

Rapid communications

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

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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)

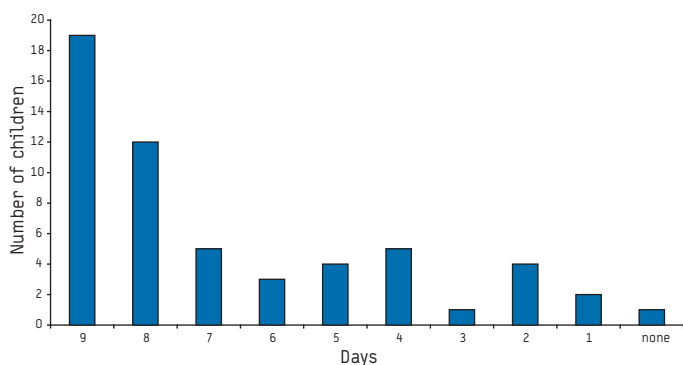
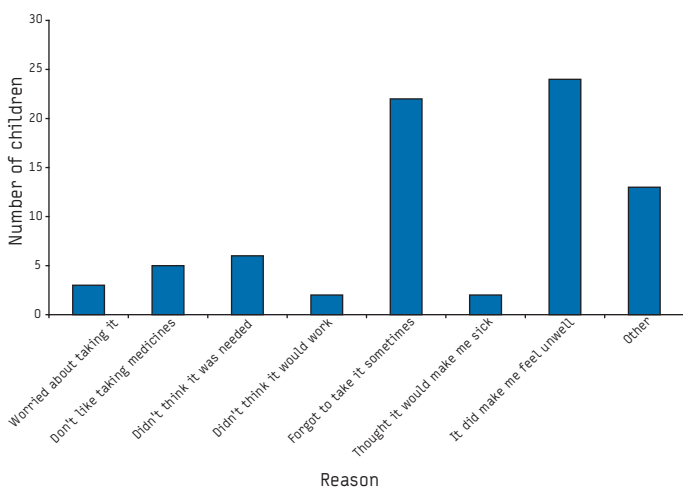


FIGURE 2
Reported reasons for non-compliance with oseltamivir prophylaxis, school in South West England, May 2009 (n=56)



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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