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Pandemic influenza A(H1N1) 2009 virus outbreak among boarding school pupils in Madagascar: compliance and adverse effects of prophylactic oseltamivir treatment

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Abstract

Introduction: In October 2009, the first outbreak of pandemic influenza A(H1N1) 2009 virus in Madagascar occurred at a school in Antananarivo. Among the first 12 cases, five were reported in boarding pupils at the school. The school closed 10 days into the outbreak. Mass oseltamivir prophylactic treatment was used to contain the outbreak. This study aimed to determine the transmission of infection among boarding school pupils and to evaluate the adverse effects of oseltamivir chemoprophylactic treatment and their impact on compliance.

Methodology: After conducting an initial investigation of the outbreak we administered a questionnaire to 132 boarders who were present after the school re-opened. Questions addressed symptoms of influenza-like illness, compliance with chemoprophylaxis, and adverse effects.

Results: Of 59 boarders, 20 (45.0%) had confirmed pandemic influenza A (H1N1) infection. Among the asymptomatic boarders, compliance with oseltamivir chemoprophylaxis was moderate: 56.2% took the full 10-day course, and 66.9% completed at least seven days. In contrast, among symptomatic boarders, only two did not take the full course of oseltamivir. Fifty percent of the boarders receiving oseltamivir experienced symptoms such as fatigue (38.7%), difficulty concentrating (22.6%) and headaches (19.4%). Bad compliance was not associated with adverse effects.

Conclusion: Since the symptoms of pandemic influenza A(H1N1) 2009 virus were generally mild, the burden of adverse effects must be considered when deciding on mass oseltamivir chemoprophylaxis among teenagers.

Key words: Influenza A(H1N1)v; boarders; Madagascar

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Introduction

Annually, there are one million deaths from influenza worldwide [1], and this incidence is higher during pandemics [2]. Since the first human cases of pandemic influenza A(H1N1) 2009 virus were identified in Mexico and the United States, the infection spread rapidly worldwide. The first cases of pandemic influenza A(H1N1) 2009 infection in Madagascar were confirmed in August 2009 and by October 2009, only 16 cases were reported, all occurring in patients who had travelled to affected areas (internal communication from the Malagasy National Influenza Center).

Since April 2009, different countries have had many outbreaks within schools [3-6]. In some countries [4, 6], closing affected schools and offering antiviral prophylaxis with oseltamivir were the initial policies. Other countries decided to close schools

when there was a marked increase in hospitalization or when school operations were affected by absenteeism [5]. Social distancing interventions such as school closure are among the initial means to control the epidemic spread of a novel influenza virus [7,8]. The risk of disease transmission may be further reduced by antiviral prophylactic treatments such as oseltamivir. However, limited evidence is available concerning the effectiveness of these measures during a real outbreak [9,10].

The objectives of this study were to determine the extent of pandemic influenza A(H1N1) 2009 virus transmission among boarding school pupils, and to evaluate the adverse effects of oseltamivir chemoprophylactic treatment and their impact on compliance to help establish appropriate management strategies for boarding schools.

Methodology

An outbreak of pandemic 2009 influenza infection occurred at a school in Antananarivo, Madagascar, with a population of 1,941 consisting of 314 staff members and 1,627 pupils including 143 boarders. The first cases of pandemic influenza A(H1N1) 2009 infection were identified on Friday, 8 October, one week before the school holidays. The outbreak subsequently spread among boarders during the weekend. Because school closure was not decided, the following control measures were implemented particularly for boarders: survey for active case finding, treatment for infected pupils, and prophylaxis for contacts. Subsequent cases were confirmed in all classes of the school. After informing parents by email and cellular phone (SMS), infected day pupils were evicted from the school. A recommendation previously had been given to parents to keep day pupils at home if ill.

Parents of boarders were informed about antiviral prophylaxis and were asked for written consent. Boarders were offered prophylaxis with oseltamivir 75 mg once daily for 10 days starting on 12 October. Confirmed cases of pandemic influenza A(H1N1) 2009 infection among boarders were isolated and offered treatment with oseltamivir 150 mg once daily for five days.

An assessment and collection point was established at the school to assess and offer treatment to all pupils, staff members, and families. The school was closed for holidays from 16 October until 1 November. A second survey was administered to evaluate the compliance of antiviral prophylaxis or treatment, and the adverse effects among boarders who had been given prophylaxis.

Case definition

During the outbreak period, swabs were taken mostly from boarders who had respiratory symptoms such as cough, shortness of breath, sore throat and nasal discharge with and without fever.

Pandemic influenza A(H1N1) 2009 infection was confirmed by real-time RT-PCR using a panel of oligonucleotide primers and dual labeled hydrolysis (Taqman®) probes (InfA, swInfA, swH1) according with The CDC Realtime RTPCR (rRTPCR) Protocol for Detection and Characterization of Swine Influenza[11].

Compliance and adverse effects study

An anonymous questionnaire designed by the Institut Pasteur from Madagascar was given to

boarders to obtain demographic, epidemiologic, and clinical information on illness and adverse effects after taking oseltamivir. This was completed in writing on 2 November under supervision. Parents were informed about the questionnaire and were free to opt out of its completion.

Statistical analysis

Data were entered using double data entry into a relational ACCESS database and checked for errors. Statistical analyses were performed with R software [12]. Descriptive analyses were comprised of frequency distributions and proportions for each variable category. Group comparisons were performed with Fisher's exact test for categorical variables and ANOVA for continuous variables. P values were two-sided.

Logistic regression analysis was performed to measure the association between compliance and each independent variable. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from β coefficients and their standard errors.

Ethical clearance

The study was approved by the Ministry of Health and the National Ethics Committee of Madagascar. Informed consent was obtained from at least one parent of each child.

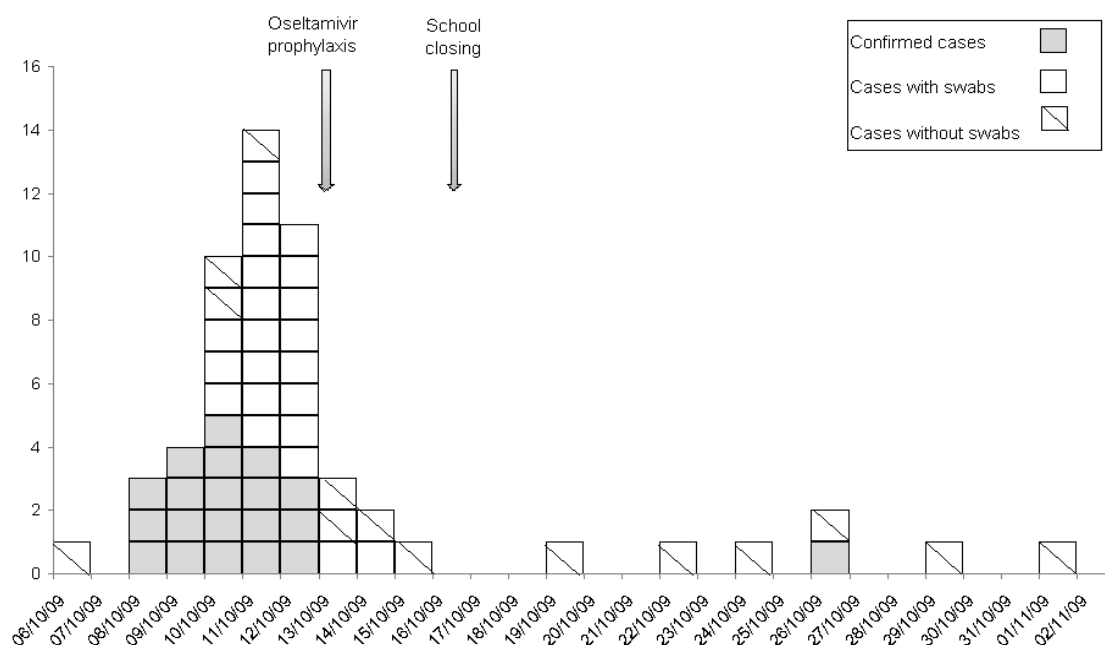
Results

Description of the outbreak among boarders

The pupil presenting on 6 October complained only of cough without fever or other symptoms. A history of fever plus two or more other relevant influenza-like illness (ILI) symptoms did not start in the boarders' population before the first confirmed case on 8 October.

Nasopharyngeal swabs were collected from three boarders who visited the school sickroom on 8 October complaining of ILI symptoms. Laboratory analyses confirmed pandemic influenza A(H1N1) 2009 infection. Other pupils in the same school but from different classes also tested positive for pandemic influenza A(H1N1) 2009 infection on the same day.

Between 6 October and 2 November, there were 59 cases with at least one influenza-like symptom among the 132 boarders (Figure1). Nasopharyngeal swabs were taken from 42 symptomatic cases (71.2%) during the outbreak while of the rest of the 17 cases, six were no longer symptomatic at the time the school was opened, one was symptomatic before

Figure 1. Numbers of symptomatic cases on a day-by-day basis

the outbreak was recognized, seven did not visit the school infirmary, and three had developed the illness at an unknown date. Of 42 symptomatic cases, pandemic influenza A(H1N1) 2009 infection was confirmed in 20 cases (47.6%).

Clinical epidemiology

Information on the prevalence of ILI symptoms among boarders was obtained the week before school closure and during the holidays. Boarders with clinical or confirmed pandemic influenza A(H1N1) 2009 infection were notified during sampling and other pupils were notified during retrospective interviews. The distribution of symptoms among confirmed and clinical cases is shown in Table 1. Confirmed cases showed a distribution of ILI

symptoms such as cough (85.0%), sore throat (70.0%), and nasal discharge (70.0%). There were no hospitalized cases. Information on the duration of symptoms was not available.

Compliance with prophylaxis

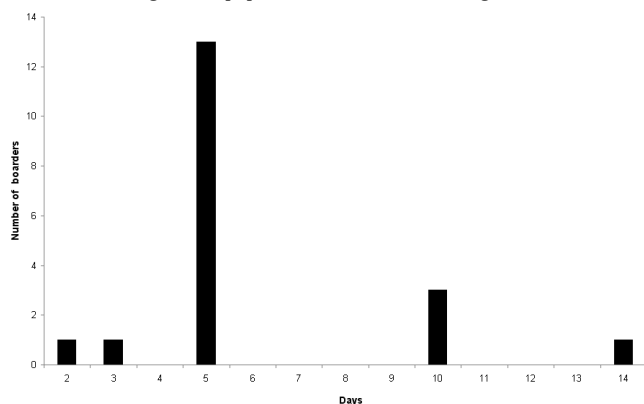
The questionnaire was given to all 132 (92%) boarders present at school on 2 November (71 girls and 61 boys mean age 16.9 years). All boarders completed the questionnaire. All confirmed cases were offered antiviral treatment and other boarders were offered antiviral prophylaxis.

Among the 20 boarders who were pandemic influenza A(H1N1) 2009 positive, only two (10.0%) did not take the full course of oseltamivir treatment (Figure 2) while four took a prolonged course (> 5

Table 1. Clinical manifestations of symptomatic patients

	H1N1v Positive		H1N1v Negative		Cases with ILI (Without lab confirmation)		P-value
	(1)	(%)	(2)	(%)	(3)	(%)	
	n=20		n=22		n=17		
Fever	15	(75.0)	12	(54.5)	2	(11,8)	0.07
Cough	17	(85.0)	8	(36.4)	11	(64,7)	0.82
Sore throat*	14	(70.0)	6	(27.3)	7	(41,2)	0.71
Headache	18	(90.0)	6	(27.3)	10	(58,8)	0.08
Myalgia	11	(55.0)	6	(27.3)	8	(47,1)	0.91
Shortness of breath	3	(15.0)	3	(13.6)	3	(17,6)	0.62
Nasal discharge	14	(70.0)	2	(9.1)	5	(29,4)	0.15
Diarrhea	1	(5.0)	1	(4.5)	4	(23,5)	0.81

*All patients with sore throat also had cough.

Figure 2. Duration of oseltamivir treatment among confirmed cases (n = 20) of pandemic A (H1N1) 2009 infection among a population of boarding school pupils in Antananarivo, Madagascar.

days) according to associated risk factors (*e.g.* asthma).

Of the 112 contacts or negative cases, eight (7.1%) did not take oseltamivir prophylaxis, while 75 (66.9%) took the medication for at least one week and of them, 63 (56.2%) reported that they had taken the full ten-day course (Figure 3).

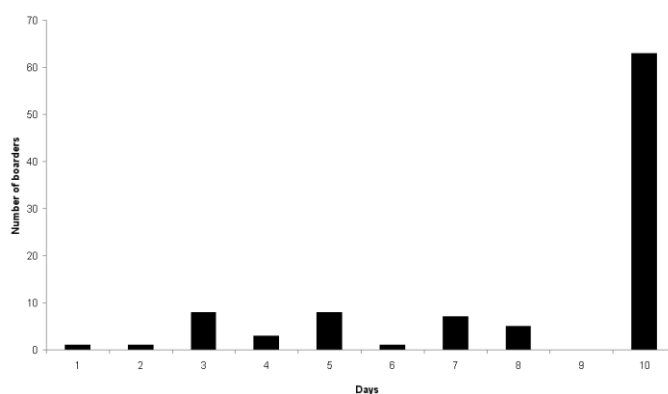
Among contacts, 38 out of 59 girls (64.4%) completed the full course compared with 23 of the 43 boys (53.4%). These differences in compliance according to sex were not significantly different (n = 102; P = 0.2). The course of treatment was completed by 45 (61.6%) of the 73 boarders who did not report any illness in the weeks before or during school closure, and 18 (46.1%) of the 39 boarders who reported any influenza-like symptom (between group P = 0.11).

As shown in Figure 4, the most commonly reported reasons for non-compliance with oseltamivir treatment were as follows: forgetting to take medication (n = 22) and not feeling sick (n = 15). Fifteen boarders reported more than one reason for not taking the tablets. Of the eight children who did not take any doses, three did not feel sick, two were worried about taking it, one did not like taking the medicine, and two did not specify any reason for non-compliance.

Adverse effects of treatment

Of the 124 children who took at least one oseltamivir tablet, 63 (50.8%) reported at least one symptom associated with adverse effects of oseltamivir therapy, and 46 (37.1%) reported more than one symptom. The frequency of reported symptoms is given in Table 2.

Of the 63 children reporting possible adverse effects, 41 (65.1%) completed the course, compared

Figure 3. Duration of oseltamivir prophylaxis among boarding school pupils in Antananarivo, Madagascar

with 35 of the 50 children (70 %) who did not report symptoms (between group P = 0.6). Nineteen children did not answer this question.

Having at least one adverse effect was not associated with bad compliance (OR = 1.03; 95% CI: [0.4-2.5]). No symptom described as an adverse effect was associated with compliance: headache (OR = 1.4; 95% CI: [0.5-4.2]), fatigue (OR = 1.2; 95% CI: [0.5-2.9]), difficulty concentrating (OR 1.7; 95% CI: [0.6-4.9]), sleeping sickness (OR = 0.7; 95% CI: [0.2-2.5]).

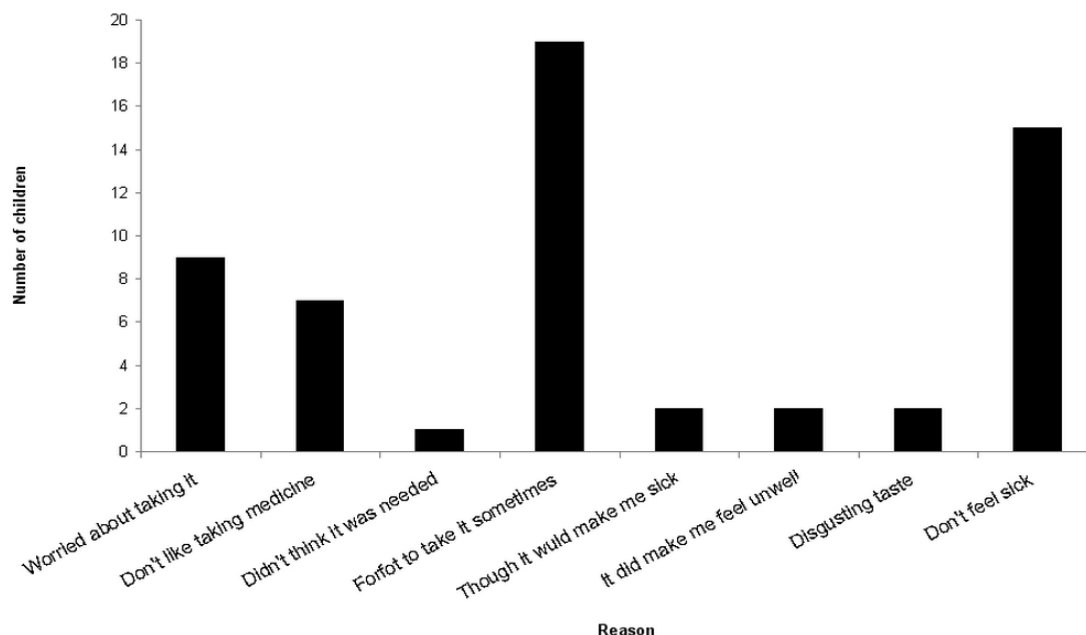
Discussion

This study concerns the first reported outbreak of pandemic influenza A(H1N1)2009 virus in Madagascar. We investigated a particular strategy for the 143 boarders in the school that was implemented by medical staff because officials chose not to close the school. All the boarders who were present at school on the day the survey was administered completed the study. This high response rate was largely due to the survey being conducted in the

Table 2. Frequency of different adverse effects among boarding school pupils in Antananarivo, Madagascar who took at least one oseltamivir tablet

Symptoms	Number of pupils	Percentage (%)
Nausea	10	8,1%
Headache	24	19,4%
Tummy ache	4	3,2%
Feeling tired	48	38,7%
Vomiting	4	3,2%
Hard to concentrate	28	22,6%
Sleeping sickness	15	12,1%
Diarrhoea	2	1,6%
Skin rash	4	3,2%

(n = 124)

Figure 4. Reported reasons among boarding school pupils in Antananarivo Madagascar (n = 57) for non-compliance with oseltamivir prophylaxis during October 2009

school under supervision. However, completion of the survey in the school may have introduced bias and influenced pupils' answers to the anonymous questionnaire.

All the pupils who reported symptoms associated with pandemic influenza A(H1N1) 2009 infection during the active surveillance period (within seven days of exposure to the last reported case) were tested. After this period, boarders were advised to contact their own general practitioner (GP) if they developed any symptoms. If they presented, it is unlikely that they were tested for pandemic influenza A(H1N1) 2009 infection for the following reasons: all were already aware of the outbreak, their symptoms were relatively mild, and boarders were from areas of Madagascar where relevant laboratory tests were unavailable.

This study provides the first clear evidence of community transmission of the pandemic influenza H1N1 virus within Madagascar. School students are a well-documented source of community influenza transmission and represent markers for more widespread community transmission [13]. In the early stages of a pandemic, schools with a wide geographic catchment area may therefore accelerate the spread of infection. Understanding the epidemiology of pandemic influenza A(H1N1) 2009 virus within schools is crucial to prevent such outbreaks in future. In the present study, the

transmission and the severity of illness was consistent with influenza outbreaks in previous seasons [14]. The reported symptoms were also consistent with seasonal influenza although the population of boarders studied was a relatively small sample.

The survey shows that after the first three days of the outbreak and after antiviral prophylaxis for all the boarders, no more boarders were reported ill during the following week. At the same time, attendance rates for the school showed an increase in absenteeism each day. Thus the outbreak was spreading in the overall school population while we observed a decrease within the sub-population of boarders. This also indicates that if transmission occurred first within the school, it subsequently occurred outside over the following weeks.

Our study also suggests that oseltamivir prophylaxis may help to contain outbreaks of influenza. However, a high proportion of schoolchildren might have experienced adverse effects from oseltamivir medication. Over half of those who took the medication reported at least one possible adverse effect including headaches, difficulties concentrating and tiredness. If these symptoms reflect the recognized adverse side effects of oseltamivir prophylaxis, they are higher in frequency compared with the manufacturer's information. When used for prevention purposes, the manufacturer has reported that 18% of people

receiving oseltamivir may experience headaches and 8% may experience asthenia [15]. In some cases who received oseltamivir for prophylaxis, it is possible that symptoms were due to other illnesses and mistakenly attributed to the use of oseltamivir. This explanation is nevertheless unlikely to account for all the symptoms that were experienced during prophylaxis.

Relatively high frequencies of adverse effects of oseltamivir treatment have been reported in a recent study conducted in England [16]. The authors of the study pointed out the young age (11-12 years) of their school population compared with the populations in the original studies that investigated adverse drug effects. However, in our study, the boarders were teenagers (mean age 16.9 yrs), so the age of the study population does not explain these differences. Although the severity of the perceived adverse effects was not assessed, it is likely that most of the symptoms were relatively mild as boarders continued to take the medication.

The findings of our study and those of Wallensten *et al.* contrast with a Cochrane review on the use of neuraminidase inhibitors to prevent and treat influenza in children. The only adverse effect that was more common than with treatment with placebo was vomiting [17].

Although adverse effects of oseltamivir were common, other concerns, such as the risk of resistance development, should be considered when evaluating the policy of mass prophylactic therapy for novel strains of influenza. This is especially so when the adverse effects are generally mild.

The effectiveness of antiviral prophylaxis is dependent on compliance with the medication. In this study, compliance with oseltamivir prophylaxis was moderate. Compliance was poorer among those who reported symptoms of influenza-like illness, as well as among those who reported symptoms that were likely to have been adverse effects of treatment. This evaluation of oseltamivir chemoprophylaxis among schoolchildren during an outbreak of pandemic influenza A(H1N1) 2009 virus was similar to the evaluation performed by Wallensten *et al.* [16]. The reason compliance was moderate, despite the fact that this was the first school in Madagascar to be affected by pandemic influenza A(H1N1) 2009 virus, may be due to the illness being considered as mild in severity. In turn, this may be affected by many factors such as the severity of the perceived threat of disease, the way in which treatment was offered, and

the anticipated and real adverse effects of the medication.

The apparent success in containing the outbreak among the boarding pupils may be linked to the absence of community transmission of the virus, and to the isolation measures that were taken. The success of all intervention also depends on its timing and on the transmission properties of the specific virus strain.

To our knowledge in Madagascar, most illnesses due to pandemic influenza A(H1N1) 2009 infection were generally mild. However, understanding the spread of pandemic influenza A(H1N1) 2009 virus within a school setting and the impact of measures to interrupt transmission is important in helping to prepare for future influenza virus pandemics.

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