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Outbreak, Surveillance and Investigation Reports

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An Investigation of a Human H5N1 Influenza Case by a Joint Thai and Lao Team, February 2007

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Introduction

Sporadic cases of human infection with avian influenza H5N1 have been reported since 1997. Beginning in late 2003, sporadic human zoonotic infections with high fatality have been associated with large and recurring outbreaks of avian influenza H5N1 in poultry in several Asian countries. Following outbreaks among migratory birds in China during 2005, H5N1 spread rapidly through Mongolia and Russia to many European, Middle Eastern and African countries¹. As of January 2007, 270 human cases had been reported to the World Health Organization from Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey and Vietnam². Although there have been a few cases of limited human-to-human transmission³, the species barrier between poultry and humans remains significant¹. However, the virus has pandemic potential and therefore, surveillance for human cases is implemented particularly in areas with confirmed poultry outbreaks.

On 23 Jan 2007, the Thai Ministry of Public Health reported an H5N1 outbreak among poultry in Srichaingmai District, Nong Khai Province which borders Sisattanak District in Lao PDR. Following this report, in early February, a Lao PDR investigation team conducted a rapid assessment in 198 villages near the Thailand-Lao PDR border aimed at active surveillance for human and avian H5N1 infections.

As a result, poultry outbreaks of H5N1 were found

in Sisattanak District and 20 villages were identified as belonging to the red zone (1km radius) around the infected poultry farm. Results of cloacal swabs from healthy poultry in Sisattanak District, Vientiane Province, Laos were reported as positive for H5N1 infection. Active surveillance for possible human infections was conducted during February to first week of March 2007.

Although forty one (0.5%) of the 7,800 residents have had Influenza-Like Illness (ILI), none of them were positive for influenza by rapid tests. In addition, the Lao PDR investigation team identified three suspected cases, one reportedly admitted to Sethathirath Hospital, Vientiane. The Lao PDR investigation team learned that the suspected case had been transferred to a hospital in Nong Khai, and informed the Nong Khai Provincial Health Office by telephone on 19 Feb 2007. An investigation of the hospitalized case was started on 20 Feb 2007 by the local teams. At that time, specimens for H5N1 were taken, and the patient was transferred from a private hospital to the public hospital where isolation facilities were available.

On 21 Feb 2007, the Nong Khai Surveillance and Rapid Response Team (SRRT) informed the Bureau of Epidemiology that a Laotian was admitted to the Nong Khai General Hospital with severe pneumonia and Acute Respiratory Distress Syndrome (ARDS). The patient was found positive for avian influenza H5N1 by RT-PCR at the National Institute of Health (NIH). This test result was confirmed by the Siriraj Hospital on 23 Feb 2007. The exposure history of the patient was uncertain. Hence, a team composed of field epidemiologists from the Thai and Lao PDR Ministries of Health participated in the joint cross-border investigation on 24-25 Feb 2007 to describe the epidemiological and clinical characteristics of the

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case, identify the mode of transmission and recommend measures to prevent additional cases and control spread of the disease.

Methods

This investigation was conducted in Nong Khai, Thailand and Vientiane, Lao PDR by a team composed of staff from the Thai SRRT team (Nong Khai Provincial Health Office, FETP Thailand and staffs from Bamrasnaradura Infectious Disease Institute) and the Lao PDR investigation team (Health Department in Vientiane Capital, Sisattanak Distirct Health Office, National Center Laboratory and WHO epidemiology staff in Lao PDR).

We reviewed medical records and interviewed clinicians at the hospital in Lao PDR and the private hospital in Nong Khai and the Nong Khai General Hospital where the case was treated in order to obtain the clinical history of the patient. The specimens obtained from the patient included blood; nasopharyngeal, nasal and throat swabs; endotracheal secretions; sputum; fluid washed from chest drain; stool; urine and instruments used for the patient (terminal end of endotracheal tube, nasogastric tube, intercostal drainage catheter, foley catheter). Specimens were submitted to the Thai NIH and laboratories of the Siriraj Hospital, Mahidol University in Bangkok for H5N1 virus detection. Lao PDR Ministry of Health also sent the samples to the WHO reference laboratory in Tokyo.

All specimens were tested by conventional Reverse Transcription Polymerase Chain Reaction (RT-PCR) analysis, real-time RT-PCR, cell culture and embryonated egg inoculation for viral isolation, including two or three blind passages, as previously described⁴⁻⁶. Paired serum samples were tested for H5-specific antibody by microneutralization assay using autologous isolate, A/Laos/Nong Khai 1/2007 (H5N1), as the test virus. The serum samples were serially diluted from 1:5 to 1:640 and assayed in duplicate⁷.

We interviewed the patient's relatives and neighbors who visited her at the Nong Khai Hospital. The interviews focused on getting an accurate timeline of events and possible *poultry exposure*. *Poultry exposure* was defined as any of the following: contact with sick or dead poultry by any means including buying, selling, carrying live or dead poultry or poultry meat; having freshly butchered or live poultry in the home within two weeks prior to onset of illness; a history of butchering poultry or living in

a poultry farm within two weeks prior to onset of illness.

The joint investigation team also conducted environmental surveys to assess the risk of exposure in the areas surrounding the patient's residence and poultry farms around the house where she had visited two weeks prior to onset of illness. We also reviewed the process of screening and patient referral at the Lao PDR and Thai border checkpoints.

Preliminary findings of the investigation were presented and discussed at a conference held on 25 Feb 2007 at the Nong Khai General Hospital. Clinicians and epidemiology staff from Thailand and Lao PDR, infectious disease specialists from Bamrasnaradura Infectious Disease Institute, Thailand and WHO Lao PDR country office staff attended the meeting.

Results

Clinical History

The patient was a 15-year-old female residing within the red zone in a suburb of Vientiane, Lao PDR, where an H5N1 outbreak among poultry had been confirmed on 7 Feb 2007⁸. She became sick on 10 Feb 2007. Initial symptoms were fever, headache, coryza and myalgia. From onset of illness to admission to a hospital in Vientiane, she did not have any respiratory symptoms. Figure 1 shows the sequence of events from onset of illness to death of the patient.

Table 1. Medications given to the patient in the Nong Khai-based hospitals by number of days after the onset date (17 Feb-7 Mar)

Drugs	Number of days after the onset date (10 Feb 2007)																		
	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Oseltamivir																			
Cefoperazone																			
Sulperazole																			
Vancomycin																			
Amikacin																			

*shaded days are the days those medicines were given

At the private hospital in Nong Khai Province, as the patient presented fever and rapid progressive dyspnea with patchy infiltration at both lungs, severe pneumonia caused by bacterial and/or viral infection was suspected. The other differential diagnosis was *Pneumocystis carinii* Pneumonia (PCP), however, it was ruled out due to her negative result on anti-HIV testing. Volume overload as a result from treatment of dengue infection which was first diagnosed in Sethathirath Hospital was also

mentioned. In response to two possible viral infections of severe pneumonia, the antiviral drug (oseltamivir) as well as antibiotics (a combination of cefoperazone and sulperazole) were prescribed on day 8 of admission (17 Feb 2007) in the private hospital. At Nong Khai Provincial Hospital, sputum culture yielded *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

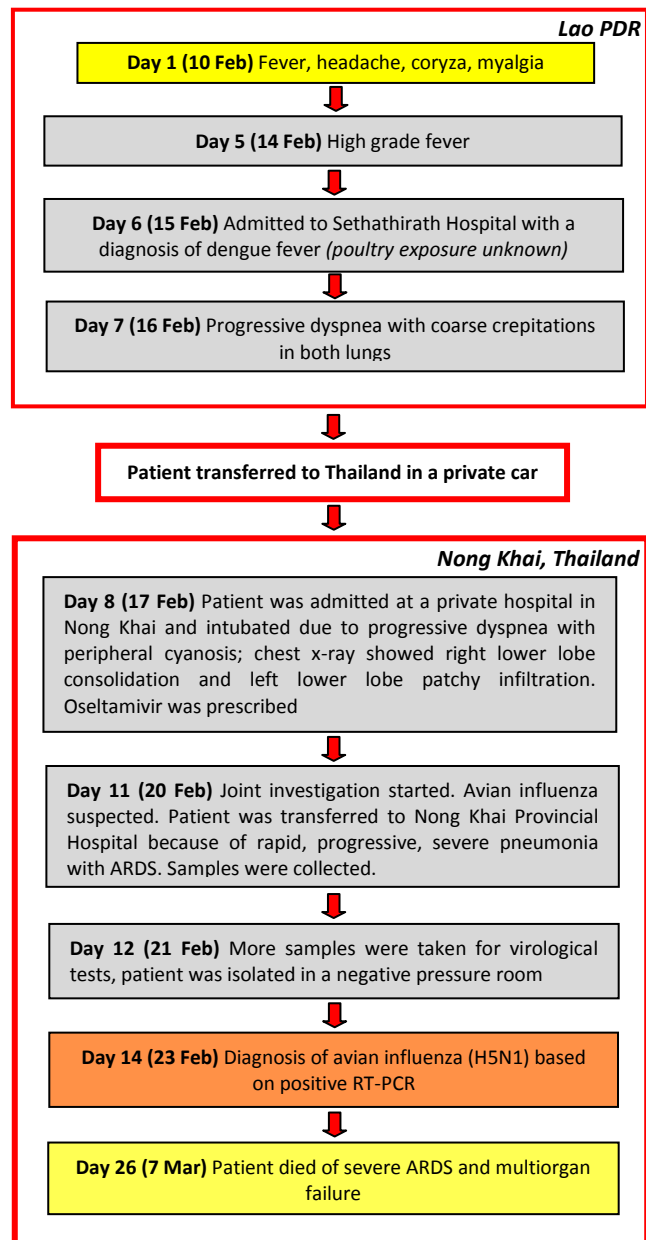


Figure 1. Clinical progression of illness of avian influenza (H5N1) case from 10 Feb to 7 Mar 2007 in Vientiane, Lao PDR

Laboratory Results

Laboratory investigation at private hospital and Nong Khai Hospital found rapid test negative for Flu A and B. Nasopharyngeal swab, nasal swab and throat swab on 20 Feb 2007 were negative for H5 by RT-PCR at Thai NIH.

The endotracheal suction specimen collected on 21 Feb 2007 (day 12 of illness) was positive for H5N1

based on RT-PCR tests performed at the Thai NIH and Siriraj Hospital. Subsequent samples collected on 25 Feb 2007 were also RT-PCR positive as tested by the Siriraj Hospital laboratory and WHO Collaborating Laboratory, NIID in Japan.

Highly pathogenic H5N1 virus was isolated from endotracheal secretion collected on 21 Feb 2007. A four-fold increase in neutralizing antibody titers from 80 to 320 was detected in paired blood specimens collected on 25 Feb and 1 Mar 2007, as assayed against the autologous virus. The virus isolation result was negative for endotracheal samples collected on 25 Feb and 1 Mar 2007. Puthavathana, et al give a more detailed description of the virus isolated from the patient and virological test results in their letter to the editor of the *Emerging Infectious Diseases Journal*⁷.

Environmental Survey

The patient's house was located in a red zone in Sisattanak District, Vientiane, Lao PDR. Aside from the patient, six other relatives lived in the house (two parents, two brothers, an uncle and an aunt). At the time of our visit on 24 Feb 2007, no poultry was found in the house or nearby. About 100 meters from the house was a farm which previously had some poultry. During our visit, we did not see any live poultry in the farm and in neighbors' houses. Residents claimed that in early February 2007, three to ten chickens began to die gradually followed by about 200 chickens died in the farm.

At that time, all the remaining live chickens were sold. A patient's friend said that "we cooked and sold the grilled internal organs of dead chickens from the farm in a market". However, this was not confirmed by the patient's family members.

The patient was transferred from the hospital in Vientiane to the hospital in Nong Khai in a private vehicle without any referral documents, no screening was done at the border checkpoints.

Discussion

The patient was the first confirmed human case of avian influenza H5N1 in Lao PDR. This cross-border investigation by a joint team of Thai and Lao health staff was helpful for both sides. It enabled us to get a better understanding of the circumstances regarding the case, and showed us the areas in surveillance and response that needed to be strengthened.

On initial presentation at the hospital in Lao PDR, a positive tourniquet test, leucocytopenia and

borderline thrombocytopenia (platelet count of 100,000/cu.mm.), an unclear history of poultry exposure and low index of suspicion led to a misdiagnosis of dengue fever. The health sector did not know there was suspected H5N1 activity in poultry while the patient was initially admitted to the hospital, so avian influenza was not considered as a differential diagnosis. Oseltamivir was started on day 8 of illness. Avian influenza was just suspected on day 11, and confirmed on day 14 of illness. The isolation of *Klebsiella pneumoniae* and *Acinetobacter baumannii* from sputum suggested the possibility of nosocomial infection.

Another opportunity was missed when the patient was transported to Nong Khai. Screening procedures at the border checkpoint failed to detect and refer a suspected case of avian influenza.

In Nong Khai, the patient was first brought to a private hospital where the routine surveillance for severe acute respiratory infections was not conducted. In addition, public health policy on confining the avian influenza cases to a designated public hospital was not done as the disease was not suspected. Private hospitals did not have negative pressure rooms and might not have adequate personal protection equipments (PPEs) for health workers who attended the patient. Health staff in Thailand were also unaware of the areas in Lao PDR with confirmed H5N1 poultry outbreaks.

Despite extensive collection of clinical specimens, only endotracheal secretions were found positive for H5N1 virus. The reasons were likely that the virus was staying deep in the lower respiratory tract, and the patient was already receiving oseltamivir when the specimens were taken.

The patient was likely to be infected with the H5N1 virus in her neighborhood since she lived in a red zone. Handling internal organs of an infected chicken without gloves may have been the mode of exposure.

Public Health Action and Recommendations

Close contacts to the patient (family members and health care workers) were identified and were monitored daily. The adults were provided with oseltamivir prophylaxis. None of the contacts developed influenza-like illness during the monitoring period. The Ministry of Health in Lao PDR has announced the first human case of infection with the avian influenza H5N1 virus to the public on 27 Feb 2007⁹, and her death was reported on 8 Mar 2007¹⁰.

Surveillance activities were strengthened in Lao PDR, and a second case (42-year-old female) was identified in Vientiane. She became febrile on 26 Feb 2007, and was hospitalized on 1 Mar 2007. She died on 4 Mar 2007. A duck positive for H5N1 virus was found in her household. None of her close contacts showed signs of infection¹¹.

This investigation highlighted the importance of health staff awareness on the occurrence of poultry outbreaks in their areas and the possibility of encountering human cases. Surveillance in areas with poultry outbreaks should include private health facilities. Referral mechanisms between private and public hospitals should be strengthened. In the future, it would be useful to collect endotracheal specimens at the time of initial intubation from cases with severe pneumonia.

Cross-border cooperation among veterinary and health staff should be strengthened, and adequate border screening procedures should be in place to detect and refer suspected avian influenza cases. A key outcome of this case investigation was that the Mekong Basin Disease Surveillance (MBDS) group implemented a Nong Khai–Vientiane cross-border project in 2009.

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Suggested Citation

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Interventions and Respiratory Specimen Screening of Close Contacts to Control an Outbreak of Pandemic Influenza A (H1N1) Virus in a Tour Group, China, 2009

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Introduction

Pandemic influenza A (H1N1) (2009 H1N1) has emerged and spread rapidly among people worldwide since mid-Apr 2009, with over 18,036 deaths reported from 214 countries as of 9 May 2010¹. Based on the epidemiologic data, 2009 H1N1 is believed to spread in similar ways as seasonal influenza virus, mainly through droplet route and close contact with infected cases during the infectious period², yet clinically indistinguishable from seasonal influenza. However, when outbreaks caused by the virus spread globally³⁻⁴, a quick response and appropriate interventions are necessary.

In mainland China, the first case of 2009 H1N1 virus infection was identified in Sichuan Province on 9 May 2010⁵. The province subsequently experienced a rapid increase in infected cases, notably involving a tour group with 30 members during 2-8 Jun 2009⁶. As a response, close contact tracing and 7-days medical observation were implemented as soon as the outbreak was detected. Meanwhile, respiratory specimen screening was also conducted among close contacts to control spreading of infection. The results of that effort were reported and measures imposed on this 2009 H1N1 outbreak of the tour group were described to provide as a reference and experiences for response to similar outbreaks.

Methods

*Outbreak Investigation*⁶

The tour group departed on 3 Jun 2009 from Chengdu to Jiuzhaigou, and returned on 5 Jun 2009. During the three-day trip, air-conditioned bus was the major vehicle that took the tour group members to each scenic spot. There were no assigned seats on the bus and seating changes became possible after each stop.

The index case-patient of 2009 H1N1 infection developed illness during flight from Chengdu to Jiuzhaigou, and joined the tour group with her

husband and daughter the next day. She stayed together with the tour group most of the time. She presented at a hospital on 5 Jun 2009, accompanied by her family, and was reported and isolated for treatment on the same day.

Secondary cases were nine (30%) tour group members who had talked with the index case-patient, and one airline passenger who was not a tour group member and sat two rows away from her in the flight. None of the 14 tour group members who had not talked with the index case-patient became ill.

Definition and Classification of Close Contact

Generally, once the index case is detected, the case definition for outbreak control and close contact tracing should be established⁷. The infectious period of a confirmed case-patient is defined to be one day prior to and through seven days after onset of illness or resolution of symptoms, whichever is longer⁸. Here, the infectious period for the index case-patient was from 1 to 5 Jun 2009, when the index case-patient was isolated. Potential close contacts were classified into five categories according to WHO guideline⁹: health care workers (HCW), household, tour group, passengers and social contacts. In order to compare the interventions taken with the close contacts, the five categories were, then, grouped into three groups according to the documented or general perception of decreased risk of infection.

Group I (HCW): Any doctor, nurse or staff who worked in the hospital and provided direct medical service to a confirmed case-patient without appropriate Personal Protective Equipments (PPEs).

Group II (Household and tour group close contacts): Tourists and the tour guide traveling together every day who had higher chance to closely contact with other group members, including direct physical contact, indirect close contact (<2 m) and face-to-face conversations. A household close contact was defined as a relative or family member living together with confirmed case-patient.

Group III (Passengers and close social contacts): A passenger close contact was defined as any crew who provided face-to-face service to confirmed case-patient or any passenger seated in the same row or within three rows in front of or behind confirmed

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case-patient. A social close contact was defined as a person, besides the previous four types of close contacts, known to have been within two meters of the index case-patient or of a secondary case for any length of time during infectious period, including bus passengers, co-workers, restaurant waiters and taxi drivers.

Close Contact Tracing and Medical Observation

Information from HCW close contact was collected during field investigation in hospital and was double-checked with information obtained from interview with case-patients. Information of household close contact was obtained directly from interview with case-patients. Registration and contact information of tour group close contacts was collected from interview with case-patients and the travel agency. The information of passengers and air crews was gathered from the airports and airline company.

Detailed information on exposure was double-checked with information from interview of case-patient. Close social contact information was collected from related institutions and agencies, such as bus and taxi companies, where case-patients had worked, visited, or used their vehicles. Subsequently, China CDC staff tried to contact the identified close contacts and double-checked the information by telephone. If no telephone number was available, CDC staff would visit the close contacts in person.

Afterwards, close contacts were gathered at designated places, such as hospital or hotel, for seven-day medical observation. A set of structured questionnaire was used to collect demographic and exposure information from each close contact during medical observation. Some close contacts were instructed to stay at home for seven days. Interview with the questionnaire was conducted by face-to-face interview or telephone.

Contacts who developed febrile respiratory illness within seven days were considered as suspected cases of 2009 H1N1, which was defined as a patient with fever (temperature 37.5°C), and/or recent onset of at least one of the followings: rhinorrhea, nasal congestion, sore throat, or cough, and were immediately admitted to a designated hospital and placed in a private room or a room with negative pressure if available, for isolation and antiviral treatment. All HCW caregivers followed standard precautions of contact and respiratory infection control such as wearing N95 mask and PPE for

possible risk of aerosol transmission of virus¹⁰. A confirmed case was defined as a suspected case with laboratory evidence of 2009 H1N1 virus infection diagnosed by real-time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) test in laboratory examination of respiratory specimens.

Respiratory Specimen Screening

To determine the infection and clarify the diagnosis, a respiratory specimen screening regimen was implemented, including collection of sequential throat swabs from all close contacts. The first throat swab was collected as soon as the person was identified as a close contact by the trace back investigation. Subsequent throat swabs were collected during medical observation.

All specimens were placed in sterile viral transport medium for 2009 H1N1 virus testing following a standard protocol. RNA was extracted and tested by rRT-PCR with pandemic 2009 H1N1-specific primers and probes following the WHO protocol. These assays were performed at biosafety level (BSL) two facilities in Sichuan Centers for Disease Control and Prevention.

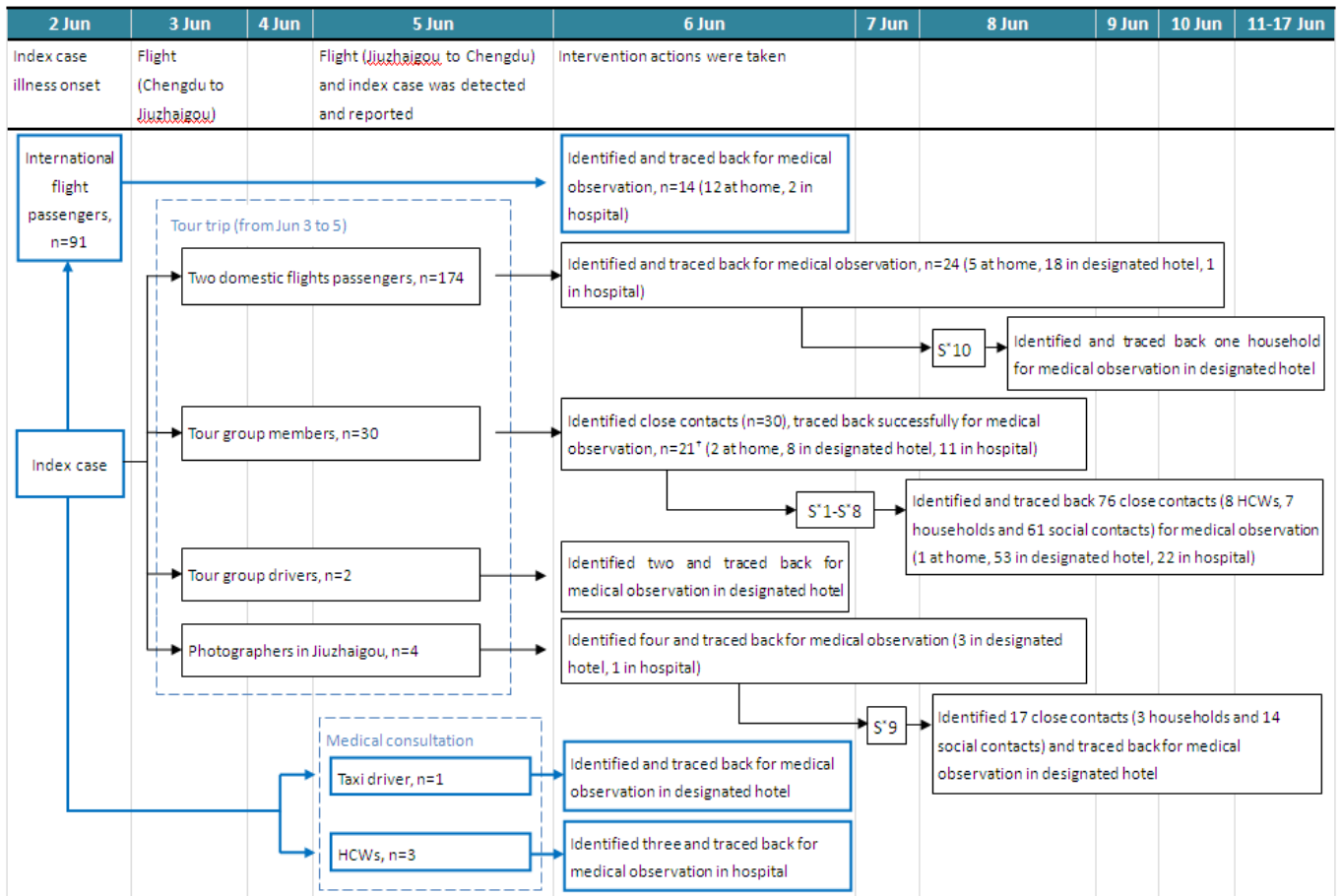
Statistical Analysis

Median and range values were used for continuous variables and medians were compared between the three close contact groups with the Wilcoxon rank sum test. Positive proportion and 95% confidence intervals were calculated according to the binomial distribution. Frequencies and percentages for each of the three close contact groups were calculated and compared using the Chi-square test; Fisher's exact test was employed when cells had less-than-five frequency. All statistical tests were two-sided with a significance level set at 0.05.

Results

This is the first known outbreak of 2009 H1N1 in China among tourist group⁶. From 6 to 8 Jun 2009, a total of 172 close contacts were identified. Among them, 163 (95%) were successfully traced back for medical observation by 17 Jun 2009 (Figure 1 and table 1).

During the medical observation, 11 contacts developed symptoms and were classified as suspected case-patients; 10 of the 11 (91%) were confirmed as secondary cases. The remaining one suspected case-patient was a 26-year-old woman who was a friend of secondary case 6 and joined the same tour group with the index case.



* S denotes secondary case.

[†] Nine of 21 (43%) tour group members were not successfully contacted and placed under medical observation before returning home, because these nine tour group members left Chengdu on the same day that the index case was detected. As for their destinations, two went to Liaoning Province, two to Chongqing municipality, two to Xinjiang Province, two to Hubei Province and one to Singapore. We contacted local health authorities to follow up their health status. Of these nine tourists outside Sichuan, eight were placed under medical observation at home or in a designated hotel for seven days at once by provincial CDCs in Mainland China, and no one developed symptoms during medical observation. However, the person who returned to Singapore could not be traced back. Sichuan CDC notified the diplomatic affairs agency so that Singapore could implement close contact tracing and medical observation.

Figure 1. Flow chart of close contact tracing and components of a 2009 H1N1 tour group outbreak in China, 2009

During the medical observation, being without fever, she began to cough on the second day after her last exposure. Three throat swabs were collected from her; one each on the second, fourth and fifth day after her last exposure. She was excluded from 2009 H1N1 virus infection because all swabs were tested negative.

Of the 163 close contacts who were successfully traced back and kept under medical observation, 122 (75%) close contacts had at least one throat swab collected, with mean of two days after last exposures (range 1-8).

A total of 181 swabs were collected and numbers of swabs collected from day 1 to 8 after last exposure were 32 (18%), 46 (25%), 21 (12%), 23 (13%), 25 (14%), 7 (4%), 23 (13%) and 4 (2%). Among these 122 close contacts, 34 (28%) and 10 (8%) had two or three sequential swabs, respectively. The reasons for not

collecting swab or second swab were either the contact refused or attempt to contact was failed.

A total of 17 swabs collected from 10 secondary cases whom were symptomatic contacts (suspected case-patient) positive with 2009 H1N1 virus. Asymptomatic cases were not tested positive of 2009 H1N1 virus. Positive proportions among group-1 HCW, group-2 tour group and household, and group-3 passengers and social close contacts were none of 11 (0.0), 8 of 41 (0.20) and 2 of 120 (0.02), respectively (Table 1).

All of the 17 swabs collected from day 1 to 5 after last exposure were 6 (35%), 2 (12%), 5 (29%), 3 (18%) and 1 (6%). Positive proportion by days of swab collection after last exposure showed a high ratio on day 1 (0.19), before sharply decreased to a valley on day 2 (0.04) and surged to a peak on day 3 (0.24). After day 3, it was declined to zero from day 6 and onwards (Figure 2).

Table 1. Comparison of interventions and respiratory specimen screening among three close contacts groups in a 2009 H1N1 tour group outbreak in China, 2009

Intervention and respiratory specimen screening	Total (N=172)	HCW (N=11)	Tour group and household (N=41)	Passengers and social contacts (N=120)	P-value
Proportion of close contacts successfully traced back, n (%)	163 (95)	11 (100)	32 (78)	120 (100)	<0.001*
Medical observation					
At home (%)	20 (12)	0 (0)	2 (6)	18 (15)	
At designated hotel (%)	103 (63)	1 (9)	15 (47)	87 (73)	
In hospital (%)	40 (25)	10 (91)	15 (47)	15 (12)	<0.001*
Centralized management (%)	143 (88)	11 (100)	30 (94)	102 (85)	0.182*
Symptomatic close contact (%)	11 (7)	0 (0)	9 (28)	2 (2)	<0.001*
Swab collection from contacts under medical observation	122 (75)	6 [†] (55)	21 [‡] (66)	95 [§] (79)	0.013*
Only one swab (%)	78 (64)	6 (100)	7 (33)	65 (68)	
Two swabs (%)	34 (28)	0 (0)	5 (24)	29 (31)	
Three swabs (%)	10 (8)	0 (0)	9 (43)	1 (1)	
Two or more swabs collection (%)	44 (36)	0 (0)	14 (67)	30 (32)	<0.001*
Days from last exposure to first swab collection, media (IQR)	2 (1, 8)	1 (1, 3)	1 (1, 2)	2 (1, 8)	<0.001 [¶]
Days from last exposure to second swab collection, media (IQR)	5 (2, 7)	NA ^{**}	3 (2, 6)	5 (3, 7)	0.132 [¶]
Days from last exposure to third swab collection, media (IQR)	4 (3, 7)	NA ^{**}	4 (3, 7)	6	0.400 [¶]
Positive with 2009 H1N1 virus, n (%)	10 (8)	0 (0)	8 (38)	2 (2)	<0.001*

* Frequencies were compared among three groups using Chi-square test; Fisher's exact test employed once the cells had expected count less than 5.

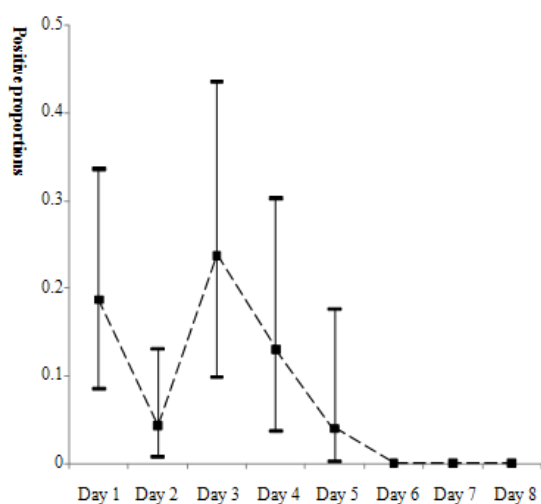
[†] Only six HCWs had swabs collected for rRT-PCR testing. The remaining five HCWs acute-phase sera collected and tested negative by HI assay.

[‡] Five tour group members and six household close contacts of secondary case-patients refused to have swabs collected.

[§] 25 social close contacts, including six co-workers, five bus or taxi drivers and 14 roommates, refused to have swabs collected.

[¶] Medians were compared among three groups with the Wilcoxon rank sum test.

** NA denotes not available.



Error bars indicate 95% confidence intervals.

Figure 2. Positive proportions of swabs collected from 122 close contacts in a tour group outbreak of 2009 H1N1 in China, 2009

Discussion

The tour group members came from various provinces throughout China with potential to spread

the disease widely and quickly upon their return after the short tour. This was a special and extraordinary risk to accelerate the disease spread. To achieve the optimal control of 2009 H1N1 during this outbreak in the tour group just as the disease was making a debut in China, tracing back the close contacts and placing them under centralized medical observation was one of the effective interventions since the tour group could play a critical role in spreading such a communicable disease. The urgent need for strict interventions with this tour group was considered to be crucial and technically valuable in order to establish a detailed disease transmission model during the early stage of the 2009 H1N1 pandemic.

In addition to tracing back the close contacts and managing them, other interventions were also necessary and complement each other, such as enhanced surveillance, border entry screening, vaccination campaign and chemoprophylaxis with antivirals. Each intervention had advantages and

disadvantages. In enhanced surveillance, more case-patients might be detected, but the number of investigated cases would be probably increased, including those were not actually infected, resulting in a lower specificity and burdensome to health workers because of a broad surveillance case definition. In this outbreak of 2009 H1N1 in China, due to low risk for seasonal influenza infection among the close contacts and absence of effective vaccine for 2009 H1N1 virus with inadequate stockpile of effective antiviral drugs, only non-pharmaceutical control measures were used, such as hand hygiene, social distancing, risk communication, and travel screening and restrictions.

Respiratory specimen screening was one of the exceptional actions taken to control this outbreak. Sequential specimen collection could clarify the diagnosis of close contacts in time, validate effectiveness of interventions and provide information on virus shedding. In this outbreak, 10 secondary cases were confirmed among close contacts of the index case while there was no infected case among close contacts of secondary cases. No infection had been identified among asymptomatic cases in this outbreak which was differed from seasonal influenza's asymptomatic infection rate of about 33%¹¹.

The positive proportion was remarkably high on day 1 and day 3, and decreased to zero on day 6. This pattern was consistent with and elaborated more details to previous reports, which showed most patients shed virus from one day before onset of symptoms through five to seven days after or until symptoms resolve^{2,12}.

Failing either to find contacts to engage in interview or to provide swabs lessened the potential effectiveness of this implementation strategy of close contact tracing and timely respiratory specimen collection. As for response to this outbreak, nine tourists were not contacted successfully and 35 contacts refused to have respiratory swabs collected. This hindered the power of our observation on identification of 2009 H1N1 virus among asymptomatic close contacts.

In conclusion, a tour group represents a special circumstance with a high potential to spread disease further and quickly. Group members from many different places gather for a few days and then return home. If an emergent or re-emergent disease occurs in any tour group, immediate and effective actions are necessary to prevent the spread of

disease, including comprehensive close contact tracing and medical observation of all contacts.

Timely respiratory specimen collection and testing can accommodate early detection of asymptomatic cases and provide more information for better understanding of the disease. However, well-designed studies to evaluate this further are needed to provide more supporting evidences.

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Rubella Outbreak in a Boarding School, Malaysia, April 2007

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Introduction

Rubella, also known as German measles, is a vaccine preventable disease. It has an average incubation period of 14 days, with a range of 12 to 23 days¹. The virus is shed in the nasopharynx of symptomatic cases for approximately seven days before and after the rash is visible. The virus is present in the nasopharyngeal secretions, blood, faeces and urine during the clinical illness although patients with subclinical disease are also infectious. Often presenting with mild symptoms, up to 50% of rubella cases may be subclinical or inapparent. Maculopapular rash is usually the first manifestation. In older children and adults, there is often a 1-5 days prodrome with low grade fever, malaise, lymphadenopathy and upper respiratory symptoms preceding the rash. In the earlier stage of the disease, the clinical signs and symptoms are similar to measles. Infection with rubella virus in early gestation can cause congenital defects in newborn babies.

Measles vaccine was introduced into the Expanded Programme for Immunization (EPI) of Malaysia in 1982. Rubella vaccine was added in 1986. Since 2002, a trivalent vaccine, Measles, Mumps and Rubella (MMR) is used. Measles vaccine is given to both boys and girls nowadays. During the earlier phase of the rubella vaccination program, only girls were vaccinated to prevent the occurrence of Congenital Rubella Syndrome (CRS). Rubella vaccine is effective in preventing clinical rubella as it is associated with high antibody titers in vaccinees². However, there was a reported case of CRS delivered by a mother who was vaccinated before conception, and developed low titres of rubella antibody³.

On 9 Apr 2007, the State Health Department of Selangor was informed of an unusual occurrence of febrile illness associated with maculopapular skin rash among 13 students of Sekolah Menengah Sains

(SMS) Kuala Selangor, whom had sought treatment from Kuala Selangor Health Clinic. The provisional diagnosis made by the attending doctor in the health clinic was measles.

SMS Kuala Selangor was a fully residential school situated about 2 km from the town of Kuala Selangor and less than a kilometre from the nearest health clinic i.e., Kuala Selangor Health Clinic. With 874 staff and students, this school had an enrollment of 777 students; 392 females and 385 males. Majority of the students came from various districts in Selangor. There were 46 dormitories and each dorm housed an average of 18-20 students. There was no recent history on outbreaks of febrile illness in this school and neither was there any similar outbreak elsewhere in Kuala Selangor.

Outbreak investigation was initiated by the Kuala Selangor District Health Office (DHO) on the same day. The investigation team consisted of Kuala Selangor DHO team, and was assisted by the epidemiology team and Epidemic Intelligence Program (EIP) team from Selangor Health Department. The investigation aimed to verify the outbreak, confirm the diagnosis, describe the outbreak epidemiologically and recommend preventive measures.

Methods

A cross-sectional study was conducted to describe the outbreak in relation to person time and place. Line-listed data were collected by using Microsoft Office Excel and analysed using SPSS version 15. Descriptive statistics were used to describe the distribution of cases, and Chi-square test was used to detect significance of association between categorical variables. The level of significance was taken at 0.05.

Any student or staff of the school who presented with history of maculopapular rash with or without fever anytime from 19 Mar to 16 Apr 2007 was defined as a suspected case. Confirmed positive cases were suspected cases positive for rubella IgM.

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Upon receiving the notification, active case detection was carried out immediately by the district investigation team on 9 Apr 2007. All students and residential staff of SMS Kuala Selangor who had similar signs and symptoms were interviewed and examined. Retrospective record search was also conducted at the Kuala Selangor Health Center, which was the nearest clinic, to look for similar cases from the same school or surrounding areas.

Information on patient identification such as name, dormitory and classroom; demographic details such as age, gender, ethnicity, travel history; clinical data on signs and symptoms, date of onset; and laboratory findings were gathered. The vaccination status of the students was obtained from the school health records.

About 5 ml blood were taken from each case and sent to the National Public Health Laboratory (NPHL) in Sungai Buloh for rubella and measles IgM testing by ELISA method.

The ventilation status and distance between beds in the dormitories and classrooms were examined. General cleanliness in the dormitories and toilets were also inspected.

Results

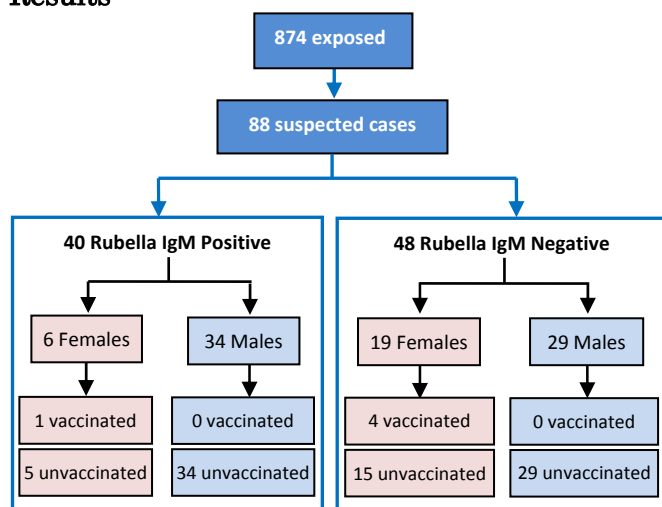


Figure 1. Distribution of suspected and confirmed rubella cases in SMS Kuala Selangor

Of 874 people who studied or worked in the school, 88 (10%) met the case definition; 45% of whom were confirmed IgM positive for rubella. None of the suspected cases was positive for measles. Record search from the school health cards revealed that only 40% of the female students had rubella vaccination recorded while all male students were not vaccinated. Of asymptomatic female students, approximately half had no record of vaccination given.

Forty of the suspected cases (45%) were confirmed positive for IgM rubella with male significantly more than female cases ($p < 0.001$) (figure 1). Of confirmed cases, only one was a female student who was vaccinated in the past year. Both the suspected and confirmed cases were predominantly male students as seen in figure 2. The mean age of the cases was 15 years (range 13 to 17 years).

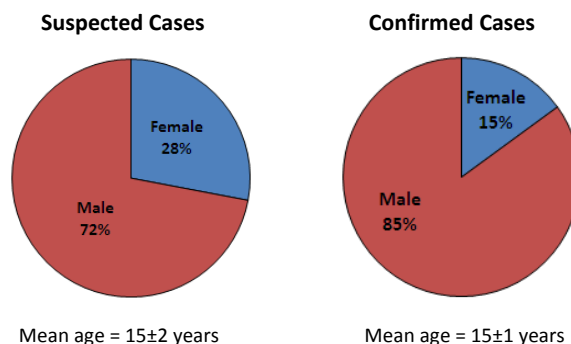


Figure 2. Distribution of cases by gender

Retrospective case-records search done at the nearest health center did not show any unusual cluster of similar cases prior to this outbreak. All cases presented with maculopapular rash. Figure 3 shows the maculopapular rash as seen on one of the infected students. Eighty eight percent presented with fever with mean body temperature of 37.7°C. Other manifestations are as shown in figure 4.



Figure 3. Maculopapular skin rash on the back and chest of a student

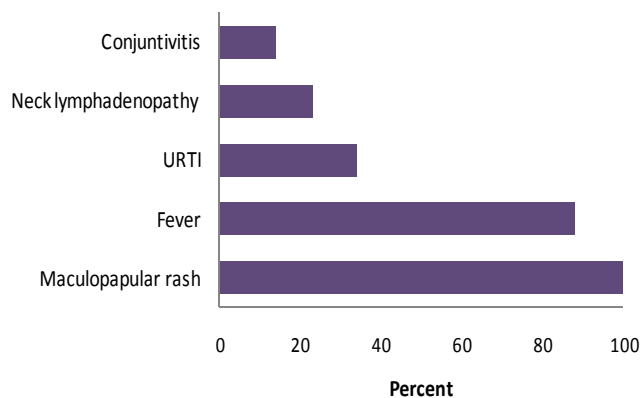


Figure 4. Distribution of clinical presentations of cases

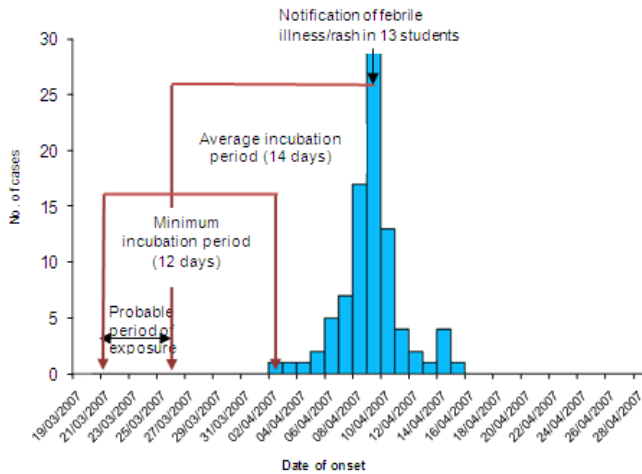


Figure 5. Epidemic curve showing onset dates of cases

The epidemic curve illustrates a common source infection with a steady increase in the number of cases over time. The onset of illness for the first case was on 2 Apr 2007, the cases peaked on 9 Apr 2007 and declined thereafter for a period of six days. There were no new cases reported after 16 Apr 2007.

A 13-year-old boy was the case with the earliest onset. He did not have any history of contact with anyone with similar illness. We were not able to identify the index case in this outbreak. Based on the epidemic curve and incubation period of rubella, the probable period of exposure was between 21 to 26 Mar 2007.



Figure 6. Environmental inspection of one of the dormitory

From the environmental inspection, each dormitory was 48 square meter in size which housed 18 to 20 students. The ventilation was good with adequate windows, and there were 6 wall fans attached to each dorm as shown in figure 6. General sanitation of the dormitories, toilets and surrounding areas were satisfactory.

Discussion

This was a common source outbreak of rubella in a boarding school in Kuala Selangor which had lasted for 15 days. For a fairly large outbreak in a small geographical area, this outbreak was well contained within one incubation period. In situation like this,

there was potential for an extensive spread of rubella in a short duration of time because of its large population living in closed quarters. A similar outbreak with larger magnitude had been reported in previous year in a military vocational training school involving 303 cases⁴.

Measles is a notifiable disease in this country, but not rubella; hence, cases with maculopapular rash are often diagnosed and notified as measles especially by young doctors although the clinical presentation is more suggestive of rubella. However, the 'misdiagnosis' that led to 'misnotification' as seen in this outbreak had sparked the attention of the public health authorities to review the burden of rubella and its vaccination program in the country. Although the index case was not known in this outbreak, this is not surprising as rubella is a mild disease and often 20-50% of infected people may not notice any symptoms at all¹.

A mass measles immunization program was carried out extensively in this country in 2004. Therefore, most of the students, both male and female, would have received the monovalent measles vaccine, but not mumps or rubella through the MMR vaccination program. The youngest cohort of cases in this outbreak was born in 1994 while MMR was only introduced into the EPI in 2002. During the early phase of rubella vaccination, it was given only to females at the age of 12 years^{6,7}. With the selective vaccination strategy adopted by the Ministry of Health Malaysia, those who were not in the target group for vaccination remained as potential sources of infection, and this explains why males were predominantly affected in this outbreak. This study showed that only 21% (164) of the students were vaccinated for rubella, and they were all female; a level far below the rubella immunity threshold of 80-85% needed to give protection to the subpopulation in order to prevent an outbreak.

During the investigation, we also encountered a female confirmed case who had received vaccination (batch no. EU 394) approximately nine months prior to this outbreak. This has raised the possibility of vaccination failure. In a study of rubella immunity and response to vaccination, it was reported that the seroconversion rate was 92%⁹. In another study by Ehrengut and Florent, there were cases reported to have been repeatedly vaccinated with rubella but failed to seroconvert. The reason for these apparent vaccination failure could be a residual immunity following either rubella infection in utero or in earliest childhood¹⁰. A seroprevalence study would

be useful to evaluate the effectiveness of the vaccination program in this country.

Public Health Action and Recommendations

Rubella was confirmed as the cause of this outbreak. The outbreak was contained within 15 days because of the confined locality which enabled prompt actions to be taken. This study illustrated the importance of vaccination to all students irrespective of gender. It has also showed that vaccination of students joining residential schools is crucial. Therefore, it is recommended that students born before the incorporation of MMR vaccination into the national EPI should be given rubella vaccination, especially those in residential boarding schools.

Since the inception of the EPI in Malaysia, measles and rubella cases have become rare. Hence, younger doctors may not be able to differentiate the two diseases. It is highly recommended that doctors should update their knowledge and expertise on immunizable diseases. Where difficulty in differentiating the diseases clinically arises, laboratory confirmation should become a priority.

Remedial actions were instituted promptly to prevent further transmission. These included setting up of a mobile clinic within the school premise to identify and treat all symptomatic cases. The symptomatics were cohorted in designated dormitories as shown in figure 6 and were condoned from other students for a period of at least seven days from onset of rash since the period of infectivity was stated as seven days before and after onset of rash².



Figure 6. Students with symptoms were cohorted in designated dormitories as marked by the arrows

Pregnant staff were advised to keep away from the dormitories and health education was given on signs and symptoms of rubella. Anxious parents were allowed to bring their sick children home with advise to confine the children at home for one week and have no contact with pregnant women. Health talks on self hygiene and the possible risk of transmission to pregnant mothers was given to all

students, staff and guardians. Following this outbreak, rubella vaccination was not given to all students.

Awareness about rubella and measles was immediately circulated through a bulletin and updated to all doctors in the affected districts. Continous Medical Education sessions were carried out at other districts in Selangor. The outbreak has also alerted the Ministry of Health (MOH) Malaysia to produce a guideline for rubella control. The MOH has also embarked on a laboratory-based surveillance for rubella, and NPHL as the reference laboratory for measles and rubella. This will provide a better picture of the burden of these diseases in this country.

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