A PSEUDO-OUTBREAK OF HUMAN A/H5N1 INFECTIONS IN GREECE AND ITS PUBLIC HEALTH IMPLICATIONS

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The recent wide geographic spread of the highly pathogenic avian influenza A/H5N1 virus has important public health implications. Several wild migratory birds were confirmed to be infected with avian influenza A/H5N1 in Greece in February and March 2006. The aim of this paper is to report data from potential H5N1 human cases that presented to local hospitals during this period with a respiratory infection and expressing concern about exposure to avian influenza.

A case-control investigation was conducted that included case identification with the use of a structured definition, review of epidemiological and clinical characteristics and molecular testing for avian influenza A/H5N1. The setting was the entire country of Greece during February and March 2006. The main outcomes were rates of possible cases (meeting both a clinical and an epidemiological criterion) and clinical or epidemiological characteristics differentiating them from potential cases that met either one of the criteria of a possible case, but not both.

Twenty six potential patients (81% of whom met a clinical criterion, and 39% of whom met an epidemiological criterion) presented and most (85%) were admitted in local hospitals during the period of interest. The majority of cases (85%) were observed in northern Greece where most of the confirmed A/H5N1 avian cases were documented. Five of the 26 evaluated patients met the definition of a possible case. These clustered within the early period of confirmed A/H5N1 cases in wild migratory birds (P=0.05). Molecular testing was negative for all possible cases. Application of a revised case definition constructed according to newer European Union guidance resulted in the exclusion of two possible cases.

Several potential A/H5N1 human cases were recently identified in Greece. Both the timing of identification and the geographical location of potential cases suggest an increased awareness on the part of the general public, as well as poor interpretation of the case definition by the clinicians.

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Introduction

The recent wide geographic spread of the highly pathogenic avian influenza A/H5N1 virus in the avian population has important public health implications. This spread has been currently attributed to the long distance carriage of the virus by migratory birds from Asia to Europe; however, this is still an issue of scientific debate [1]. The virus has affected birds in several European countries [(2,3] and was identified in other hosts besides avian species, including cats, dogs and stone martens [3-8]. An increased risk has been recognised for humans involved in commercial poultry farming [9-12]. Data on suspect human cases in European countries are scarce [13,14]. In this report we describe data on potential A/H5N1 human cases examined in Greek hospitals during the recent epizootic of confirmed migratory bird cases found infected in Greece (February-March 2006), according to an initial and a revised definition for a possible case.

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Methods

Initial case definition

A specific standard operating procedure was in place for all suspect bird or human cases during the period from 1 February 2006 to 27 March 2006 (this period includes 14 days that were added after the date of last identification of dead migratory birds in Greece i.e. 13 March; the two weeks equal two times the incubation period). These procedures were put in place by the Hellenic Center for Diseases Control and Prevention (HCDCP -also known as KEELPNO), the Ministry of Health, and the Department of Avian Pathology in the Ministry of Rural Development and Food, Greece. All cases fulfilling a clinical or an epidemiological criterion were considered potential cases, whereas cases meeting both criteria met the case definition of a possible case [TABLE 1]. The whole country of Greece was considered an affected area, despite lack of confirmed human or poultry cases.

Revised case definition

The definition of a possible case was revised [TABLE 1] after the publication of the 30 March 2006 guidance document from the European Centre for Disease Prevention and Control (ECDC) [15]. Greek prefectures with suspect or confirmed A/H5N1 cases in birds and their neighbouring prefectures were considered to be affected areas [TABLE 1].

Standard operating procedure

All human cases were reported to the HCDCP's Department of Epidemiological Surveillance and Intervention. The HCDCP prepared notification forms for each case with all relevant epidemiological and clinical information. Laboratory investigation for both seasonal influenza (types A and B) and the highly pathogenic avian influenza A/H5N1 virus was conducted for all potential cases by RT-PCR and/or real time PCR in the National Influenza Reference Centres. If antiviral medications were deemed necessary, they were prescribed immediately by the treating physician from the local or national stockpile. Antivirals were discontinued if the laboratory investigation was negative. The patients admitted for observation were admitted to hospital isolation rooms specifically reserved for such cases in each hospital. Most tertiary care hospitals in Greece have had suitable negative pressure rooms since the time of the SARS global epidemic in 2003 or the Athens 2004 Olympic Games. Specific guidance documents were issued by the HCDCP for handling and admission of potential cases in such isolation rooms, to prevent transmission. However if the local hospital did not have negative pressure wards, the guidelines were to admit potential cases to single bed isolation rooms with appropriate precautions. For suspect bird cases, a standard operating procedure was enforced by the Ministry of Rural

Table

Comparison between initial and revised case definitions for possible influenza A/H5N1 human cases in Greece, February-March 2006

INITIAL CASE DEFINITION FOR A POSSIBLE INFLUENZA A/H5N1 HUMAN CASE[1]		
Clinical criteria		**Epidemiological criteria**
Temperature ≥38 °C **AND** respiratory symptoms including cough or shortness of breath **OR** death from unexplained respiratory illness	**AND**	Travel or residence 7 days before onset of symptoms to one of the areas affected by avian influenza A/H5N1 **AND** close contact (≤1 metre) with live or dead domestic fowl or wild birds or swine in any place, including bird markets. **OR** a) close contact with another case of serious respiratory disease or unexplained death coming from the affected areas, b) the case was part of cluster of cases of unexplained serious respiratory disease in a healthcare worker, c) the case is a laboratory worker with potential exposure to influenza A/H5N1 virus.
REVISED CASE DEFINITION FOR A POSSIBLE INFLUENZA A/H5N1 HUMAN CASE[1,2]		
Temperature ≥38 °C **AND** acute respiratory infection **OR** death from acute unexplained respiratory illness		At least one of the following exposures (a, b, c) within 7 days prior to onset of symptoms: a) *Human contact*: Having been in close contact (within one metre) of a person reported as probable or confirmed case of influenza A/H5N1 b) *Laboratory contact*: Having worked in a laboratory where there is potential exposure to influenza A/H5N1 c) *Contact with poultry or wild birds* (not game birds): Resides in or has visited an area of Greece or another country where influenza A/H5N1 is currently suspected or confirmed **AND** has been in contact with sick or dead domestic poultry or wild birds (not game birds) in the affected area **OR** has been in an environment (residential or systematic breeding) where sick or dead domestic poultry have been reported in the previous six weeks in the affected area The affected area in Greece was defined as a prefecture with suspect or confirmed cases of A/H5N1 in birds (domestic or wild) and their neighbouring prefectures

1. HCDCP : Hellenic Centre for Diseases Control and Prevention
2. Major differences are underlined in the revised case definition (see text for details)

Development and Food's Department of Avian Pathology. Laboratory testing of the bird cases was performed at the National Veterinary Reference Laboratory and confirmatory testing was performed at the Weybridge World Health Organization and European Community Reference Laboratory in the United Kingdom.

Greece has a standard sentinel surveillance system collecting data for influenza-like illness (ILI) and laboratory confirmed influenza from primary care centers and private physicians (approximately 200 physicians). Data from this system were compared for the entire country and between prefectures affected and not affected by confirmed H5N1 bird cases.

Statistical analysis

Data on subjects meeting the definition of a possible case were compared to data from potential cases meeting either of the criteria of a possible case but not both. Data compared included dates of presentation (before or after 15 February), rates of admission, and variances in geographical characteristics. The cases were classified according to which of the 51 prefectures and the 13 geographical regions of Greece was affected and furthermore if they were from northern or southern Greece. The Mann-Whitney procedure was used to compare non-parametric data between the two groups. The entire dataset was re-examined with the application of the revised HCDCP definition.

Results

During the period from 1 February to 27 March, 2006, 33 migratory birds were identified as being infected with highly pathogenic avian influenza A/H5N1 virus [FIGURE 1]. During the same period, 26 potential patients [48.7% male, median age 30 years, range 17.5-45.8 years] presented to local hospitals throughout Greece [FIGURES 1, 2] with respiratory tract infection symptoms and expressing concern about possible exposure to highly pathogenic avian influenza. Nineteen potential cases (73.1%) reported exposure to birds but only 10 of these 19 cases (52.6%) met the epidemiological criterion regarding the time of exposure (7 day interval). Thirteen potential cases (50%) reported exposure to wild migratory birds and 6 (23.1%) contact with domestic live or dead poultry while 7/26 (26.9%) had no exposure to birds. Only one patient was exposed to a bird (a dead swan) that was later confirmed to be A/H5N1 positive. Six of the 26 patients (23.1%) were hunters or were otherwise exposed to game meat. Seven patients had no exposure to birds. Four had travelled from A/H5N1 affected areas (two from Turkey and two from Nigeria), but did not report of exposure to local fowl or wild birds. Three reported exposure to surfaces potentially contaminated with bird droppings. Twenty two of the 26 potential cases (84.6%) were admitted to isolation units in regional hospitals for observation. All potential cases were submitted to molecular testing that disclosed negative results for influenza A/H5N1 and positive results for influenza B in 3 cases. One patient (3.8%) received treatment with oseltamivir that was discontinued after the results of the molecular testing.

Twenty one of the 26 potential H5N1 patients (80.8%) met the clinical criterion (the remaining five did not have fever but had other respiratory infection symptoms) and 10/26 (38.5%) the epidemiological criterion for a possible case [FIGURE 3]. Five of the 26 cases (19.2%) met both criteria and were classified as possible cases according to the definition [FIGURE 3]. The rest 21/26 (80.8%) cases were potential cases meeting either of the criteria of a possible case but not both [FIGURE 3]. Sixteen from these 21 (76.2%) cases met the clinical criterion and 5/21 (23.8%) met the epidemiological criterion. Subjects meeting the criteria of a possible case differed from the rest only for the epidemiological criterion [5/5 (100%) versus 5/21 (23.8%), P=0.004] whereas for the clinical criterion the difference was not significant (P=0.5). There was no difference between the two groups regarding age (P=0.5), sex (P=0.6), exposure to wild migratory avian species (3/5 (60%) versus 10/14 (71.4%) respectively) or involvement in hunting activities (P=0.6). All five patients meeting the definition for a possible case and the majority (17/21, 81%) of the rest were admitted to the local hospital for observation (P=0.54 for between group comparison). The median duration of stay was short (2 days, IQR: 1.5-3). Most (14/21, 66.7%) of the potential cases that met only one criterion occurred after 15 February 2006, whereas patients meeting the possible case definition clustered before 15 February 2006 (P= 0.05 for between group comparison).

FIGURE 1

Avian influenza A/H5N1 cases in birds and potential human cases in Greece, February-March 2006

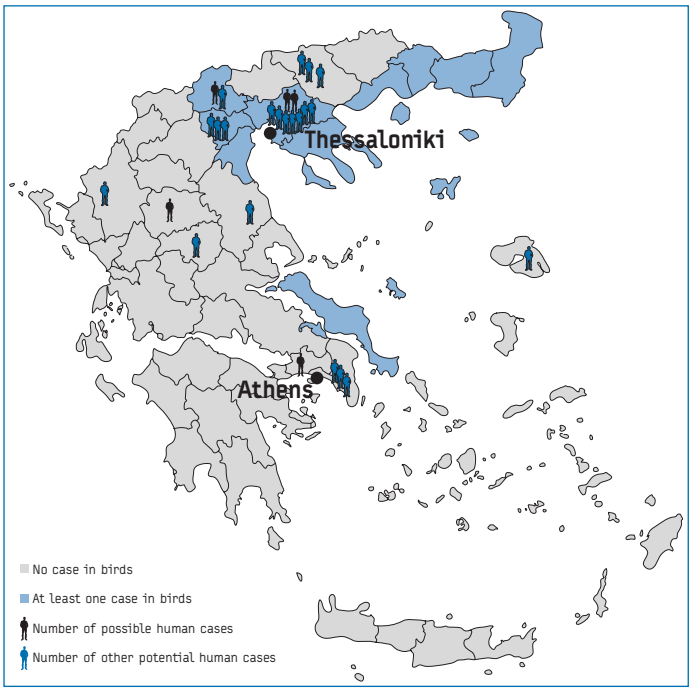
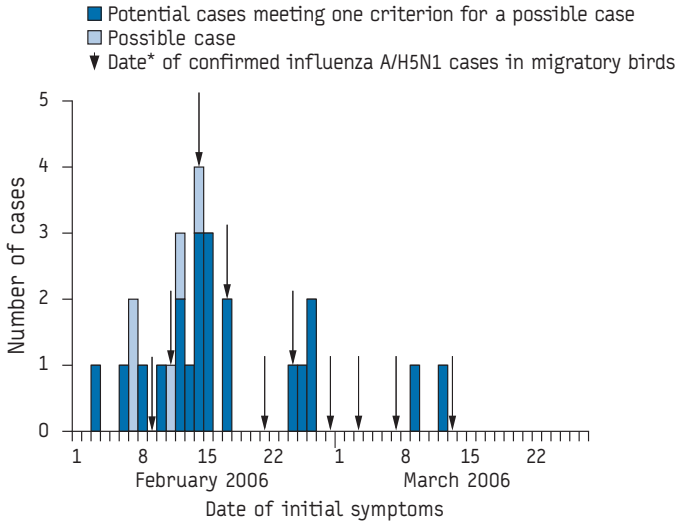


FIGURE 2

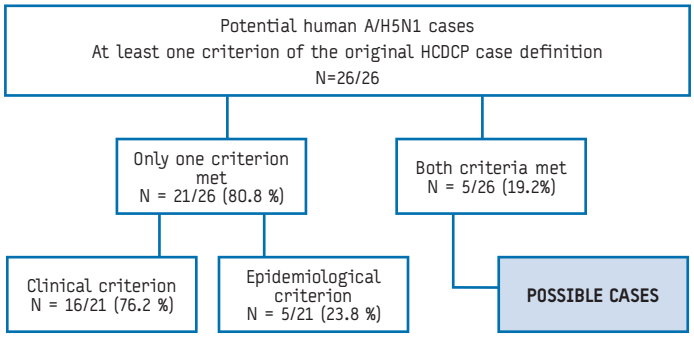
Potential human A/H5N1 cases over time and dates of A/H5N1 in birds, Greece, February-March 2006



* Date of H5 testing completion (all later confirmed to be H5N1 positive)

FIGURE 3

A flow chart showing evaluated cases and their classification according to the original definition of a possible case, Greece



Note : The original definition is the one from the Hellenic Centre for Diseases Control and Prevention (HCDCP)

Human A/H5N1 cases were suspected in 9 of the 51 (17.6%) prefectures of Greece. Most of them (84.6%) presented in northern Greece [FIGURE 1]. Confirmed A/H5N1 cases in migratory birds were detected in 10 of the 51 (19.6%) prefectures of Greece, mostly in northern Greece [FIGURE 1]. In 3 of the 51 prefectures, both confirmed A/H5N1 cases in birds [12/33 (36.4%)] and potential human cases were identified. The majority of potential human cases (61.5%) clustered in these three prefectures [3/5 (60%) met the possible case definition versus 11/21 (52.4%) meeting one criterion only, P=NS]. Four of the five patients meeting the possible case definition were seen from the northern geographical prefectures [FIGURE 1] with confirmed A/H5N1 cases in wild migratory birds [FIGURE 1].

The application of the revised HCDCP definition in the dataset resulted in the exclusion of two of the five patients who met the definition of a possible case. Both had exposure to birds relating to hunting activities and one of them was not living in a prefecture with confirmed A/H5N1 cases or in a neighbouring prefecture.

In Greece the 2005-2006 influenza activity increased from between the fifth and thirteenth week of 2006, but it was lower than that observed during the influenza season of 2004-2005. During the period February-March 2006, 3080 ILI cases over 123 921 visits (2.5%) were reported for the entire country (482 ILI cases over 30 296 (1.6%) visits for any cause in the districts affected by A/H5N1 in migratory fowl versus 2598 cases of ILI over 93 625 (2.8%) visits for the rest of the country).

Discussion

Several potential human cases were identified after the recently confirmed highly pathogenic avian influenza A/H5N1 cases in migratory birds in Greece. These cases were more likely to present in areas with confirmed cases in migratory birds. A case definition that combined clinical and epidemiological criteria assisted in identifying patients more likely to exhibit a true infection (possible cases according to the definition). Possible cases clustered around early February 2006, which was when the first avian influenza cases in dead wild migratory birds were identified in Greece. The case definition, together with molecular testing, assisted in excluding real H5N1 human infection.

In the initial phase of the epizootic in wild birds, a more sensitive approach in defining a possible case was considered appropriate by the Greek public health authorities. However this approach may be associated with several practical problems. The application of a crude epidemiological criterion by physicians in the emergency departments could lead to over-diagnosis and unnecessary admissions. Most of the potential cases evaluated were admitted to hospital for observation in isolation. In addition, molecular testing was performed for all potential cases, regardless of whether or not they met the definition of a possible case. Despite the fact that these cases were quickly discharged after the results of molecular testing, this rate of admissions indicates anxiety and fear on the part of both healthcare workers and the patients asking for extra attention. Other organisations, such as the Health Protection Agency (HPA) in England and Wales, have devised a structured algorithm including in the clinical criterion defining a possible case the decision to hospitalise or not [16]. In the HPA case definition it is implied that only seriously ill cases in need of hospital care will be admitted. Obviously, using such a criterion in a case definition requires good training of physicians and would not have worked well in Greece during this particular period of time. However, all case detection and surveillance systems based on detecting people with moderate to severe respiratory symptoms must be expected to detect cases continuously. In Thailand, a country heavily hit by outbreaks of A/H5N1 in poultry all people with severe respiratory problems are investigated. Between 1 January and 31 August 2006, 4500 cases of clinical influenza or pneumonia cases were evaluated in Thailand, and only 2 positive A/H5N1 cases were detected [17]. It would be more worrying if a surveillance system was not detecting suspect H5N1 cases coming through it continuously such as the ones

presented here. A detailed textual guidance document on handling such cases, such as the one proposed by the French public health authorities [18], may be more appropriate. As more experience is gathered, more detailed documents, harmonised at a European level, on, for example, clinical criteria for hospital admission, may accompany the formal definitions, in order to avoid multiple variants of case definitions in each country. In Greece, it seemed that the question of whether or not the epidemiological criteria was met, was as important as the severity of the clinical picture in deciding to admit them. A contributing factor was the anxiety experienced by the evaluating physicians.

An interim case definition for human avian influenza possible cases was proposed by the ECDC almost two months after the initial cases in migratory birds in Greece. The revised HCDCP definition followed the ECDC guidance and differs from the initial HCDCP definition in several regards. The clinical criteria of symptoms are broader and include not just cough or shortness of breath but acute respiratory infection as a syndrome [TABLE 1]. Death is attributed to an acute unexplained respiratory illness, not simply any respiratory illness. In the epidemiological criteria [TABLE 1]. the contact must be with sick or dead avian species (not simply any live species of wild birds, as was the case with the initial HCDCP definition). This definition further excludes contact related to hunted birds. Moreover, the term 'affected area' includes only prefectures with suspect or confirmed cases of A/H5N1 in birds and their neighbouring prefectures rather than the entire country. This definition, when applied to the initial observations, excluded two of the five cases that met the original definition of a possible case.

The revised case definition was applied to the original data some time after the initial case evaluation (April-May 2006). Since only two cases meeting the definition of a possible case were excluded, one can speculate that these patients might have avoided admission to hospital. However the majority of the other cases (17/21 potential cases not meeting the case definition of a possible case) were also admitted. If the reaction of the evaluating physicians was appropriate, no patients except for those meeting the definition of a possible case should have been admitted. In addition, the admitted patients should have been discharged when the laboratory tests results were found to be negative, since the clinical picture was not severe.

The revised definition opted for more specificity with the addition of several epidemiological parameters. The geographical criterion for surveillance was reduced to include the local and the neighbouring prefectures with H5N1 cases in avian species, rather than the entire country. The area of 10 km around a confirmed H5N1 bird case was still much wider than the zone used for biosecurity measures, to ascertain that no human cases would be missed. The geographical criterion for surveillance can be treated in a more specific manner depending on the level of animal surveillance as well as the level of communication between human and veterinarian public health authorities. Communication between central and local public health authorities is of great importance in this respect, in addition to educational activities and specific exercise testing with active participation of the local public health personnel. As these are enhanced, the affected area definition can be modified to include smaller geographical areas, further increasing specificity in identifying possible cases. The revised case definition also takes viral characteristics into consideration. The current low transmissibility of avian influenza A/H5N1 virus from avian species to humans [9] justifies stricter approaches in defining a possible case. Although no predictions can be made about the future transmission potential of the A/H5N1 virus, several genetic barriers need to be surpassed for such a major event to occur [19]. If this happens, the possibility of a virus that is associated with milder clinical features cannot be excluded [10]. Nevertheless, defining a possible case is a continuously evolving process and should be modified according to the specific clinical and epidemiological characteristics of the circulating virus.

With regards to the cost of admissions no specific data were available. The cost was low since no patient was hospitalised in an intensive care unit, and the length of stay was short. However, if many similar cases had presented to local hospitals the cost would have dramatically increased.

These observations highlight the need for immediate and direct education that should target first healthcare workers and then the general public. In a more serious scenario, actions like the ones observed in this study could rapidly lead to a depletion of healthcare resources. Nevertheless the Greek authorities including the HCDCP and the Ministries of Health and Rural Development and Food made every possible effort to educate, protect and inform both healthcare workers and the public. Healthcare worker training included 'training the trainers' sessions (committees on infectious diseases in each hospital), seminars delivered locally by HCDCP personnel, guidance on standard operating procedures and formal exercise testing in the hospitals. In addition a 24/7 on-call duty system operates in the HCDCP, with a command centre evaluating urgent phone calls relating to communicable diseases from the entire country. However, the decision to admit in all these cases was always left with the treating physician. The authors believe that this system during the specific period did not lead to the avoidance of unnecessary admissions, because of the anxiety experienced by the physicians and the pressure to admit from patients and their families. During this period, a discharge from hospital that felt 'safe' for physicians could only come about after negative laboratory results.

The intense media attention both in Greece and elsewhere likely contributed to some of the observations, along with genuine concern following fatal cases in other countries. The public needs to be completely and accurately informed about the risks from avian influenza. In Greece, public information activities during that period and afterwards included: a) participation in press conferences, television shows and video spots on national television b) issuing oral and written statements to the press, c) publication of educational leaflets for the public and travellers, both on paper and on the official web sites of the authorities d) local visits in the affected areas and high-risk prefectures, ('for example' those with confirmed H5N1 cases in wild fowl and affected neighbouring countries) and e) special educational activities and printed materials for farmers and poultry workers. These activities will be continued in autumn and winter 2006-2007, but should be accompanied by a quality control procedure.

It has previously been shown that media campaigns have helped to convey appropriate preventive healthcare messages, especially when targeting specific high-risk groups [20]. However, this is not always an easy task. Just before the 2005-2006 influenza season in the United States, there was a surge in the purchasing of influenza antivirals as evidenced by a surveillance system targeting syndromic data [21]. Nevertheless, this increase was not associated with true epidemiological markers of influenza activity and it was simultaneously observed with the media coverage of avian influenza A/H5N1 and the possibility of an influenza pandemic [21]. The role of the media in the conveyance of appropriate messages to the public as we prepare for pandemic influenza is of critical importance. Accurate information should be aimed particularly at carefully selected high-risk groups. In Europe the ECDC has issued a scientific guidance document to be used by national authorities in drafting public messages for at risk populations [22]. Such clear messages are essential in future attempts by local governments to control the anxiety associated with the continuous flow of data about the disease, especially when avian and/or animal cases are observed locally.

The findings of the current work have important implications for public health systems dealing with confirmed cases in wild migratory birds and suspect potential cases in humans. Well-organised surveillance systems with the assistance of expert molecular testing can effectively handle these cases. Continuous healthcare worker training is necessary. Collaboration of local authorities with media experts is essential in conveying the appropriate messages to help decreasing unspecific fear in the public so that the health system does not get overwhelmed.

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ORIGINAL ARTICLES

Outbreak report

A MEASLES OUTBREAK IN CHILDREN UNDER 15 MONTHS OF AGE IN LA RIOJA, SPAIN, 2005-2006

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This paper describes a measles outbreak in La Rioja, Spain, which began in December 2005 and mainly affected children under 15 months of age who were not yet immunised with MMR vaccine. The measles cases were detected by the mandatory reporting system, under which laboratories must report every confirmed measles case. Cases were classified in accordance with the National Measles Elimination Plan: suspected and laboratory-confirmed. In the period 14 December 2005 to 19 February 2006, 29 suspected cases of measles were investigated, and 18 were confirmed. The mean incubation period was 13.8 days (range: 9 to 18). Of the 18 confirmed cases, only two were in adults. MMR vaccination was recommended fpr all household contacts, as well as for children aged 6 to 14 months who attended the daycare centres where the cases had appeared. At these centres, the second dose of MMR was administered ahead of schedule for children under three years of age. It was recommended that the first dose of MMR vaccine be administered ahead of schedule for all children aged 9 to 14 months. During an outbreak of measles, children aged 6 months or older, who have not previously been vaccinated against measles, mumps and rubella, should receive a first dose as soon as possible, and those who have had a first dose should receive a second dose as soon as possible, provided that a minimum of one month has elapsed between the two doses.

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