009, a number of London schools were advised to close due to confirmed cases of influenza A(H1N1)v in schoolchildren and antiviral prophylaxis (oseltamivir, Tamiflu®; a neuraminidase inhibitor) was offered to close contacts in the school setting. Anecdotal evidence (from family doctors in London) was suggestive of non-compliance (because of side effects) particularly when it was offered to children and adolescents. There was an urgent need to understand and provide preliminary information on adherence to, and side effects from oseltamivir, to assist decisions about strategic direction and operational policy in relation to antiviral use in United Kingdom schools.

The main objectives were: to measure the degree of adherence to oseltamivir; to measure the extent of self-reported adverse drug reactions (ADRs) to oseltamivir; and to describe reported ADRs.

Methods

We conducted a cross-sectional anonymised online survey among pupils from one primary and two secondary schools in London

with confirmed influenza A(H1N1)v cases. The schools emailed a weblink to the questionnaire to parents, with a letter describing the study, seeking consent and participation. Parents/guardians were also offered the opportunity to complete the questionnaire with the child (e.g. for younger children).

As the main method of communication of each school with parents or guardians was via email, internet access (email use) was not a decisive criterion in selecting participants. The selection process varied depending on which classes the confirmed cases were in, which year groups had been offered prophylaxis, and on negotiation with school management regarding feasibility. In two schools (one primary and one secondary school) we selected all classes who were offered prophylaxis, i.e. all pupils in the primary school (age range 4-11 years; n=122), and all of one year group in the secondary school (age range 13-14 years; n=68). In the other secondary school, while the whole school was offered prophylaxis, the questionnaire was offered only to pupils in two classes in the year group with the highest attack rate, and pupils in two classes in a year group with no confirmed cases (age range 11-13 years; n=66).

The questionnaire included questions on student class and year group; whether they took any oseltamivir if offered it and for what duration; presence or absence of influenza-like symptoms before taking oseltamivir; other medication taken with oseltamivir; and symptoms after taking oseltamivir (including specific gastrointestinal and neuropsychiatric symptoms). The questionnaire included a section for parental comments.

As preliminary information was required quickly, the weblink to the questionnaire was emailed to parents/pupils on the morning of Thursday 14 May asking for completion by midnight that night. Data from the initial responses was downloaded on Friday 15 May, and a preliminary report produced. The survey closed at 09.00 on Monday 18 May.

Due to concerns raised by the schools regarding deductive disclosure (i.e. discerning of an individual respondent's identity and responses through the use of known characteristics of that individual), particularly where there were small numbers of cases in a class or school, pupils were not directly asked if they had been prescribed oseltamivir for treatment or for prophylaxis. As previously stated, questions were asked about the presence or absence of influenza-like symptoms, the duration of oseltamivir course taken, and the school year and class of the respondent. This helped to determine those given oseltamivir for prophylaxis. Children without symptoms could not be a case (as they would not meet the clinical criteria for testing) and therefore would have been offered oseltamivir for prophylaxis; those with influenza-like symptoms could be a confirmed case (and offered 5-day treatment course) or a discarded case (and offered 10-day prophylaxis course). Hence, no symptoms or course duration of 6-10 days would imply a course of prophylaxis (according to a tiered weight-based dosing regimen, see Table). In addition, as the specific classes of all cases were known, pupils in other classes could not have been cases.

Results

Response rate

The weblink was sent to 256 schoolchildren, with a final overall response rate of 40% (103/256); 35% (43/122) in the primary school, and 42% (28/66) and 47% (32/68) in the secondary schools respectively.

Adherence to oseltamivir when offered for prophylaxis

Ninety-five schoolchildren (41 in the primary, and 54 in the secondary schools) were estimated to have been offered oseltamivir for prophylaxis, of whom 85 (89%) actually took any. The ten children who took none of the prescribed course were all primary school pupils.

Two thirds (66%, 56/85) of those who took 'any oseltamivir' completed (or said they would complete) a full 10-day prophylaxis course. However, less than half (48%, 15/31) of primary schoolchildren completed a full course, compared to three-quarters (76%, 41/54) of secondary schoolchildren.

Adverse drug reactions (ADRs)

More than half (53%, 45/85) of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. The most frequently reported symptom overall was nausea (29%), followed by stomach pain/cramps (20%) and problems sleeping (12%).

Gastrointestinal side effects (defined as one or more of the following symptoms - feeling sick/nauseous, vomiting, diarrhoea, stomach pain/cramps) were reported by 40%, and almost one in five schoolchildren (18%) reported a neuropsychiatric side effect (one or more of the following symptoms - poor concentration/unable to think clearly, problems sleeping, feeling dazed/confused, bad dreams/nightmares, behaving strangely). A neuropsychiatric side effect was more commonly reported by secondary (20%) than primary (13%) schoolchildren (see Figure).

Parental comments

Comments showed that parents often made their own risk assessment as to the likely benefit of oseltamivir to their child. Despite oseltamivir (Tamiflu®) being recommended by healthcare professionals, parents often appeared sceptical of the need for medication, especially when the indication was to prevent onward transmission rather than give a specific benefit to the individual asymptomatic child. Many parents questioned the scientific basis of our advice, recognising that prophylaxis would not confer longer lasting immunity or protection. They also raised the possibility that

we may be doing more harm than good i.e. in relation to the 'risk' (potential side effects) from oseltamivir compared to the 'risk' from influenza A(H1N1)v. There were also comments on the need to have sufficient information about the type and nature of any potential side effects in order to enable parents to make informed decisions.

Discussion and conclusion

This study was undertaken in the containment phase of the response to influenza A(H1N1)v in the United Kingdom (UK). It provided preliminary information on adherence to, and side effects from oseltamivir in schools; and a useful snapshot of attitudes and behaviours regarding oseltamivir use.

Managing school incidents is always challenging, ensuring communications are appropriate and often managing high levels of anxiety. Containment through interventions at school level is hindered by the high level of mixing between children in schools (siblings in different years and/or different schools, facilities shared with other schools, children involved in complex inter-school networks due to shared after-school activities - formal and informal). Case identification, risk assessment, and organisation of mass

TABLE

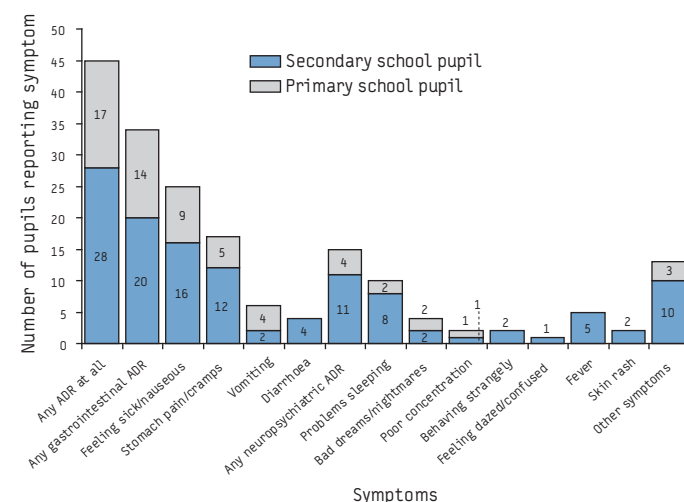
Tiered weight-based dosing regimen for 10-day course of oseltamivir prophylaxis in children

Age	Weight	Dose*
Children aged 1-13 years	<15 kg	30mg once daily
	15-23 kg	45mg once daily
	24-40 kg	60mg once daily
	> 40 kg	75mg once daily
Adolescents > 13 years	—	75mg once daily

*Adjust dose in renal failure: If creatinine clearance (CrCl) <30, reduce dose by 50%

FIGURE

Main symptoms reported by schoolchildren taking oseltamivir for prophylaxis in three London schools, May 2009 (n=85)



ADR = Adverse drug reaction

prophylaxis will frequently be outside the 48 hours quoted in the literature for the use of oseltamivir for prophylaxis [11]. In addition, little is known about how children adhere to such prolonged treatment (5-day course) and prophylaxis (10-day course).

A key component of influenza therapy and prophylaxis is the possibility for development of resistance. The magnitude and duration of neuraminidase inhibitor concentrations at the site of infection are thought to be an important factor in determining the likelihood of drug resistance arising in influenza viruses [2]. Low drug concentrations which only partly block viral replication and result in suboptimal virus suppression could enhance the risk by providing an environment for drug-resistant virus to emerge [2,3]. In our study, not all who started a course of oseltamivir for prophylaxis completed that course. While some reported discontinuing the course due to side effects, others reported doing so due to concerns about the effectiveness of oseltamivir and its necessity. Such incomplete adherence to the recommended course of oseltamivir could contribute to the development of drug-resistant virus.

The commonest adverse effect reported in the literature on oseltamivir is dose-related nausea [4-8], which occurs twice as frequently (as with placebo) when used as prophylaxis [9]. In controlled clinical trials, approximately 10% of patients reported nausea without vomiting, and an additional 10% experienced vomiting [5,10]. Insomnia has also been reported [5].

In recent years, there have been a number of post-marketing case reports (mainly from Japan) of neuropsychiatric events (such as delirium, hallucinations, confusion, abnormal behaviour leading to injury, convulsions, and encephalitis [4,11]), particularly in children younger than 16 years [4]. While a review of the available information on the safety of Tamiflu® in paediatric patients by the United States (US) Food and Drug Administration (FDA) suggested that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to Tamiflu® in that population, and a coincident period of intensive monitoring of adverse events [4], this prompted the addition of associated precautions to the US product label for oseltamivir [12]. A retrospective cohort study funded by Roche (who make Tamiflu®) noted a higher rate of episodic mood disorders among those aged 17 years and below receiving oseltamivir compared to those who received no antiviral treatment [12].

In our study, more than half of all schoolchildren taking prophylactic oseltamivir reported one or more side effects. The commonest symptoms reported were gastrointestinal, most frequently nausea, as in the published literature [4-8]. Although no serious neuropsychiatric events were described in our study (as have been described in Japanese case reports [4,11]), almost one in five respondents reported a neuropsychiatric symptom, most frequently difficulty sleeping, bad dreams/nightmares and poor concentration, which would impact on school and studying for those concerned. This may be of particular concern to exam-year students (and their parents).

The possibility of group psychological effects leading to an apparent cluster of symptoms has been suggested. The children are socially linked, and social contact may facilitate spread of “psychogenic” symptoms [13,14], but not typical “biological” symptoms. However, previous reports suggest such symptoms often remit with dispersion of the group [14]. The three schools in our study were closed for the period when children were taking oseltamivir prophylaxis.

Many of the children will have been told to take oseltamivir rather than seeking it out; this may also result in higher self-reported side effects. If it is rumoured that side effects are frequent, students may over-report through a desire to conform. However, while the possibility of “autosuggestion” through discussion of symptoms on Facebook was raised by a parent of one secondary school pupil, there was no increased reporting of similar symptoms from other students in the same class.

While the high level of reported side effects may have had a “psychogenic” component, e.g. children with high anxiety levels (due to the outbreak or due to other factors such as concomitant exams) might somatise and exhibit more nausea and vomiting, or have more difficulty sleeping, comments made by some parents regarding the nature of side effects experienced by their children (particularly in relation to observed disturbed sleep, altered behaviour, and being unusually tearful) are not likely to have been influenced by this. A telephone survey of 1,000 residents (over 18 years of age) of England, Scotland and Wales, carried out between 8 and 12 May just prior to our survey, explored public perceptions, anxiety and behaviour change in relation to the influenza A(H1N1)v outbreak [15]. Results from this survey suggest that anxiety among the general public about the outbreak at this time was low, with only 24% of participants reporting any anxiety and only 2% reporting high anxiety [15].

There are some striking similarities to the literature on adherence to antimicrobial prophylaxis (to prevent inhalational anthrax) among postal workers during the 2001 anthrax incidents in the United States [16,17]. In an environment characterised by uncertainty, and also by changing recommendations for screening or treating at-risk individuals as more was learned during the outbreak investigation, study participants in the anthrax incidents used multiple sources of information and support as they weighed the risk from anthrax against their perceptions of the advantages and disadvantages of antibiotics [16]. Anxiety [18], experiencing adverse events to prophylaxis [18], and following the advice of private physicians [16] who often contradicted public health recommendations regarding antibiotic prophylaxis, were all risk factors for discontinuing anthrax prophylaxis [16]. Changing recommendations were often perceived as conflicting information and advice [16].

In this study also, comments showed that parents often made their own risk assessment as to the likely benefit of oseltamivir to their child. It was suggested, in the comments in our survey, that some parents had on occasion received different advice from other healthcare professionals than that given by the Health Protection Agency. There was also a suggestion of a possible impact of changing recommendations, as in the anthrax studies [16].

A number of limitations apply to our study. The numbers are small. As the survey had to be done quickly, there was limited time for a full negotiation with schools regarding methodological issues, and limited time to give to pupils and their parents to complete the survey (initial responses were requested from pupils and their parents by the end of the same day they received the survey), which may have influenced the low response rate.

Regarding representativeness, the three schools surveyed were independent (non-state) schools, with a bias towards well educated parents from higher socio-economic groups, who are used to debate/negotiation (using information from multiple sources) before reaching an individual decision. They are thus not representative of the broader UK school population (but perhaps of pupils attending similar schools in London and elsewhere). The low

uptake of antivirals seen in our study was also reflected in another outbreak in an independent boarding school in South East England, where estimated uptake of antivirals among those for whom it was recommended was only 48% [19].

However, while there may be sources of bias in the methodology and results, we believe the comments made by parents are legitimate and provide insight into parental attitudes and concerns. As such they are very helpful as they reflect factors which may have an influence on implementation of national policy in future. The use of an online questionnaire format (with internet-aware parents and pupils) enabled this survey to be done quickly, providing timely information with which to assist decisions about operational policy in an evolving incident.

The study findings formed part of the body of growing evidence that contributed to policy change in the UK. Current UK advice is to limit antiviral prophylaxis in schools to the small number of contacts considered most at risk. Further studies are planned in other schools in London and nationally to provide further information about attitudes, including child and parental perception of risks associated with Influenza A(H1N1)v, as well as behaviours and practical implementation of antiviral prophylaxis in the current influenza A(H1N1)v outbreak. In addition, these studies will explore the possible role of psychological mechanisms in generating “adverse drug reactions”.

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Rapid communications

COMPLIANCE AND SIDE EFFECTS OF PROPHYLACTIC OSELTAMIVIR TREATMENT IN A SCHOOL IN SOUTH WEST ENGLAND

A Wallensten (anders.wallenstein@hpa.org.uk)^{1,2}, I Oliver^{2,3}, D Lewis², S Harrison^{4,5}

1. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

2. Health Protection Agency South West, Regional Epidemiology Unit, Stonehouse, United Kingdom

3. Bristol University, Department of Social Medicine, Bristol, United Kingdom

4. Torbay NHS Primary Care Trust, Torquay, United Kingdom

5. Health Protection Agency South West, South West Peninsula Health Protection Unit, Dartington, United Kingdom

School closure along with mass prophylactic oseltamivir treatment of pupils have been used in England and elsewhere to contain school outbreaks of influenza A(H1N1)v. We evaluated the protective effect, compliance with and side effects of oseltamivir chemoprophylactic treatment with a ten-day course of 1x 75mg given to 11-12-year-old pupils in one school year in a secondary school in South West England closed for ten days in response to a symptomatic laboratory-confirmed pupil. We distributed a questionnaire to pupils in the affected school year in class after the school had re-opened. Questions included symptoms of flu-like illness, compliance with chemoprophylaxis and side effects. All present on the day, 248 (93.2%) participated. Compliance with chemoprophylaxis was high, 77% took the full course, 91% took at least seven days. Fifty-one percent experienced symptoms such as feeling sick (31.2%), headaches (24.3%) and stomach ache (21.1%). Although some children were ill with flu-like symptoms, those tested did not have A(H1N1)v infection. Compliance with oseltamivir chemoprophylaxis was high, although likely side effects were common. The burden of side effects needs to be considered when deciding on mass oseltamivir chemoprophylaxis in children especially given that the symptoms of A(H1N1)v influenza are generally mild.

Introduction

Social distancing interventions such as the closing of schools has been considered as a means to slow down epidemic spread of a

novel influenza virus and models have been created which suggest that it could be effective [1,2]. In addition to school closure, the risk of transmission may be reduced further by giving prophylactic treatment with antivirals like oseltamivir that are active against influenza viruses. However, it is difficult to predict how effective these measures will be during a real outbreak and the evidence is limited [3,4]. Even though children stay away from school, they may still meet in large groups outside school and the effectiveness of antiviral prophylaxis is dependent on compliance with taking the medication. This may in turn be affected by many factors such as, the severity of the perceived threat of disease, the way the offer of treatment is presented and the anticipated and real side effects of the medication. The success of the interventions will also depend on the timing and the transmission properties of the specific virus strain. There have been many outbreaks in schools in different countries including the United States (US) [5] and the United Kingdom (UK) during the current outbreak of influenza A(H1N1)v. The initial policy in the UK has been to consider closing affected schools and to offer antiviral prophylaxis with oseltamivir [6].

On 29 April 2009 the Health Protection Agency South West received confirmation from the Health Protection Agency Centre for Infections that a child who attended a secondary comprehensive school in South West England had tested positive for A(H1N1)v after returning from Cancun in Mexico. The child had attended school while symptomatic on 22-24 April. The school was closed

TABLE 1

Sickness prevalence and absenteeism, school in South West England, May 2009 (n=248)

	Reported sickness (n=answered question)	Absent from school (data provided by school)	Number of pupils that met clinical criteria for a possible case out of those reporting sickness
Week before closure	23 (n=246)	13	5
During closure	37 (n=244)	N/A	11
Week after re-opening	20 (n=242)	11	10

Note: Some children are included in more than one week. Absent from school data calculated from attendance percentages provided by school.

and all other 266 pupils in the same school year as the affected child were offered prophylaxis with Tamiflu® 75mg once daily for 10 days starting on the day confirmation was received. Active surveillance was undertaken for all children in the same school year until seven days after the last exposure after which passive surveillance continued. Symptomatic school contacts were assessed according to the Health Protection Agency recommendations. Three school children and two teachers were identified as possible cases. They all tested negative for influenza A. One of these school children tested positive for parainfluenza virus. The school reopened on 11 May. No other cases associated with the school have been identified since then.

We undertook a survey of compliance with treatment and incidence of side effects and illness among the school children who had been given prophylactic treatment with the aim of informing future public health action in schools.

FIGURE 1

Number of days oseltamivir prophylaxis was taken among those children who did not comply with the full 10 day course, school in South West England, May 2009 (n=56)

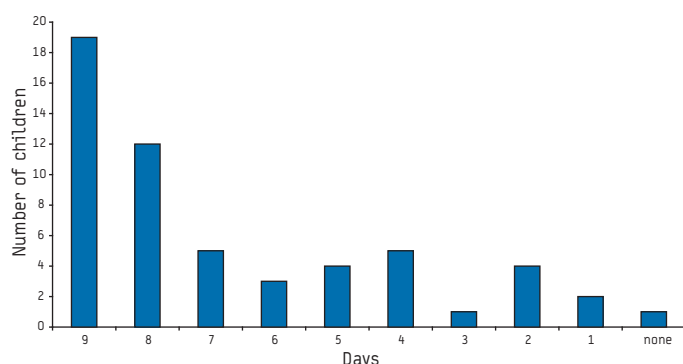
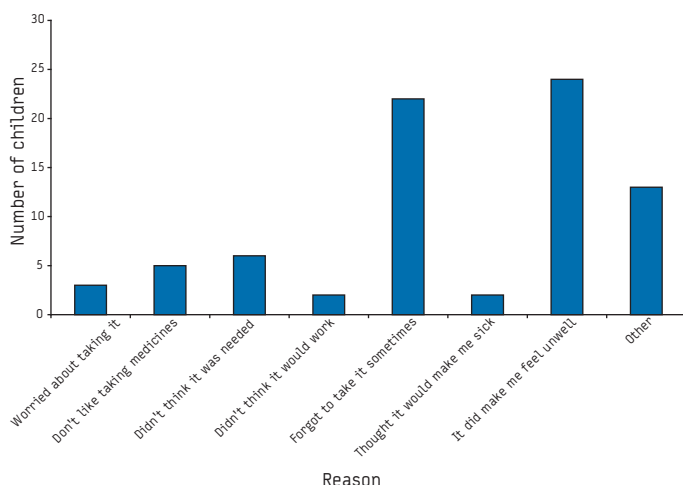


FIGURE 2

Reported reasons for non-compliance with oseltamivir prophylaxis, school in South West England, May 2009 (n=56)



Methods

An electronic anonymised questionnaire designed by the Health Protection Agency South West, with some additional questions incorporated by the school, was administered to children in the relevant year group at the school. This was undertaken on 22 May, in class under teacher supervision, using a web based questionnaire. Parents were informed about the questionnaire and given the opportunity to opt out prior to its administration.

Results

The questionnaire was offered to all year seven pupils present at school (248 children, 93.2% of all year seven pupils including 126 girls and 121 boys (one child did not provide info on sex)) on the 22 May. All children completed the questionnaire.

Sickness and absence from school

Information was obtained about the prevalence of flu-like symptoms among students in the week prior to school closure, during school closure and the week after re-opening (Table 1). Thirty-five children reported at least one flu-like symptom and of these 17 children reported symptoms that could be compatible with the Health Protection Agency's case definition of A(H1N1)v: a history of fever plus two or more other relevant symptoms and whose illness did not start before the index case [7].

The median length of illness among the children who reported symptoms and length of illness that could be compatible with the case definition for a suspected case of influenza A(H1N1)v was four days, range 2-11 days

The most commonly reported symptom was feeling feverish or having chills. Sore throat, cough, runny nose, headache and sneezing were also common. 12 of the 35 children (34.3%) reporting symptoms had a history of hay fever and 10 (28.6%) had asthma.

Compliance with prophylaxis

All children were offered the antiviral prophylaxis. Of the 246 pupils who answered this question, 190 (77.2%) reported that they had taken the full ten-day course, and 91.9% took the medication for at least seven days. Only one child did not take any doses (Figure 1). There was no difference in compliance by sex among those with known sex (n=245). Ninety-eight out of 125 girls (78%)

TABLE 2

Frequency of different side effects among children who took at least one Tamiflu® tablet, school in South West England, May 2009 (n=247)

Symptom	Number of pupils	Percentage (%)
Feeling sick	82	33.2%
Headache	60	24.3%
Tummy ache	52	21.1%
Feeling tired	42	17.0%
Vomiting	27	10.9%
Hard to concentrate	19	7.7%
Diarrhoea	17	6.9%
Skin rash	3	1.2%
Other	15	6.1%

completed the full course compared with 92 of the 120 boys (77%) who answered this question.

Of the 195 children who did not report any illness in the week before or during school closure, 156 (80%) completed the medication while of those 52 who reported having had any influenza-like symptom only 34 (65%) completed the course.

Of the 14 pupils who had disease compatible with the clinical case definition and reported being ill the week before or during school closure only 6 (43%) completed the full course.

In general, the reported reasons for non compliance were most commonly that the tablets made them feel unwell (n=24) or that they forgot to take them (n=22) (Figure 2). Six children reported more than one reason for not taking the tablets. The child who did not take any doses did not specify the reason.

Information on side effects

One hundred and twenty-six children (50.8%) reported that they felt unwell while taking oseltamivir and 125 (50.6%) reported at least one symptom compatible with side effects of oseltamivir therapy. The frequency of reported symptoms are given in Table 2. Many children reported more than one symptom.

There was little difference in compliance between those reporting possible side effects of oseltamivir medication and those who did not. Of the 125 children who reported possible side effects, 94 (75.2%) completed the course, compared with 95 completing the course among those 118 who did not report symptoms (80.5%).

School questions

The school included some questions on satisfaction with the overall management of the incident and homework undertaken during school closure. Of the 228 pupils who answered the question, 159 (69.7%) reported that they thought the swine flu incident had been handled well, 24 (10.5%) did not think so and 45 (19.7%) were undecided. 227 children answered questions on schoolwork during the school closure. Of those who answered, 105 (46.3%) reported not doing any schoolwork at all, 24 (10.6%) did some every day, 98 (43.2%) only did schoolwork on some days.

Discussion

We achieved a high participation rate in this survey. All children present at school on the day it was administered completed it. The fact that it was completed in school under supervision during school time was crucial to the high response. This was possible thanks to good working relations between the local Health Protection Agency, the local National Health Service (NHS) and the school, resulting in the high level of satisfaction with the way the swine flu incident was handled.

We believe that it is unlikely that the completion of the survey in school introduced bias and affected the way the pupils answered as the questionnaire was anonymised and, for example, the questions about the amount of homework undertaken while the school was closed appear to have been honestly answered.

The survey results showed that more children reported being ill in the week when the school was closed than the week before and after, and that 17 children reported symptoms that were compatible with the HPA case definition for being a possible A(H1N1)v case.

However, attendance rates provided by the school showed that attendance was almost identical in the week before school closure and the week after reopening (95.3% vs 95.5%) and the affected school year had the highest attendance rates for both weeks. Whether or not the higher numbers of ill pupils in the week when the school was closed signified spread of A(H1N1)v or were due to other reasons is difficult to assess. Those ill may not have been true cases as the symptomatology of A(H1N1)v is not very different from respiratory illness caused by other viruses. The testing done as part of the outbreak investigation found one case of parainfluenza virus and some children reported suffering from asthma and hay fever suggesting that at least some of the reported symptoms were not due to A(H1N1)v infection. The main limitation however is that not all children who reported feeling ill had laboratory tests for influenza. All who reported compatible symptoms during the period of active surveillance (within seven days of last exposure to the case) were tested, but after this period children were advised to contact their own general practitioner (GP) if they developed symptoms. Given that all had been encouraged to seek advice and that all were aware of the outbreak, it is likely that if they presented, they were not tested because their symptoms were mild. The questionnaire did not ask for details of severity. We can not rule out that the high compliance rates with oseltamivir medication may have resulted in the milder symptomatology and negative test results in infected pupils that were tested. A serological study would help to ascertain if there was further spread of disease during school closure.

More than half of those who took the medication reported at least one possible side effect including gastrointestinal symptoms, headaches and tiredness. The reported symptoms are in line with the recognised side effects of oseltamivir prophylaxis although higher in frequency. Information from the manufacturer suggests that when used for prevention purposes 18% of people may experience headaches, 8% tiredness and 1-3% gastrointestinal symptoms [8]. The higher frequencies of reported side effects may reflect a difference between our school population and the population used for the original studies on adverse drug effects in terms of age and other factors. The mean weight of 12-year-old British children is around 40 kg [9]. For pragmatic reasons, a dose of 75mg x1 was used. This dose will have been slightly higher than what is recommended for prevention by the manufacturer for any children under 40 kg, although not higher than the total daily treatment dose. Compliance was poorer among those who reported symptoms of influenza-like illness, but not among those who reported symptoms likely to have been side effects. It may be that the children experiencing influenza-like symptoms attributed them to the medication rather than disease.

To our knowledge this is the first evaluation of oseltamivir chemoprophylaxis in school children in an outbreak of A(H1N1)v and the results can therefore only be compared with oseltamivir chemoprophylaxis during influenza outbreaks with other variants. An Israeli study evaluating the use of oseltamivir prophylaxis during an avian influenza outbreak in a poultry farm reported similarly good compliance with medication, 87.6% in poultry workers, but reported side effects were much more rare, only 1.5% [10]. Our high prevalence of perceived side effects also contrasts the findings in a Cochrane review on the use of neuraminidase inhibitors for preventing and treating influenza in children. The only side effect that was considered more common than with placebo was vomiting [11].

The results of this study suggest that high compliance with oseltamivir prophylaxis can be achieved and that the policy of school closure may be helpful in containing outbreaks of influenza if implemented early. However, the study also shows that a high proportion of school children may experience side effects of oseltamivir medication. It is possible that in some instances children may have attributed symptoms that were due to other illnesses to the use of oseltamivir, however, this is unlikely to account for all the symptoms experienced during prophylaxis. Although the severity of the perceived side effects were not assessed it is likely that most of these symptoms were relatively mild as children continued to take the medication.

The apparent success in containing the school outbreak in this instance could be linked to the absence of community transmission of the virus at the time and the high compliance with chemotherapy in this incident. The reason why compliance was high, despite the high frequency of side effects, may reflect the fact that this was the first school affected by the outbreak in the UK. There was high media attention at the time and reports coming out of Mexico suggested that this novel strain could result in serious disease [12-14].

This study shows that the compliance with prophylactic oseltamivir treatment in the first school closed due to influenza A(H1N1)v in the UK was high and that perceived side effects were common. Side effects need to be taken into consideration alongside other concerns, like the risk of resistance development, when evaluating the policy of mass prophylactic therapy for novel strains of influenza especially when symptoms are generally mild.

Vivamus tempor mi quis quam. Fusce tempus, ante sed tincidunt ornare, nisi urna viverra enim, eget venenatis dui ante ut eros.

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Rapid communications

PANDEMIC INFLUENZA A(H1N1)v VIRUSES CURRENTLY CIRCULATING IN NEW ZEALAND ARE SENSITIVE TO OSELTAMIVIR

R J Hall (richard.hall@esr.cri.nz)¹, M P Peacey¹, J C Ralston¹, J Bocacao¹, M Ziki¹, W Gunn¹, A Quirk¹, Q S Huang¹

1. World Health Organization (WHO) National Influenza Centre, Institute of Environmental Science and Research (ESR) Ltd., National Centre for Biosecurity and Infectious Disease, Upper Hutt, New Zealand

New Zealand, like other southern hemisphere countries with a temperate climate, has been in the winter period with seasonal influenza activity. New Zealand has also experienced a dramatic increase in the number of cases of pandemic influenza A(H1N1)v virus. Early reports from the northern hemisphere at the beginning of the pandemic showed that the virus was sensitive to the antiviral drug oseltamivir. In this study we report that pandemic influenza A(H1N1)v viruses currently circulating in New Zealand are sensitive to oseltamivir, but seasonal influenza A(H1N1) viruses – the co-circulating predominant seasonal strain, is resistant to oseltamivir.

Since the declaration of a pandemic by the World Health Organisation on 12 June 2009, New Zealand has seen a surge in the number of cases of pandemic influenza A(H1N1)v. As of 16 July 2009, there have been 2,107 laboratory-confirmed cases in New Zealand and 10 deaths; the actual number of infections is certainly much higher. Like other southern hemisphere countries with a temperate climate, New Zealand entered the winter period with seasonal influenza activity. The national influenza surveillance system detected co-circulation of pandemic A(H1N1)v virus and seasonal influenza strains. Infection with pandemic A(H1N1)v has rapidly outnumbered seasonal influenza viruses within just a month [1].

The current recommended antiviral drug for treatment of pandemic A(H1N1)v is the neuraminidase inhibitor oseltamivir (Tamiflu®). Oseltamivir has been used in New Zealand to limit entry and spread of the virus since an initial incursion on 26 April 2009, for the treatment of quarantined cases and as prophylaxis for close contacts during the containment phase, and now mainly for the treatment of cases during the management phase.

Surveillance for oseltamivir-resistance in pandemic A(H1N1)v viruses currently present in New Zealand was undertaken using a fluorometric neuraminidase inhibition assay on cultured viral isolates (n = 20) from MDCK and MDCK-SIAT1 cells [2,3]. This assay determines neuraminidase activity using a fluorogenic substrate in the presence of increasing concentrations of oseltamivir. The 50% inhibitory concentration (IC₅₀) is the value at which neuraminidase activity is inhibited by 50%. All pandemic A(H1N1)v viruses were identified as being susceptible to oseltamivir, with IC₅₀ values ranging from 0.183 nM to 0.745 nM (Table). Sequencing of the neuraminidase gene of 10 viruses showed that none harboured

the H275Y mutation (N1 numbering) that is known to confer oseltamivir-resistance. Sequencing of the M2 (matrix) protein from four of the cultured isolates showed that these viruses contain the S31N mutation in the M2 protein that confers resistance to the adamantane class of anti-influenza drugs. This data are in agreement with previously published findings on antiviral drug resistance for pandemic A(H1N1)v viruses [4].

In conjunction, oseltamivir-resistance in the predominant seasonal influenza A(H1N1) that is co-circulating with pandemic A(H1N1)v in 2009 was determined. Seasonal A(H1N1) viruses (n = 24) showed 100% incidence of oseltamivir-resistance with IC₅₀ values ranging from 305 nM to 7912 nM (Table). This represents a 1,400-fold increase from the mean IC₅₀ = 0.94 nM detected for previous oseltamivir-sensitive viruses in New Zealand from before 2008 (unpublished data). Sequencing of the neuraminidase gene (n = 10), and restriction fragment length polymorphism analysis [5] (n = 28) in seasonal A(H1N1) viruses revealed that viruses contain the H275Y mutation (N1 numbering) and share a high level of sequence identity with other seasonal A(H1N1) oseltamivir-resistant viruses that were first detected in Norway in January 2008 [6].

These data show that the use of oseltamivir will be effective for the treatment of pandemic A(H1N1)v infection, but will not be effective for the treatment of seasonal A(H1N1). Surveillance for oseltamivir-resistance in pandemic A(H1N1)v is important given that oseltamivir is one of the few pharmacological interventions available before an effective pandemic vaccine becomes widely available. In addition, the presence of oseltamivir-resistant seasonal

TABLE

Sensitivity to oseltamivir (Tamiflu) of influenza viruses isolated in New Zealand from January to July 2009

Influenza type	Seasonal A(H1N1)	Pandemic A(H1N1)v
Number of viruses	25	20
Mean IC ₅₀ (nM)	1,399	0.372
IC ₅₀ standard deviation	1,990	0.145
Minimum IC ₅₀	305	0.183
Maximum IC ₅₀	7,912	0.745

A(H1N1) viruses co-circulating in the community demonstrates that influenza can be resistant to neuraminidase inhibitors without any apparent compromise in fitness or transmissibility. Close monitoring of antiviral susceptibility of pandemic A(H1N1)v is of increasing importance given the three recent isolated cases from Denmark, Japan and Hong Kong which are oseltamivir-resistant [7]. Furthermore, New Zealand faces a unique challenge where the oseltamivir-resistant seasonal A(H1N1) strain and oseltamivir-sensitive pandemic A(H1N1)v are co-circulating in the community, thus having the potential for re-assortment.

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Rapid communications

EPIDEMIOLOGIC ANALYSIS OF THE LABORATORY-CONFIRMED CASES OF INFLUENZA A(H1N1)v IN COLOMBIA

M Á Castro-Jiménez (1,2), J O Castillo-Pabón¹, G J Rey-Benito¹, P A Pulido-Domínguez¹, J Barbosa-Ramírez¹, D A Velandia-Rodríguez¹, E S Angulo-Martínez¹, on behalf of the Virology Group and the Communicable Diseases Surveillance Group¹

1. Instituto Nacional de Salud (National Institute of Health), Bogotá, Colombia

2. Grupo GUINDESS, Departamento de Salud Pública, Universidad Industrial de Santander, Bucaramanga, Colombia

From 2 May to 16 July 2009, a total of 183 laboratory-confirmed cases of influenza A(H1N1)v were reported in Colombia, 117 (63.9%) of these had travelled outside the country. Hospital admission was necessary in 26 (14.21%) cases and seven patients died (fatality-case ratio: 3.8%). The infection affected younger age-groups and the symptoms most frequently reported were cough, fever and sore throat. Our findings are consistent with recent reports from other countries.

Background

Since the first human cases of influenza A(H1N1)v were identified in Mexico and the United States, a rapid spread of this infection has been observed across the world [1,2]. On 11 June 2009, the World Health Organization declared influenza pandemic [3]. On 24 April 2009, the Colombian public health authorities implemented the National Plan for Prevention and Control of Pandemic Influenza and they reported the first cases in travellers including a group of athletes returning from a sporting event in Orlando, United States. This paper describes the main demographic and clinical characteristics of the first cases of influenza A(H1N1)v in Colombia reported during the period from 2 May to 16 July, 2009.

Methods

A suspected case was initially defined as a patient with acute respiratory symptoms and a history of travel to Mexico, United States or any other affected country within seven days before the onset of symptoms or a history of close contact with a confirmed or probable case. However, this definition has been updated due to the rapid spread of infection and the presence of laboratory-confirmed cases in patients who had not travelled outside the country. The current definition of suspected case includes history of travel in any affected country or acute respiratory illness requiring hospitalisation. A probable case is defined as an individual with an acute febrile respiratory illness who is positive for influenza A but classified as undetermined for the new virus by using a specific Real Time-PCR (rRT-PCR) from CDC (protocol reference: I-007-005). A confirmed case is defined as a patient with acute respiratory symptoms who tested positive for influenza A(H1N1)v using the specific rRT-PCR. In a few patients, the presence of the virus was confirmed by gene sequencing [4,5].

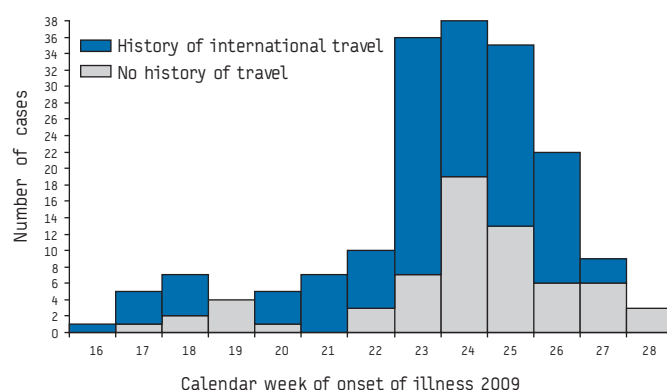
Demographic, clinical, and epidemiologic data of patients meeting these criteria for surveillance were sent to the National System of Public Health Surveillance (SIVIGILA) by public and private hospitals. This information was validated using photocopies of the

clinical records if they were available and face-to-face or telephone interviews of the patients (or their families) who were diagnosed as having the infection. Respiratory samples by throat swabs from patients with respiratory symptoms who had been defined as suspected cases of this virus were tested by rRT-PCR. In some of the patients who died, tissue samples (lung, trachea and bronchia) were also collected and analysed. Additionally, in a few patients, direct immunofluorescence (DIF) test has also been used in order to evaluate concomitant infection of other respiratory viruses such as seasonal influenza A or B virus, respiratory syncytial virus, parainfluenza virus (1, 2 and 3) and adenoviruses.

Categorical variables were presented as percentages and Pearson's or Fisher's exact tests were employed to compare groups. Quantitative variables were statistically tested for the normality of distribution by using the Shapiro-Wilk test. A non-normal quantitative variable was summarised as median and interquartile range (IQR) and two medians were compared using the Wilcoxon rank-sum test. P-values less than 0.05 were considered as statistically significant.

FIGURE 1

Number of laboratory-confirmed cases of influenza A(H1N1)v by week of onset and history of travel, Colombia, reported 2 May - 16 July 2009 (n=182*)



Note: The first patient was a woman returning from Mexico whose onset of symptoms was on 14 April (week 16).
*One patient (in week 23) was excluded because of unknown history of travel.

Results

On 2 May 2009, the first confirmed Colombian case of influenza A(H1N1)v was reported. By 16 July, 183 cases have been confirmed (including four cases confirmed by gene sequencing). Of these, 96 (52.4%) were men. The distribution of cases by week of onset of symptoms is shown in Figure 1. A history of travel outside the country was found in 117 (63.9%) patients, most of them had travelled to United States (n=71), Argentina (n=12), México (n=7) and Chile (n=7). In 65 (35.5%) confirmed cases there was no history of travel outside Colombia and for one patient this information was not available. The majority of cases were from the provinces of Bogotá, Valle, Antioquia and Atlántico.

The median age of cases was 27 years (IQR: 17-38). Cases ranged in age from 0 to 72 years and 80% of cases were aged less than 40 years. There were no differences in the median of age of cases by

sex (women: 28 years; IQR: 18-39; men: 25 years, IQR: 16.5-36.5; $p=0.24$). The distribution of laboratory-confirmed cases of influenza A(H1N1)v by age group and history of travel is shown in Figure 2.

The clinical manifestations are listed in the Table. Headache and shortness of breath were observed more frequently in women than in men, but these differences were not significant. The symptoms most frequently reported included fever, cough, sore throat, nasal discharge and headache (n=78; 84.8%).

Twenty six patients (14.2%) were admitted to hospital because of complications. Patients who experienced shortness of breath were more likely to be hospitalised than those without this symptom (28.4% and 2.1%, respectively; $p<0.001$) while patients who reported headache were less likely to be hospitalised ($p=0.031$). Seven patients who were hospitalised died, including five women. Only two of the fatal cases had underlying medical conditions, including obesity (n=1) and underweight (n=1). The case-fatality ratio was 3.8%.

The medical complications related to hospitalisation and deaths were acute respiratory failure, pneumonia, hypoxia, pneumothorax, acute tracheitis, tracheobronchitis and sepsis. No influenza A(H1N1)v-related deaths have been reported in pregnant women.

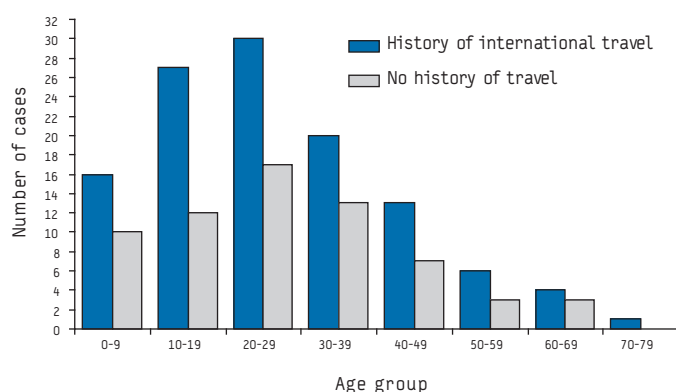
The analysis of the first eight cases who have also been tested for other respiratory viruses showed coinfection of influenza A(H1N1)v with parainfluenza type 1 and influenza B viruses in one patient, and with parainfluenza type 3 virus in another patient, while the remaining six were negative.

Discussion

Our results show that 35% of laboratory-confirmed cases had no history of travel outside the country which is an evidence of local transmission. Data also suggest that young people were affected more often than older people. It is very noticeable that the proportion of people younger than 40 years of age among the first 40 cases reported was the same as in the dataset analysed here (80%) but, in the rest of the cases, the infection has expanded the age range from 40-54 to 40-72 years.

FIGURE 2

Number of laboratory-confirmed cases of influenza A(H1N1)v by age group and history of travel, Colombia, reported 2 May - 16 July 2009 (n=182*)



*One patient who was nine years old was excluded because of unknown history of travel

TABLE

Distribution of laboratory-confirmed cases of influenza A(H1N1)v by sex and clinical manifestations, Colombia, reported May 2 - July 16 2009

Symptoms	Female		Male		Total		p-value
	Cases	%	Cases	%	Cases	%	
Fever (n=180)	75	87.2	78	82.9	153	85.0	0.427
Cough (n=181)	84	96.5	92	97.8	176	97.2	0.672*
Sore throat (n=177)	65	76.4	68	73.9	133	75.1	0.694
Headache (n=177)	67	78.8	61	66.3	128	72.3	0.063
Myalgia (n=177)	49	57.6	58	63.0	107	60.4	0.463
Shortness of breath (n=178)	44	51.1	37	40.2	81	45.5	0.175
Nasal discharge (n=176)	63	74.1	63	69.2	126	71.5	0.473
Malaise (n=173)	25	30.1	24	26.6	49	28.3	0.614
Conjunctivitis (n=176)	9	10.7	11	11.9	20	11.3	0.795
Diarrhea (n=180)	6	7.2	4	4.4	10	5.7	0.523*

Note: n indicates the number of cases who provided information on the particular symptom. Three children aged less than one year were discarded for calculating the proportion of symptoms related to pain and malaise.

*Fisher's test was used.

The age distribution of cases was similar to that observed by researchers in other countries [6,7]. Our number of confirmed cases is relatively low and we were unable to find any significant differences between sexes. Clinical manifestations reported by our patients were similar to those described by other authors [7,8].

The majority of fatal cases had no underlying medical conditions. Obesity has recently been considered as a possible risk factor for severe disease [9]. This condition was found in one of the fatal cases. Finally, we considered that one reason for the relatively high case-fatality ratio observed in this dataset is that we took into account only the laboratory-confirmed cases.

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Rapid communications

HOW THE MEDIA REPORTED THE FIRST DAYS OF THE PANDEMIC (H1N1) 2009: RESULTS OF EU-WIDE MEDIA ANALYSIS

B Duncan (ben.duncan@ecdc.europa.eu)¹

1. European Centre for Disease Prevention and Control, Stockholm, Sweden

The European Centre for Disease Prevention and Control (ECDC) commissioned an in-depth review of European media coverage of the opening days of the pandemic (H1N1) 2009. A total of 3,979 articles were collected from 31 European countries in the period 27 April until 3 May 2009. National and international public health authorities were by far the leading source of information on the new virus. They were identified as the main source of information in 75% of the articles analysed. 94% of the articles were either neutral, relaying factual information (70%), or expressing support for the authorities' handling of the situation (24%). These results seem to vindicate the communication strategy adopted by the public health authorities.

Introduction

One of the key principles of the World Health Organization's (WHO) Outbreak Communication Guidelines is that public health authorities need to "*announce early*" – i.e. engage with the media proactively as soon as they become aware of a major public health event, such as the emergence of a new virus [1]. The rationale for this advice is that, in the modern era of 24 hour media and instant international communication, news travel fast. No major development stays secret for long. Unless the authorities rapidly establish themselves as the main source of reliable information, the media will report rumours and speculation.

On Monday 27 April the European Centre for Disease Prevention and Control (ECDC) placed an order with its media monitoring contractor to collect and analyse articles in the European media relating to the new influenza virus that had just emerged in North America. The aim of the study was to capture a Europe-wide picture of how the media reported the opening days of the new pandemic. WHO, and national public health authorities, largely acted in accordance with the Outbreak Communication Guidelines. Therefore the study can also cast light on the effectiveness of the "announce early" strategy.

Methods

Articles were collected by the contractor's offices across Europe from the top three national newspapers and the website of the main broadcaster in each country. A total of 124 sources were monitored. The 31 countries surveyed were the 27 European Union (EU) Member States plus the four European Free Trade Association (EFTA) countries (Iceland, Liechtenstein, Norway and Switzerland).

TABLE 1

Articles related to pandemic (H1N1) 2009 published from 27 April to 3 May 2009, breakdown by country (n=3,979)

Country	Number of articles
United Kingdom	1,070
Norway	234
Spain	233
Switzerland	217
Denmark	209
Germany	206
Greece	165
Ireland	143
Italy	140
Austria	129
Netherlands	118
France	117
Luxembourg	105
Portugal	104
Sweden	97
Finland	91
Lithuania	81
Belgium	73
Czech Republic	70
Poland	63
Romania	55
Hungary	53
Iceland	51
Bulgaria	50
Malta	28
Cyprus	23
Estonia	14
Liechtenstein	14
Slovakia	13
Slovenia	7
Latvia	6
Total	3,979

TV and radio were not included in the survey due to the high cost of monitoring these media.

The search was performed for media articles that either mentioned the term “swine flu” or which were about the emergence of a new type of influenza in the United States and Mexico. The articles were to be analysed in terms of the main source of information being reported in the story: was it from international or national authorities; was it from academic experts or non-governmental organisations? In addition, if the source quoted was a national authority, was it the authority of the country of the media report or another country? Which spokespeople were being most widely quoted in the media?

FIGURE 1

Articles related to pandemic (H1N1) 2009 published in 31 European countries, by date of publication from 27 April to 3 May 2009 (n=3,979)

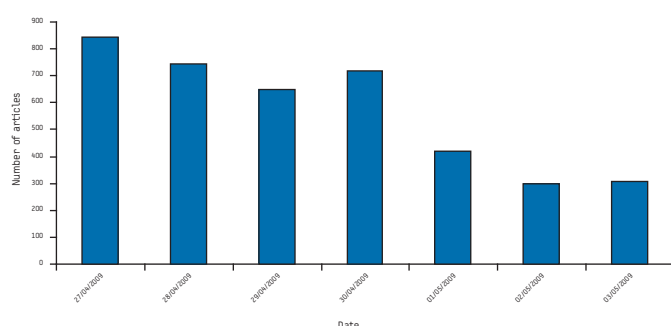
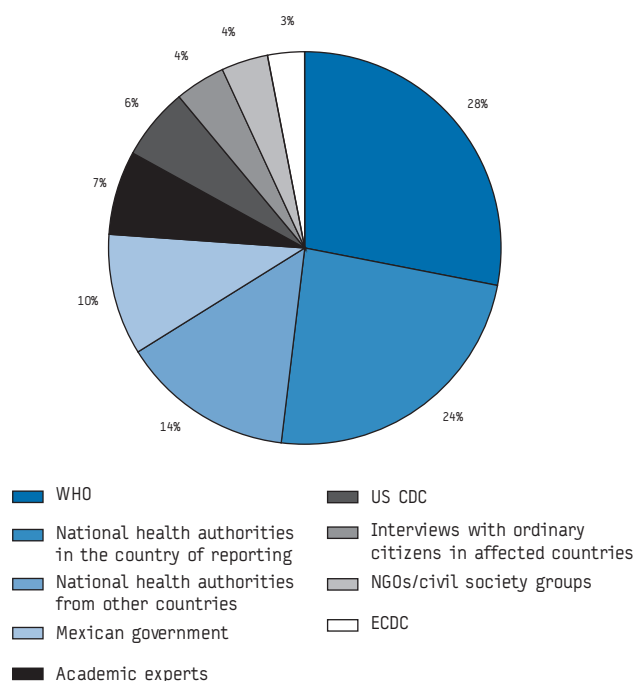


FIGURE 2

Institutions/organisations mentioned in relation to pandemic (H1N1) 2009, articles published in 31 European countries, 27 April to 3 May 2009



The messages featured in the story were also evaluated to see whether articles were supportive, critical or neutral concerning the actions of the authorities.

The contractor used was an international media monitoring company. The same company has been conducting Europe-wide monitoring and analysis of the impact of ECDC's media activities since 2006, so their analysts have some familiarity with infectious disease issues.

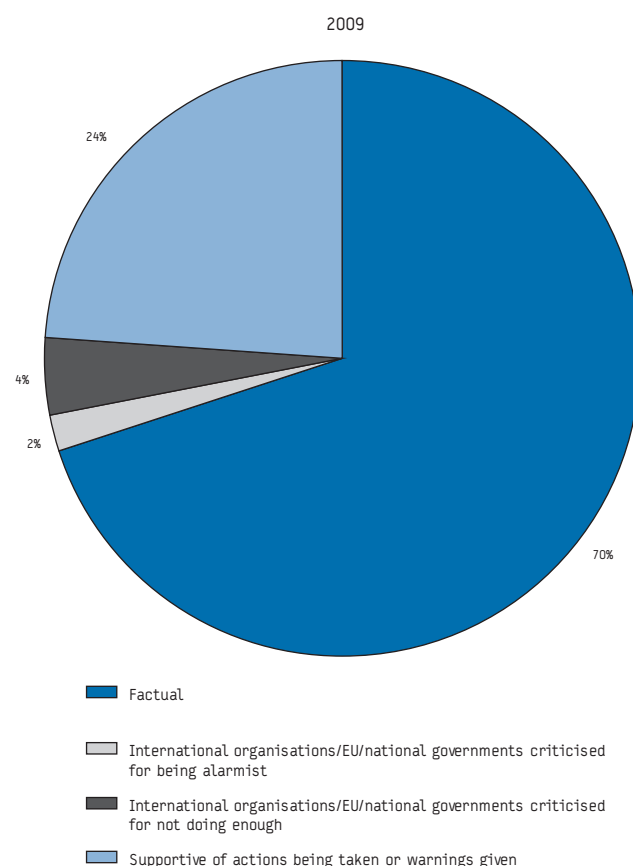
In early 2009 ECDC used this contractor to conduct an analysis of all health-related stories published in the media of 33 European countries (27 EU Member States plus Croatia, Former Yugoslav Republic of Macedonia, Iceland, Liechtenstein, Norway and Turkey) between 15 January and 15 February. Some of the data from this study is used for comparative purposes in this article.

Results

For the week 27 April – 3 May 2009, a total of 3,979 articles that mentioned the new influenza A(H1N1)v virus were identified (Table 1). Of these articles, 3,463 were from media in the EU 27 countries. To put this figure in perspective, an earlier survey of all health-related stories found a total of 2,824 articles in the EU 27 media during a period of one month (15 January – 15 February 2009).

FIGURE 3

Tone of coverage related to pandemic (H1N1) 2009, articles published in 31 European countries, 27 April to 3 May 2009



The highest number of articles (842) was recorded on 27 April, the day WHO raised the level of influenza pandemic alert to phase 4 (Figure 1). There was a smaller, though still large, peak of the number of media articles on 30 April (717 articles). This appears to be linked to WHO's announcement of pandemic alert phase 5 at 22:00 Central European Time on 29 April: many of the European media reports about this were published on 30 April. Media interest dropped considerably after 30 April.

National and international public health authorities were by far the leading source of information on the new virus. They were identified as the main source of information in 75% of the articles analysed (Figure 2). WHO was the main source of information in nearly a third of articles (28%).

70% of the articles surveyed were found to be factual accounts of the situation. A further 24% of the articles were supportive of the actions taken by the authorities (Figure 3).

During the week surveyed, the most widely quoted spokesperson in the European media was the Mexican Minister of Health, José Ángel Córdoba (Table).

Discussion

The dominance of public health authorities as sources of information (75% of articles) appears to vindicate the strategy of announcing early. The fact that 70% of articles were factual would seem to show that if the media are provided with authoritative and reliable information they will report it in a balanced way. And, indeed, they will give it greater prominence than rumours or speculation.

The low number of articles critical of the authorities (6%) seems to indicate that they succeeded in establishing a relationship of trust with the media. The fact that the critical articles were almost evenly split between commentators saying the authorities were not doing enough, and commentators saying they were doing too much may be an indication that they got the response about right.

It is interesting to note the high prominence of the Mexican and United States health authorities as sources of information in Europe during the period surveyed (10% and 6% of articles (Figure 2).

This emphasises the international nature of news relating to the pandemic. Comments made by spokespeople from WHO and by the European Commissioner for Health, Androulla Vassiliou, were also widely reported.

Many more articles were found in the United Kingdom than in other countries, although the number of sources analysed was equal. This is consistent with the findings of the earlier study of 15 January – 15 February which showed greater interest by the main United Kingdom national media in health-related stories than national media in other countries.

Conclusion

Proactive engagement with the media by international and national public health authorities resulted in factual, non-alarmist reporting of the first stages of the pandemic (H1N1) 2009.

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TABLE 2

Prominent spokespeople mentioned in articles on pandemic (H1N1) 2009, published in 31 European countries, 27 April to 3 May 2009

Spokesperson	Number of articles
José Ángel Córdoba, Minister of Health, Mexico	281
Keiji Fukuda, World Health Organization	152
Barack Obama, President of the United States	135
Androulla Vassiliou, European Union Commissioner for Health	133
Margaret Chan, Director-General of the World Health Organization	131
Nicola Sturgeon, Scottish Deputy First Minister and Cabinet Secretary for Health and Wellbeing	97
Richard Besser, United States Centers for Disease Control and Prevention	92
Trinidad Jiménez, Minister of Health and Social Policies of Spain	78
Alan Johnson, United Kingdom Secretary of State for Health	76
Felipe de Jesús Calderón Hinojosa, President of Mexico	65

Research articles

VALIDITY OF ROUTINE SURVEILLANCE DATA: A CASE STUDY ON SWEDISH NOTIFICATIONS OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

M Stenhem (mikael.stenheim@smi.se)^{1,2}, Å Örtqvist^{3,4}, H Ringberg⁵, L Larsson⁶, B Olsson-Liljequist⁷, S Hæggman⁷, M Kalin³, K Ekdahl⁸, the Swedish study group on MRSA epidemiology⁹

1. Department of Epidemiology, Swedish Institute for Infectious Disease Control, Karolinska Institutet, Solna, Sweden

2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden

3. Department of Medicine, Infectious Diseases Unit, Karolinska Institutet, Solna, Sweden

4. Department of Communicable Diseases Control and Prevention, Stockholm County Council, Stockholm, Sweden

5. Regional Center for Communicable Disease Control and Prevention, Skåne Region, Malmö, Sweden

6. Department of Hospital Hygiene, Sahlgrenska University Hospital, Göteborg, Sweden

7. Department of Bacteriology, Swedish Institute for Infectious Disease Control, Solna, Sweden

8. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

9. The members of the group are listed at the end of the article

Surveillance of communicable diseases is a public health corner stone. Routine notification data on communicable diseases are used as a basis for public health action as well as for policy making. While there are agreed standards for evaluating the performance of surveillance systems, it is rarely possible to analyse the validity of the data entered into these systems. In this study we compared data on all Swedish cases of methicillin-resistant *Staphylococcus aureus* (MRSA) routinely notified between 2000 and 2003 with follow-up information collected for each of these cases as part of a public health project. The variables *Reason for testing* (clinical sample, contact tracing, screening of risk group), *Clinical presentation* (disease, colonisation), *Transmission setting* (healthcare-acquired, community-acquired), *Country of acquisition* (Sweden, abroad) and *Risk-occupation* (yes, no) were analysed for sensitivity, positive predictive value and completeness of answers. The sensitivity varied between 23% and 83%, the positive predictive values were generally higher (55% to 97%), while missing answers varied from 11% to 59%. The proportion of community-acquired cases was markedly higher when excluding either cases of MRSA colonisation or cases found through public health-initiated activities (contact tracing or screening of risk groups). We conclude that the quality of routine surveillance data may be inadequate for in-depth epidemiological analyses. This should be taken into account when interpreting routine surveillance figures. Whether or not the case definition includes cases of MRSA colonisation may have a significant impact on population-wide estimates of MRSA occurrence.

Background

The overall aim of disease surveillance is to collect information for public health action. Disease control measures are costly both from a public health and from a healthcare perspective. For the healthcare system, diseases that spread nosocomially are particularly expensive. Disease control actions become more efficiently focused when based on valid surveillance data. However, it is rarely possible to assess the validity of notification

data [1,2], and to our knowledge such an assessment has never been reported for any methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance system. The epidemiology of diseases, such as MRSA, that can be transmitted both by symptomless carriers and by individuals with clinical infection is complex and their analysis requires a level of detail that can rarely be obtained from routine surveillance data. In contrast to most other countries [3-7], a comparatively lower occurrence of MRSA has hitherto been reported from the Netherlands and the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) [8]. During the late 1990s, Sweden experienced a large regional outbreak of healthcare-associated MRSA cases, which was brought under control by resolute efforts [8,12,13]. The experience from this outbreak forms the basis for the active strategy against MRSA currently employed in Sweden, with extensive screening of risk groups and contact tracing around known cases (symptomatic cases as well as asymptomatic carriers), aiming at preventing further transmission of MRSA.

The low-endemic MRSA-situation in Sweden and the allocation of resources in the period from 2000 to 2003 to map the epidemiology of MRSA in Sweden in detail, made it possible to collect in-depth data on every case of MRSA notified in the country during that period. This was done in addition to the collection of routine surveillance data. The resulting detailed and unique dataset made it possible to fulfil the two aims of the present study, i.e. to analyse the quality of the data supplied within the routine surveillance system and to show how case finding activities and inclusion or exclusion of MRSA carriers in the case definition influenced the estimated occurrence of MRSA in the population.

Materials and methods

Material

In Sweden, cases of clinical MRSA infection as well as asymptomatic carriage are notifiable by law to the Swedish Institute for Infectious Disease Control (SMI). The notifications are made

in parallel by the clinicians who diagnosed the patients and the laboratories that identified the pathogens. All MRSA notifications referring to the same individual are merged into one case record at the SMI, using a unique personal identification number. Thus, only new cases of MRSA are counted in the notification system. In this study, we included all cases notified in the years from 2000 to 2003. MRSA isolates from these cases were also sent to the SMI, where the bacteriological diagnosis was confirmed using PCR for the *nuc* and the *mecA* genes and epidemiological typing was performed using pulsed-field gel electrophoresis (PFGE).

A prospective, active follow-up on the epidemiological investigation of each notified case was performed in addition to the routine passive surveillance. Once the epidemiological investigation of a case was completed, updated data were collected by MRSA contact persons in each of the 21 counties in Sweden, and entered into a national MRSA study database [8]. These contact persons were infection control and public health officers involved in the local public health work on MRSA, and as such had full access to all information on the MRSA cases.

Definitions for case data evaluation

We analysed a subset of the variables used in the notification forms. The variable *Reason for testing* defined the reason for taking the first bacteriological sample from which MRSA was isolated from a case, categorised as: a) clinical sample (sample taken for diagnostic purposes), b) contact tracing (sample taken from a contact of a diagnosed MRSA case in order to identify a transmission chain), or c) screening of risk groups (sample taken from a patient with an increased risk of having MRSA, e.g. with healthcare contacts abroad or clinical risk factors such as breakages of the skin barrier or urinary catheter). *Clinical presentation* was defined as a) disease or b) colonisation. *Transmission setting* was

defined as a) healthcare-acquired (HA), b) community-acquired (CA) or c) unknown. To be considered as HA (including municipal care institutions such as nursing homes), a case would need to have been in contact with a healthcare setting where other MRSA cases with the same PFGE pattern had occurred. If MRSA cases had been in close contact with each other outside any healthcare setting (e.g. family members, child daycare, girl- or boyfriend, work colleagues, sport contacts) and the PFGE patterns did not contradict transmission, or if, in the absence of an epidemiological link, the PFGE pattern was known to occur in the community, the case was considered to be CA. When neither HA nor CA could be ruled out, the transmission setting was considered as unknown. For the purpose of this study, detailed information on *Country of acquisition* was broadly grouped as a) abroad (acquired outside Sweden), b) domestic (acquired in Sweden) or c) unknown. A notified case was considered as acquired abroad if the patient had been abroad within six months preceding diagnosis and had either an MRSA strain known to have occurred in that part of the world or a strain previously unknown in Sweden and a likely Swedish source could not be found. When neither domestic acquisition nor acquisition abroad could be ruled out, country of acquisition was entered as unknown. Work in healthcare institutions, municipal care facilities and day nurseries was considered a *Risk occupation* for acquisition of MRSA (answer categories a) yes or b) no).

Data analysis

We compared the information on the routine clinical notification form of each case, with the data in the study database. In case of several clinical notifications on the same case, the first one was used for the analysis. We calculated sensitivity (the percentage of information per variable in the validated study database that was supplied correctly on the clinical notification form) and positive predictive value (PPV, the percentage of information in the first

TABLE 1

Data from the notifications of MRSA cases in Sweden, 2000-2003 (n=1,733)

Variable	Variable category	Number of cases according to study database	Number of cases according to notifications	Percentage of cases where notification data were in accordance with study database (sensitivity)	Percentage of cases where notification data were contradictory to study database	Percentage of cases where notification data were missing	Positive predictive value of notification data
Risk occupation	Yes	140	198	83% (76-89)	–	17% (11-24)	59% (51-66)
Country of acquisition	Domestic	1,265	911	69% (66-72)	7% (6-9)	24% (21-26)	96% (94-97)
	Abroad	444	376	76% (72-80)	12% (9-16)	11% (8-15)	90% (87-93)
Clinical presentation	Disease	798	653	65% (62-68)	19% (16-22)	16% (13-19)	80% (76-83)
	Colonisation	915	757	66% (63-69)	14% (12-16)	20% (18-23)	79% (76-82)
Transmission setting	Community-acquired	561	355	41% (37-45)	40% (36-44)	19% (16-22)	65% (60-70)
	Healthcare-acquired	903	563	51% (48-54)	34% (31-37)	15% (13-18)	82% (79-85)
Reason for testing	Clinical sample	203	83	23% (17-29)	18% (13-24)	59% (52-66)	55% (44-66)
	Contact tracing	437	184	41% (36-46)	24% (20-29)	35% (30-39)	97% (94-99)
	Screening of risk groups	268	136	37% (25-37)	32% (27-38)	31% (25-37)	73% (65-80)

MRSA: methicillin-resistant *Staphylococcus aureus*.

All percentages are presented with 95% confidence intervals in parentheses.

Clinical notifications were missing for 176 cases. For the variable *Reason for testing* the analysis was restricted to the 915 cases of MRSA colonisation, since this information was required in the notification form only for those cases.

notification that was in accordance with the information in the study database), with exact 95% confidence intervals. We also analysed the completeness of information on the first clinical notification form. The statistical analyses were performed in Stata version 8.2.

Results

A total of 1,733 MRSA cases were reported during the study period. Table 1 provides detailed information on each of the variables in the first clinical notifications compared to the data in the study database. It shows the sensitivity, the completeness, and the predictive capacity of the information that public health officers received in the first clinical notification, i.e. of the information available for the initiation of public health actions.

Sensitivity of data in original notification

Of 140 cases with *Risk occupations* according to the study database, 83% were correctly identified as such in the clinical notification (Table 1). Sensitivity was also high for the variable *Country of acquisition*, with 76% of patients with acquisition abroad and 69% of patients with acquisition in Sweden correctly identified in the notification. The sensitivity was low for the variable *Reason for testing*, mainly due to missing information in the original notification forms (see below).

Missing information in original notifications

Missing information for a variable (Table 1) was either due to missing information for that question or due to the fact that the clinical notification form was missing altogether. The most complete variable category was *Country of acquisition* 'abroad': this information was lacking in only 11% of cases that had acquired MRSA abroad. Other categories for which the information given in the first notification to a large extent was present were: *Transmission setting* 'healthcare' (15% missing information), *Clinical presentation* 'disease' (16% missing information) and *Risk occupation* 'yes' (17% missing information). The most incomplete information was found for the variable *Reason for testing*.

Positive predictive value of the information in the original notification

The proportion of accurate information in the original notification (PPV) was highest for the variable *Country of acquisition*, with a PPV of 96% for domestic acquisition and of 90% for acquisition abroad (Table 1). Least predictive was the information on 'clinical sample' as *Reason for testing* with only 55% of the cases being verified. The *Transmission setting* 'community-acquired' also had a low PPV (65%).

Effect of case definition and method of case finding on estimated MRSA occurrence

In order to assess the impact of different case definitions on the distribution of reported MRSA cases, we analysed the variable *Transmission setting* within the variables *Clinical presentation* and *Reason for testing* according to the study database (Table 2). Overall, 32% of cases were CA and 52% HA. If only cases with MRSA-caused disease (and not carriage) had been reported, the proportion of CA and HA cases would have been 41% and 39%, respectively. A similar effect on the distribution of cases was seen when considering only cases diagnosed by cultures that had been taken on clinical indication: the proportion of HA cases decreased significantly (43%) and the proportion of CA cases increased (35%).

Of the 1,733 cases in the study, 45 were identified through the isolation of MRSA from blood cultures. Nine of these cases were CA (20%; 95% CI 9.6-35) and 25 were HA (56%; 95% CI 40-70). The proportion of CA cases among these was thus significantly lower than among all clinical MRSA cases (Table 2).

Discussion and conclusion

Far-reaching decisions on public health interventions and policy, as well as research studies, are based on routine surveillance data. Surveillance data are also used to compare the disease occurrence over time and between populations, e.g. when making international comparisons between countries. When using surveillance data for such purposes it is essential that the case definitions and measured variables are valid and comparable. The project with the national Swedish MRSA-database 2000-2003 provided us with a unique opportunity to analyse the validity of routine surveillance case-data in Sweden. There are accepted guidelines for the general evaluation of public health surveillance systems [14], but such guidelines do not cover the evaluation of the actual data entered into the system and their validity – presumably because high quality reference datasets rarely exist to compare routine surveillance data against. The validity of notification data has been investigated for other diagnoses such as tuberculosis and human immunodeficiency virus infections/acquired immunodeficiency syndrome (HIV/AIDS) [1,2], but we are not aware of any report on MRSA surveillance and data validity. The general sensitivity of the Swedish statutory surveillance system to detect patients diagnosed with a notifiable disease has recently been analysed and was found to be very high – well above 90% [15].

TABLE 2

MRSA cases notified in Sweden between 2000 and 2003, according to the validated case information, comparing the proportion of community- and healthcare-acquired cases within the variable categories of *Clinical presentation* and *Reason for testing* (n=1,733)

Variable	Variable category	Community acquired	Healthcare acquired
		Percentage of cases (95% CI)* Number of cases	
Clinical presentation	Disease (n=798)	41% (37–44) 326	39% (35–42) 308
	Colonization (n=915)	25% (23–28) 233	64% (60–67) 582
Reason for testing	Clinical sample	35% (32–38) 332	43% (40–46) 404
	Contact tracing (n=472)	43% (38–48) 203	51% (47–56) 243
	Screening of risk groups (n=302)	8% (5–12) 25	81% (76–85) 244
Total (n=1,733)		32% (30–35) 561	52% (50–54) 903

MRSA: methicillin-resistant *Staphylococcus aureus*
The total number of cases is given for each variable category. Where cell numbers do not add up to the total of rows or columns, the difference is due to cases that did not fall under any of the categories.

*Percentages per variable category with exact confidence intervals

Pathogens like MRSA, which are able to colonise individuals as well as cause clinical disease, are particularly challenging for a surveillance system. Patients with clinical disease are more likely to seek healthcare and consequently more likely to be diagnosed and notified. The probability that a colonised individual is diagnosed and notified depends on the vigour with which case finding activities (contact tracing and screening of risk groups) are carried out. The incidence figures presented for different populations would therefore not be comparable if the proportions of colonised individuals identified through case finding activities differed, unless information on clinical presentation and/or reason for testing is specified. It has earlier been noted that differences in reported MRSA incidences can be a result of differences in case finding methods in neighbouring health-districts in England [16] as well as between hospital and community populations in an area of Manhattan, New York [17]. Studies of MRSA occurrence often include MRSA carriers [4,8,9,16-18]. To make a comparison valid, investigators need to characterise the cases for the closely interrelated variables *Reason for testing* and *Clinical presentation* (disease or colonisation), but this information is often not presented [8,11,18]. Simor et al. suspected an association between screening and colonisation among older MRSA patients in the Canadian Nosocomial Surveillance Program (CNISP) [19], but our study is to our own knowledge the first one to systematically address the effect of case finding on the incidence estimates of MRSA within a complete population on a national level.

The problem presented by an unknown proportion of carriers can be avoided by restricting the case definition to clinical infections only, or even to blood isolates only. In our study, less than two thirds of cases with MRSA colonisation and of cases with MRSA disease were shown to be correctly classified with regards to Clinical presentation. These findings indicate that the MRSA incidence would have been severely biased, if only MRSA disease had been notifiable. If only blood isolates were reported, such misclassification would be less likely. The rationale behind such an approach is that cases found through blood isolates act as a marker for the overall burden of MRSA [20]. Restricting the case definition in this way might however result in a biased estimate of the MRSA occurrence in the general population, as several studies found an association of MRSA bacteraemia with healthcare exposure [21,22]. This is substantiated by our study, in which the proportion of CA cases was significantly lower among those identified by blood culture compared to all cases with MRSA disease. A further advantage of considering all available MRSA cases is the increased statistical power and precision that comes with a larger number of study subjects. In smaller populations, such as single hospitals, this approach may be advantageous even in a high-endemic country like the United Kingdom [23]. Moreover, both MRSA carriers and those infected with MRSA are possible sources for further transmission in the population. From a point of view of MRSA control, a surveillance system should therefore include carriers. Our view is that ideally, all cases of MRSA, colonisation or disease, should be accounted for (provided there is a systematic case finding for colonised cases), along with data on the clinical presentation and/or the reason for testing, so that the analysis and interpretation of the figures can be adjusted accordingly. Public health-initiated case finding is carried out in situations where transmission is known to be high. Not monitoring cases from these settings, which generate a considerable number of new cases, is to neglect an important part of MRSA occurrence. How the surveillance of MRSA and other organisms that both colonise and cause disease is organised also depends on a number of other factors, such as the scope and level

of the surveillance (e.g. hospital, district, regional or national), whether it is done in a high-endemic or low-endemic setting, and the available resources.

In conclusion, the present study clearly showed how differences in case definitions can influence the estimated number of MRSA cases categorised as healthcare-acquired or community-acquired, as well as the overall reported MRSA incidence. If carriers are included in the case definition, the overall occurrence and distribution of cases between the categories will also depend on the extent of the efforts to control MRSA through contact tracing and screening. We could identify considerable flaws in the quality of case data from routine notifications, e.g. misclassification of cases as colonisation or disease. Consequently, restricting the case definition to clinical cases only, would not be a reliable way to estimate the occurrence and distribution of MRSA. Surveillance systems and population-based epidemiologic studies thus need to specify the proportion of carriers and the reason for testing. This will also increase comparability of figures between countries or regions and between different points in time. Data validity cannot be taken for granted in a surveillance system, but needs to be ensured. For data that ultimately rely on information about transmission chains and results of epidemiological typing, the information should ideally be collected after the completion of the epidemiologic investigation of the cases.

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Research articles

EUROPEAN ANTIBIOTIC AWARENESS DAY, 2008 – THE FIRST EUROPE-WIDE PUBLIC INFORMATION CAMPAIGN ON PRUDENT ANTIBIOTIC USE: METHODS AND SURVEY OF ACTIVITIES IN PARTICIPATING COUNTRIES

S Earnshaw (sarah.earnshaw@ecdc.europa.eu)¹, D L Monnet¹, B Duncan¹, J O'Toole¹, K Ekdahl¹, H Goossens², the European Antibiotic Awareness Day Technical Advisory Committee³, the European Antibiotic Awareness Day Collaborative Group⁴

1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

2. Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

3. The Committee members are listed at the end of the article

4. The participants are listed at the end of the article

Antibiotic resistance is a major European and global public health problem and is, for a large part, driven by misuse of antibiotics. Hence, reducing unnecessary antibiotic use, particularly for the treatment of certain respiratory tract infections where they are not needed, is a public health priority. The success of national awareness campaigns to educate the public and primary care prescribers about appropriate antibiotic use in Belgium and France stimulated a European initiative coordinated by the European Centre for Disease Prevention and Control (ECDC), and named "European Antibiotic Awareness Day" (EAAD), to take place each year on 18 November. Specific campaign materials, including key messages, logos, slogans and a media toolkit, were developed and made available for use in European countries. The focus of the first EAAD campaign was about not taking antibiotics for viral infections such as colds and flu. A post-campaign survey was conducted in January 2009. Thirty-two European countries participated in the first EAAD, producing information materials and implementing activities to mark EAAD. Media coverage peaked on 18 and 19 November. At EU level, EAAD was launched at a scientific meeting in the European Parliament, Strasbourg. The event received EU political engagement through support from the EU Commissioner for Health, the Slovenian and French EU Presidencies, and Members of the European Parliament. Critical factors that led to the success of the first EAAD were good cooperation and process for building the campaign, strong political and stakeholder support and development of campaign materials based on scientific evidence. Countries indicated wide support for another EAAD in 2009. For this purpose, ECDC is developing several TV spots as well as a second set of EAAD campaign materials targeting primary care prescribers.

Introduction

Antibiotic resistance is a major European and global public health problem, and international efforts are necessary to counteract the selection and spread of resistance. There are substantial geographical differences in the proportions of resistance to various classes of antibiotics in Europe [1], the reasons being, on the one

hand, differences in selection pressure from antibiotic usage and, on the other hand, differences in infection control practices [2-4].

The largest volume of antibiotics for systemic use are prescribed to outpatients in primary care, with respiratory tract infections (RTIs) being the most common indication. In some European countries, patients suffering from a respiratory tract infection are able to obtain antibiotics over the counter, without a prescription. Hence, reducing unnecessary antibiotic use, particularly for treatment of certain RTIs is a clear public health priority.

In November 2001, the European Union (EU) Health Ministers adopted a Council Recommendation on the prudent use of antimicrobial agents in human medicine [5] which stated that EU Member States should inform the general public of the importance of prudent use of antimicrobial agents by, in particular, raising awareness of the problem of antimicrobial resistance and encouraging realistic public expectations for the prescription of antimicrobial agents. As a result, for example, in Belgium and France, national awareness campaigns to educate the public and primary care prescribers about appropriate outpatient antibiotic use have successfully resulted in a decrease in antibiotic prescriptions [6-9]. Additionally, in both countries, the savings from reductions in antibiotic expenses for the national insurance system as a result of the public campaign largely outweighed the cost of the public campaign itself [6-7,10]. Importantly, these campaigns have included strategies to address behavioural aspects of the problem (e.g. taking antibiotics for viral illnesses), targeting both the public and primary care prescribers [11]. The success of these campaigns stimulated a European initiative coordinated by the European Centre for Disease Prevention and Control (ECDC), and named "European Antibiotic Awareness Day" (EAAD), to take place each year on 18 November.

ECDC endeavoured throughout 2008 to provide countries with a core set of tools (including visuals, key messages, a dedicated website and campaign materials) for use at country level. We present here the various steps in preparation for the first EAAD that took place on 18 November 2008, together with a post-

campaign survey regarding the materials used, and the types of activities carried out at national level, as well as suggestions for future improvement, based on a questionnaire distributed to all the participating countries in January 2009.

Materials and methods

At the beginning of 2008, ECDC set up a Technical Advisory Committee for the EAAD, including representatives from Belgium (chair), France, Greece, Poland, Spain, Sweden and the United Kingdom, as well as the Standing Committee of European Doctors (CPME), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Commission's Directorate-General for Health and Consumers (DG SANCO) and Directorate-General for Research (DG RTD) and World Health Organization Regional Office for Europe (WHO/Europe). The Technical Advisory Committee's terms of reference are to discuss in detail the strategy for EAAD, including campaign objectives, target audience, key messages and evaluation methodology.

Preparation of EAAD was achieved through a collaboration amongst ECDC, the Technical Advisory Committee and the Network of National Antimicrobial Resistance (AMR) Focal Points, which is a network of country AMR experts designated by their national authorities to support ECDC in information exchange, coordination, and strategic and scientific inputs on AMR issues. In some cases, members of the Technical Advisory Committee representing Member States were also members of the National AMR Focal Points. ECDC therefore took care to regularly report the work of the Technical Advisory Committee to the National AMR Focal Points.

A good working partnership among all these institutions and Member State representatives was achieved through regular meetings, as well as exchange of information and ideas, in preparation of EAAD. ECDC hosted two meetings of the National AMR Focal Points (in September 2007 and March 2008), where draft campaign materials were proposed and discussed, and feedback was given. The second National AMR Focal Points meeting was held in cooperation with the Slovenian EU Presidency, and included a joint meeting with the Chief Medical Officers from all EU Member States. In addition, regular electronic updates were circulated to the group for comments. The Technical Advisory Committee also met twice at ECDC (in January 2008 and June 2008).

Gaining political support for the campaign was identified early on as an important success factor. Therefore, a lunch seminar for Members of the European Parliament was held in the European Parliament, Brussels, in October 2007, where the concept of an EAAD was publicly launched. In June 2008, ECDC Director Zsuzsanna Jakab also presented plans for EAAD to EU Health Ministers at the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO) under the EU Presidency of Slovenia.

In the development of the campaign, ECDC and its partners decided to apply a social marketing approach. Social marketing is a process based on the application of marketing principles and techniques to create, communicate and deliver social values designed to influence target audience behaviours so that both society and the target audience benefit, according to the ideological framework used [12]. Taking such an approach when developing key messages, logos and slogans of a campaign can provide a greater chance to achieve sustainable behaviour changes amongst

the target population. Through the gathering of consumer insights, a social marketer is able to formulate / offer messages in a way that promotes new behaviours that are more appealing and rewarding than old ones [13]. For the EAAD, such an approach was achieved through the identification of a desired behavioural change, the

FIGURE 1

Campaign themes with the European Antibiotic Awareness Day logo, hedgehog mascot visual and key messages

A) Logo



A European Health Initiative



B) First visual and key message



A European Health Initiative



C) Second visual and key message



A European Health Initiative



setting up of focus groups to test the key campaign messages and visuals, and deciding on the section of the general public that would be most receptive to these messages as the main target audience. In addition, a post-campaign survey was conducted to gather feedback on EAAD via a questionnaire distributed to participating countries.

ECDC agreed with its partners to initially target the general public with messages about rational antibiotic use, in particular about not taking antibiotics for viral infections such as colds and flu. Other target audiences, mainly primary care prescribers, will be addressed in subsequent years. As the general public is a very broad target group, it was agreed to focus the campaign on parents and carers of children aged one to six years, as this age group has the highest rates of antibiotic consumption [7,9].

The EAAD campaign materials were developed by ECDC in close consultation with the National AMR Focal Points and the Technical Advisory Committee, as well as ECDC's Advisory Forum. The challenge of creating key messages, logos, visuals and slogans meeting the needs of 32 different countries, with many varying cultures and languages, was great. The solution was to develop a generic pill and stethoscope logo and a name that would be so uncontroversial as to be accepted by all countries. For the visuals and slogans designed to illustrate key messages on rational antibiotic use, a catalogue was developed from which countries could select visuals and slogans and adapt them at national level. The visuals included a number of hedgehog and scarf logos animating the slogans "cold, flu, get well without antibiotics" and "cold, flu, take care, not antibiotics" (Figure 1). The hedgehog was chosen as a mascot for the campaign, as it illustrates a character that is recognised as a vulnerable animal that tries to protect itself, but is nonetheless all too often the victim of human carelessness, (rather like the antibiotics).

Focus groups were set up to pre-test the key messages, logos, visuals and slogans with members of the general public representative of the main target audience in seven countries (Belgium, France, Greece, Poland, Spain, Sweden and UK). Each focus group consisted of three to four unrelated parents of children aged one to six years, and one to two unrelated day care professionals or other trained child care professionals. The feedback received from the focus groups was presented at the second National AMR Focal Points meeting in March 2008 and taken into account in the refinement of the campaign materials.

With the exception of the name of the day, which was provided translated into all 25 official EU languages, final campaign materials (key messages, logos, visuals, slogans and template materials for posters and brochures) were provided in English and translated in participating countries. These final campaign materials were disseminated to the countries in June 2008, and in September 2008, ECDC launched a campaign website aimed at the general public, with links provided to national campaign websites. A few weeks before EAAD, a complete media toolkit was made available to the National AMR Focal Points and the ECDC network of communication contact points in Member States for use by countries in the launch of national campaigns for 18 November. The media toolkit included a summary of the most recently available European data on antibiotic resistance from the European Antimicrobial Resistance Surveillance System (EARSS) [1] and on antibiotic consumption from the European

Surveillance of Antimicrobial Consumption (ESAC) [2]. It also contained template press materials, such as a press release, presentation slides, photographs and audiovisual materials, as well as individual country antibiotic resistance and consumption data reports. Data on antibiotic consumption rates from ESAC and on antibiotic resistance rates from EARSS were analysed and compiled by ECDC experts into country reports showing the current situation in comparison to previous years. In addition, an EU report on the data was included in the media toolkit to illustrate the differences in rates of antibiotic consumption and antibiotic resistance across Europe.

A European workshop on public awareness campaigns on the prudent use of antibiotics was organised by the French EU Presidency on 6-7 November 2008 [14]. Finally, two special issues of *Eurosurveillance* [8, 15-24], published in November, were devoted to the issue of antibiotic resistance, including previous successful campaigns in some Member States.

In addition to the 27 EU Member States, two EEA/EFTA countries (Iceland and Norway), and three candidate countries (Croatia, the Former Yugoslav Republic of Macedonia and Turkey) participated in the campaign. The campaign also received support from ten partnering pan-European organisations: CPME, European Federation of Nurses (EFN), Pharmacist Group of EU (PGEU), European Patients' Federation (EPF), European Respiratory Society (ERS), European Older People's Platform (AGE), European Public Health Alliance (EPHA), European Association of Bio Industries (Europabio), European Federation of Pharmaceutical Industries and Associations (EFPIA) and European Generics Association (EGA).

An EU-level launch event, with the participation of the European Health Commissioner Androulla Vassiliou, the French EU Presidency and eight Members of the European Parliament, was held in the European Parliament, Strasbourg, while activities were coordinated at national level in the 32 countries.

With regard to monitoring the impact of EAAD, ECDC contracted a media monitoring company to track media articles published during the period from 14 November to 14 December 2008 that specifically mentioned "European Antibiotic Awareness Day". Furthermore, ECDC conducted a post-campaign survey to gather feedback on EAAD. ECDC distributed electronically in January 2009 a questionnaire (see Appendix) to the National AMR Focal Points in all 32 participating countries, aiming at identifying the countries' use of the campaign materials, the types of activities carried out at national level, and the lessons learned. The questionnaire included questions on national activities, government support, stakeholders, ECDC support and EAAD campaign materials, as well as a call for information on campaign evaluation that was planned or ongoing at national level. The National AMR Focal Points were asked to coordinate with other persons involved in the campaign at national level, and produce one completed questionnaire per country. We asked for all of the questionnaires to be returned to ECDC for evaluation within a two-week deadline that was met by all countries. Finally, a score measuring the uptake of the EAAD campaign in each country was calculated as the sum of national activities, campaign materials and use of EAAD materials; giving one point for each activity/material/use listed in the Table. Association of this score with having previously had a national campaign on prudent use of antibiotics was assessed with the independent-sample t-test for equality of means. Correlation with overall outpatient antibiotic

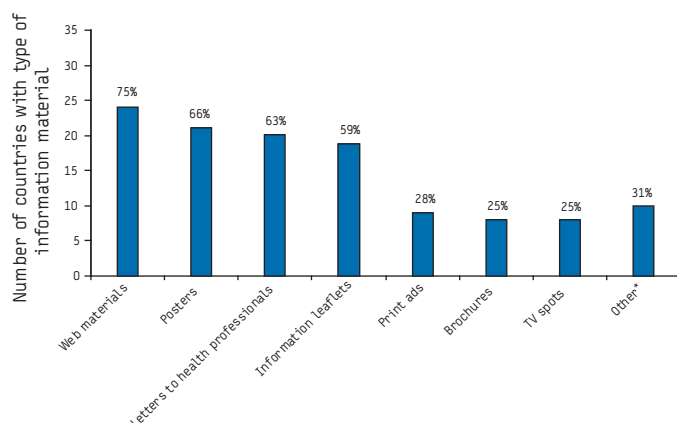
use (ATC J01) in Defined Daily Doses per 1,000 inhabitants and per day in 2006 [2] and with the percentage of penicillin-non susceptible *Streptococcus pneumoniae* from bloodstream and cerebrospinal fluid in 2007 [1] was assessed with the two-tailed Spearman's coefficient.

Results

National activities

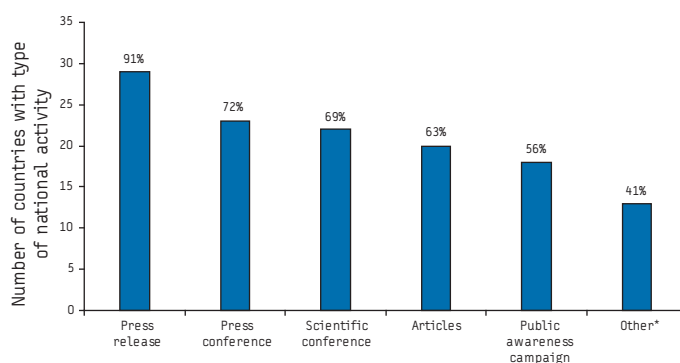
Thirty-two European countries participated in the first EAAD; all of these countries provided responses to ECDC's questionnaire. All countries produced information materials (summarised in Figure 2) and implemented at least two activities to mark the EAAD,

FIGURE 2
Information materials produced in participating countries for European Antibiotic Awareness Day in 2008



*Other: Treatment guidelines for primary care physicians (Greece), video spots in cinemas (Italy, Poland), radio spots (Luxembourg), emails to stakeholders (Spain), participation of antibiotic experts in TV game show (Bulgaria), DVD for professionals who care for children (France), and billboards outdoors (Ireland, Malta), on buses (Italy) and in the metro (Greece). Belgium reported that its awareness campaign included volunteer work to place swim armbands, the symbol of their campaign, on statues in some 30 cities across the country.

FIGURE 3
National activities on European Antibiotic Awareness Day in 2008)



*Other: TV and radio interviews, an exhibition and poster campaign, launch of a national antibiotic resistance campaign, publication of guidelines on appropriate use of antibiotics, launch of dedicated websites, an in-school competition and launch of a pilot information campaign at regional level.

with the exception of Turkey which organised a press conference (Table and Figure 3). Twenty countries reported the publication of scientific/technical articles and 18 countries had implemented public awareness campaigns. Other activities reported by different countries included television (TV) and radio interviews (Croatia, Lithuania, Belgium), an exhibition and posters campaign (Poland), the launch of a national AMR campaign (Germany), the publication of guidelines on the appropriate use of antibiotics and the launch of dedicated websites (Belgium), competitions in schools (England), a prevalence survey on antibiotic prescriptions in paediatric primary care (Slovenia) and the launch of pilot information campaigns at regional level (Greece).

Media coverage varied across the countries, with half reporting one to ten media articles, while 11 countries reported 11 to 50 articles. A survey of media articles published in the period from 14 November to 14 December 2008 tracked 355 news articles that specifically mentioned "European Antibiotic Awareness Day". Coverage peaked on 18 and 19 November, with 113 and 88 media articles, respectively. According to the survey, the regional press generated the highest number of EAAD references (146 articles), accounting for 42% of the overall coverage. The Internet and the national press followed with 103 (29%) and 67 (19%) items, respectively, ahead of the trade press with 23 (6%) items. The highest number of articles tracked originated in Finland (45 articles), the United Kingdom (41 articles) and Poland (37 articles), while the Polish, Belgian and Finnish media recorded the highest potential audience reach (2.4, 1.6 and 1.2 million persons, respectively).

Government support

Most respondents indicated that their governments supported the EAAD campaign politically and financially. Thus, 27 (84%) countries reported having political support from their governments, mainly through the endorsement of the national campaigns, the organisation of press events and scientific meetings. Twenty (63%) countries reported that senior Ministry of Health officials (minister, deputy minister, chief medical officer) attended events organised at national level. In most countries, the Ministry of Health was identified as the main contributor and supporter of the campaign.

In terms of financial support, 22 (69%) countries reported that the government allocated funds to the organisation of the EAAD at national level. Financial contributions were varied in terms of direct funding, ranging from organising a press conference and production of materials, to providing support of more than €500,000 for a national awareness campaign.

From the countries' responses it emerged that all country teams invested significant effort and time in the EAAD campaign, based on the human resources and budget available in their countries. Some of the responses pointed out that the teams involved in EAAD were handling this campaign in addition to their regular work.

Twenty respondents reported that they had already secured political support for the organisation of the EAAD in 2009. However, only a few of the respondents have a clear picture of the funding that will be available to the organisation of the Day in their respective countries in 2009.

Non-governmental stakeholders

A significant number of national campaigns (72%) had support from health professionals' organisations. In 53% of the national

campaigns, EAAD 2008 was supported by professional societies, and in 41% of the campaigns, pharmacies were identified as partners in the campaigns. Croatia and Cyprus reported financial

support by pharmaceutical companies. None of the countries reported support from patient groups.

TABLE

Summary of national activities, type of campaign materials, governmental and stakeholder support and use of materials for European Antibiotic Awareness Day in 32 European countries

Country	National activities						Campaign materials						Govt. support		Stakeholder support										Use of EAAD materials				Received the media toolkit in time					
	Awareness campaign	Scientific conference	Press conference	Press release	Articles	Other	Posters	Brochures	Leaflets	TV spot	Web materials	Print advertisements	Letters	Other	Political support	Financial support	Health professionals	Pharmacies	Patient groups	Non governmental organisations	Non- pharmaceutical companies	Pharmaceutical companies	Professional societies	Insurance system	Other	Logo	Sitting Hedgehog	Kicking Hedgehog		Scarf	Film			
Austria		•	•	•	•	•	•		•		•				•	•	•	•		•	•	•	•	•		•	•				•	•		
Belgium	•		•	•	•	•	•		•	•	•		•	•	•	•	•	•				•	•	•		•	•	•			•	•		
Bulgaria		•	•	•							•		•		•		•	•		•	•		•			•	•	•						
Cyprus	•	•	•	•			•		•		•	•			•	•	•	•				•				•	•	•				•		
Czech Republic		•	•	•	•		•		•		•	•	•		•								•	•	•		•					•		
Denmark	•	•		•	•				•		•					•		•							•	•	•	•				•		
Estonia	•	•	•	•	•						•		•	•	•		•						•			•		•				•	•	
Finland			•	•							•				•	•										•						•	•	
France	•			•	•								•		•								•	•	•									
Germany		•		•	•	•					•			•	•	•									•	•	•						•	
Greece	•		•	•	•	•	•	•	•	•				•		•	•						•			•						•	•	
Hungary	•	•	•	•			•		•		•		•		•	•										•	•	•						
Ireland	•	•	•	•			•		•		•	•		•	•	•	•	•							•	•		•					•	
Italy	•	•	•	•			•	•			•	•		•	•	•	•						•		•	•			•				•	
Latvia		•	•	•	•						•		•				•			•			•			•				•			•	
Lithuania				•	•	•	•		•		•		•	•	•	•	•			•						•	•							
Luxembourg	•		•	•	•	•	•		•	•	•	•	•	•	•	•	•	•		•				•	•	•							•	
Malta	•	•		•	•		•	•	•				•	•	•	•	•	•					•		•	•		•				•	•	
Netherlands	•		•	•	•		•	•			•		•		•	•	•	•		•	•			•		•								
Poland	•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•		•	•			•		•		•	•					
Portugal		•				•				•	•			•	•		•						•			•	•	•	•					•
Romania	•	•	•	•	•		•	•			•	•					•			•			•		•		•	•	•				•	
Slovakia		•	•	•					•		•		•			•	•							•	•	•	•	•	•				•	•
Slovenia			•	•	•		•		•	•			•	•	•	•	•	•					•	•		•	•	•	•	•			•	•
Spain		•	•	•	•	•	•		•		•		•	•	•	•	•	•							•	•	•	•	•	•				•
Sweden		•	•	•	•	•	•	•					•		•		•						•		•		•	•	•	•				
United Kingdom	•	•			•	•	•		•		•	•	•		•	•	•	•					•			•		•					•	
Iceland	•			•							•				•											•								•
Norway	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•										•							•	
Croatia	•	•	•	•		•	•		•				•			•	•	•				•	•			•	•	•					•	•
Former Yugoslav Republic of Macedonia		•	•	•			•	•							•	•	•			•						•		•					•	•
Turkey			•							•			•		•		•									•								

ECDC support

Thirty-one (97%) countries responded that they found ECDC's contribution helpful. Twenty-nine (91%) countries reported using the campaign logo. Furthermore, 18 (56%) countries used the "kicking hedgehog" visual and 17 (53%) used the "sitting hedgehog". Only four countries reported using the scarf. The visuals were used in a wide array of materials: posters (63%), web pages (53%), information leaflets (47%), letters (44%), advertisements (28%), brochures (19%) and TV spots (16%). Other ideas included a swimming armband (Belgium), drinks' coasters (England), presentation templates (Germany, Former Yugoslav Republic of Macedonia), an exhibition (Poland), billboards (Malta) and bookmarks distributed in schools (Cyprus). Twenty-one (66%) countries reported having received the media toolkit in time, and the use of materials was widespread among the different elements of the toolkit. The materials most used were the European and national data reports on antibiotic consumption and antibiotic resistance (50% and 38%, respectively), the template slides (34%), the press release (31%), the guidelines (22%), the photos and the template media invitation (19%). The audiovisual A-roll and B-roll (both narrated film and loosely edited film) were only used by three countries. Finally, 12 (38%) countries used the EAAD film.

The score measuring uptake of the first EAAD campaign in participating countries was not associated with either having previously had a national campaign on prudent use of antibiotics ($t=0.996$, $p>0.05$), or correlated with either overall outpatient antibiotic use ($r=0.164$, $p>0.05$) or the percentage of penicillin-non susceptible *S. pneumoniae* ($r=0.058$, $p>0.05$).

Suggestions for improvement

Many suggestions were received on ways to improve the EAAD website. Most countries ($n=21$, 66%) believe that more downloadable materials would be useful and multilingual versions of the website were requested by half of the respondents. A significant number ($n=13$, 40%) would also like to see more information on national campaigns available on the website. Many countries reported that evidence on the benefits of EAAD should be provided in order to secure support and funding of the future campaigns. Twenty-three (72%) countries stated that they would welcome a TV spot to illustrate the key messages of the campaign, e.g. "Cold? Flu? Take care, not antibiotics", developed by ECDC.

Discussion

The first EAAD was organised on 18 November 2008 in all 27 EU Member States, and five non-EU Member States. This event received EU political engagement through support from the EU Commissioner for Health, the Slovenian and French EU Presidencies, and Members of the European Parliament. The launch at EU level took place at a scientific meeting in the European Parliament, Strasbourg, gathering Members of the European Parliament, European Commission and Member State officials, representatives of professional organisations, leading European non-governmental organisations (NGOs) and media. Making use of the catalogue of materials developed for the campaign including key messages, visuals, logos, slogans, surveillance data, press and audiovisual materials, as well as a public website, the countries were able to develop a repertoire of approaches.

From the countries' responses to the survey questionnaire it is clear that all country teams invested significant effort and time into the EAAD campaign, based on the human resources

and budget available at national level and the resources provided by ECDC. The fact that all 27 EU Member States, Norway and Iceland, as well as the three EU candidate countries planned and implemented activities for 18 November 2008 was a key indicator that the campaign was broadly well adopted. Clearly, the cost of the campaign varied significantly from country to country, with a large campaign including TV spots costing considerably more than a lower impact campaign with a single press conference and press release. Interestingly, however, some countries were able to activate partnerships to secure support in kind for their public service campaigns, including the development by an advertising agency of TV spots for free in one country.

We believe that a number of critical factors led to the EAAD's wide implementation in its first year:

- Good cooperation and processes for building the campaign:
 - Planning well ahead – in this case, one and a half years – of the events
 - Early establishment of a group of enthusiastic and committed experts representing countries and stakeholder groups in the Technical Advisory Committee;
 - Working closely with a strong network of National AMR Focal Points meeting regularly to share information and best practice;
 - Briefing of national communication contact points prior to the campaign and sharing contact information of the National AMR Focal Points with their communications counterparts.
- Strong political and stakeholder support:
 - Strong political support and commitment at European and national level, secured at an early stage;
 - Initiation of a broad stakeholder contact programme to inform interest groups and invite contributions;
 - Good support from professional organisations
- Development of campaign materials based on a clear and rigorous approach:
 - Drafting key messages based on scientific evidence from published studies to provide a basis for the development of all campaign materials;
 - Building on existing success stories from a few countries;
 - Allowing countries to choose from a catalogue of campaign materials and take ownership of local look and feel of the campaign;
 - Pre-testing of campaign messages and visuals through focus groups.

Some aspects of a social marketing approach, which aims to achieve behavioural change considered to benefit society as a whole through the application of marketing principles and techniques, were difficult to develop at European level, given the great diversity in antibiotic consumption across Europe. In order that the campaign materials could be adapted and made appropriate for use at national level, it was agreed that the objectives of EAAD would be limited to the development of generic campaign materials, based on key messages rigorously backed up by data, that could be adapted for use by experts working at national level and delivered to the target audiences as part of national campaigns. This meant that at European level it was not possible to apply marketing principles and techniques, such as understanding the target market profile, the barriers to the desired behaviour in the target market and developing the marketing mix (product, price, place, promotion) in a way that would be fully consistent with a social marketing approach. Instead, the Technical Advisory Committee developed the

key messages and proposed campaign materials for EAAD, based on successes already achieved by existing national campaigns. For the future, it may be worthwhile to also take into account educational and/or psychological models upon which the campaign may be based.

A number of suggestions were received from the countries to improve the campaign in 2009. Of particular note, countries called for more campaign materials, more multi-lingual content in campaign materials, particularly the website, and earlier dissemination of template materials and toolkits. We also noted that whereas there was wide use of web-based materials, this was low for visual and audiovisual materials, such as high-resolution photographs and audiovisual A-roll and B-roll (only used in three countries) produced for the media toolkit to support selling in stories to TV news. For future campaigns, it will therefore be critical to develop and enrich the campaign website further, as well as develop more detailed guidance for using the visual and audiovisual campaign materials.

The lack of engagement of patient groups was identified as a missed opportunity. Although there are no groups dedicated to the problem of antibiotic resistance, it is a relevant issue for a number of disease-related (e.g. asthma, chronic obstructive pulmonary disease), as well as other health-focused NGOs. Therefore, engaging with patient group representatives at EU and national levels in order to disseminate EAAD messages and campaign materials should be addressed by future campaigns.

While organising public awareness activities in a multicultural and multilingual Europe will always remain a challenge, we believe that EAAD provides an example of how coordinated action may help to rapidly set up a European campaign. ECDC succeeded in creating a European scope and single identity for EAAD and provided support, while simultaneously allowing and enabling countries to adapt the materials to their own needs.

Reports have suggested an effect of public awareness activity on antibiotic use [6-9, 25], as well as an impact on antibiotic resistance [8,16]. However, these reports only used longitudinal surveillance data and lacked external controls. It is too early to determine if EAAD was successful in supporting behavioural change and a meaningful reduction in unnecessary antibiotic use, in particular for colds and flu, in the participating countries, and whether the campaign had an effect on antibiotic resistance. Evaluation of the EAAD campaign will require integration of longitudinal antibiotic consumption and resistance surveillance data, integrated with demographic and clinical data. Countries should be encouraged to plan prospective evaluation studies of the effect of their public awareness campaign. Several countries have already set up such evaluation studies, including the use of baseline data, which should allow assessment of the campaign's impact in these countries. Countries that did not participate in the EAAD or another campaign could be used as external controls.

Experience shows that public awareness campaigns must be repeated to achieve sustainability of behavioural change and coincide with quality assurance projects aimed at healthcare professionals. The post-EAAD survey indicated wide support from the countries for a 2009 campaign. Most countries agreed to focus on primary care prescribers and supported ECDC's intention to develop further materials and a TV spot for the campaign, and

to provide materials and website pages translated into all EU languages.

Responding to requests for campaign materials to be available earlier, ECDC will break down communications toolkits into materials that can be delivered earlier in the year and those which are dependent on data sources not available until shortly before 18 November. Because most countries demand a TV spot developed by ECDC, and because evidence from Belgium and France underscores the importance of TV advertising, ECDC will develop a European TV spot. ECDC will also further develop the campaign website and provide multi-lingual content in all EU languages. In 2009, ECDC will develop a set of campaign materials targeting primary care prescribers, including general practitioners, to complement the 2008 campaign materials targeting the general public. ECDC will continue to promote rational use of antibiotics, in particular through key messages about appropriate use of antibiotics, such as this first EAAD's message not to use antibiotics for colds and flu.

Appendix. European Antibiotic Awareness Day (EAAD) 2008 Evaluation Questionnaire (available in pdf): http://www.eurosurveillance.org/public/public_pdf/EAAD_2008_questionnaire.pdf

European Antibiotic Awareness Day Technical Advisory Committee:

H. Goossens (chairman, Belgium), J. Campos (Spain), O. Cars (Sweden), H. Giamarellou (Greece), W. Hryniewicz (Poland), C. McNulty (United Kingdom), B. Schlemmer (France), T. Verheij (Netherlands), A. de Warren (France), V. Houdry/B. Toussaint/M. Kokki (DG SANCO, European Commission), J. Bunikis/A. Lönnroth (DG RESEARCH, European Commission), K. de Jongheere/H. Kruse/V. Hafner (WHO/EURO), R. Norrby (ESCMID), L. Tiddens-Engwirda (CPME).

European Antibiotic Awareness Day Collaborative Group:

Austria - H. Mittermayer (Antimicrobial Resistance National Focal Point - AMR NFP), R. Strauss (AMR NFP), S. Metz-Gercek; Belgium - H. Goossens (AMR NFP), S. Coenen; Bulgaria - T. Kantardjiev (AMR NFP), M. Petrov; Croatia - A. Tambic Andrasevic (AMR NFP); Cyprus - D. Pieridou-Bagatzouni (AMR NFP); Czech Republic - V. Jindrak (AMR NFP); Denmark - N. Frimodt-Møller (AMR NFP), A.M. Hammerum; Estonia - K. Kutsar (AMR NFP); Finland - P. Huovinen (AMR NFP), A. Hakanen; France - J.-M. Azanowsky (AMR NFP), B. Schlemmer; Former Yugoslav Republic of Macedonia - G. Bosevska (AMR NFP); Germany - A. Barger (AMR NFP); Greece - H. Giamarellou, (AMR NFP), A. Antoniadou; Hungary - K. Böröcz (AMR NFP); Iceland - H. Briem (AMR NFP); Ireland - R. Cunney (AMR NFP); Italy - A. Pantosti (AMR NFP), P. Salcuni (AMR NFP); Latvia - S. Terela (AMR NFP), U. Dumpis; Lithuania - R. Valinteliene (AMR NFP); Luxembourg - E. Heisbourg (AMR NFP); Malta - M. Borg (AMR NFP), P. Zarb; Netherlands - J. Prins (AMR NFP), I.C. Gyssens, L. Wijgengangs; Norway, G.S. Simonsen (AMR NFP), G. Wøien, M. Lindbæk; Poland - W. Hryniewicz (AMR NFP), B. Mazinska, A. Olczak Pieńkowska; Portugal - A.C. Costa (AMR NFP), J. Melo Cristino; Romania - A. Băicuș (AMR NFP), A. Canton; Slovakia - L. Siegfried (AMR NFP), H. Hupkova; Slovenia - M. Cizman (AMR NFP); Spain - J. Campos (AMR NFP); Sweden - A. Tegnell (AMR NFP), I. Riesenfeld-Örn, O. Cars; Turkey - N. Çöplü (AMR NFP); United Kingdom - S. Wellsted (AMR NFP), C. McNulty.

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