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

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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 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

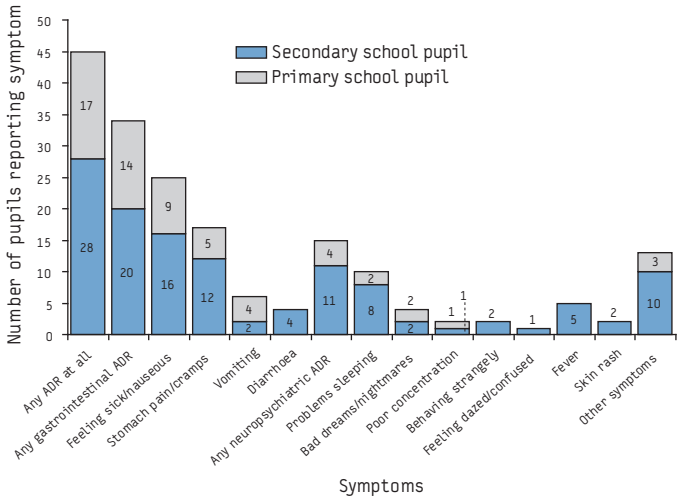
Tiered weight-based dosing regimen for 10-day course of oseltamivir prophylaxis in children

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 [1]. 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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