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Hantavirus infection: a review of global and local situation

Background

Hantaviruses are ribonucleic acid (RNA) viruses which belong to the family of bunyaviruses (*Bunyaviridae*). The *bunyaviridae* is one of the families under the big umbrella of viral hemorrhagic fevers (VHF). Rodents are the main natural host for hantaviruses and the viruses are transmitted to human as incidental hosts. Rodents infected with hantavirus do not usually manifest with symptoms.[1] Infection in human is categorised into two distinct clinical syndromes: i) hemorrhagic fever with renal syndrome (HFRS), and ii) hantavirus pulmonary syndrome (HPS).

Epidemiology

At least 23 species of hantavirus genus has been recorded by the International Committee on Taxonomy of Viruses (ICTV), together with many other unclassified hantavirus identified worldwide.[2] In general, each hantavirus species has a specific primary rodent host, and the geographical distinction of the virus prevalence correlates with the geographical distribution of the rodent host (*Fig. 1*).[3]

It is likely that the actual number of human infection with hantavirus could have been underestimated worldwide. A Finnish study estimated that at least 70% of the Puumala (PUU) virus infection was undiagnosed. A study in China found that the ratio of clinical to subclinical infection was 1:5 in some rural areas.[4] In the Americas, severe cases were noted to be less common compared to those with milder symptoms.[5] A seroprevalence study conducted at four hantavirus-endemic agroecosystems communities in Panama from 2001 to 2007

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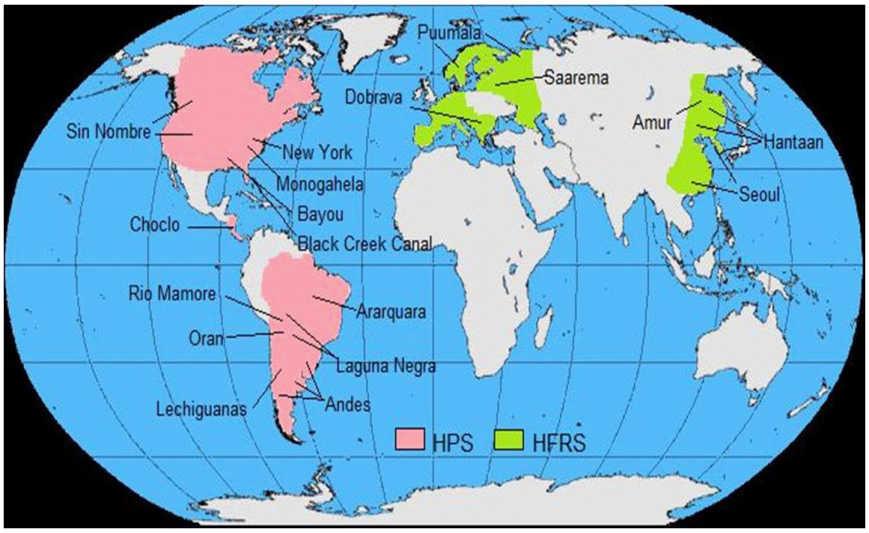
Figure 1
Global geographical distribution of hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS)



Source: Bi ZQ, Formenty PBH, Roth CE. Hantavirus infection: a review and global update. J Infect Developing Countries 2008; 2:3-23.

revealed that asymptomatic or mild infection was common. Of the 857 subjects surveyed, 70 showed serological evidence of immunity against hantavirus infection; this was equivalent to eight infections per 100 person-years. The ratio of asymptomatic/ mild infection to severe infection resulting in HPS in the study was 14:1.

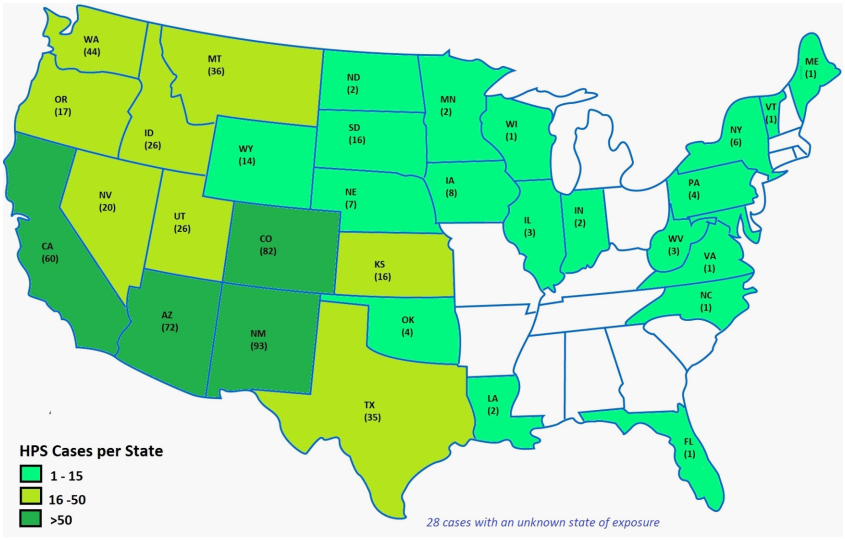
The United States

HPS is endemic in some states of the United States (U.S.) [6], however relatively low numbers of HPS of approximately 20 to 40 cases are reported each year. Between 1993 and 21 April 2014, a total of 639 cases of HPS from 34 states had been reported to the Centers for Disease Control and Prevention (CDC)[7] (*Fig. 2*). The case-fatality rate (CFR) between 1993 and 2013 was 36%.[8] Of the 637 cases reported during this period, approximately three-quarters of them resided in rural areas. Male patients constituted 63% of the total cases. The age of the cases ranged from six to 83 years.[9]

Europe

Hantavirus infection in human is widely distributed across Europe, especially in northern Europe. In 2010, the European Centre for Disease Prevention and Control (ECDC) recorded 4,196 confirmed cases from 17 Europe Union (EU) and European Economic Area (EEA) countries, an increase of 71% compared to 2,459 cases reported in 2009.[10] However, the figures in 2010 were on par with 2008, when 4,529 cases were reported.[10] Of the cases reported in 2010, 97% occurred in Finland, Germany, Sweden and Belgium. Approximately 77% of the patients were adults, ranging from 25 to 64 years of age, with the highest incidence observed in the 45 to 64 age group.[10] Similar

Figure 2
Number of hantavirus pulmonary syndrome (HPS) cases by state of exposure, U.S., 1993 - 21 April 2014



Source: Centers for Disease Control and Prevention. Hantavirus.

to the U.S., infection occurred more frequently in men than women, with a ratio of 2:1. In Europe, the three most common species of hantavirus detected were PUU virus, Dobrava-Belgrade (DOB) virus and Saaremaa (SAA) virus.[11]

Asia

An epidemiological study conducted by the Chinese Center for Disease Control and Prevention (CDC) in 2012 revealed that the annual number of HFRS cases increased steadily from early 1970s,[12] and peaked in 1986, when a total of 115,804 patients were recorded from all 31 provinces. The incidence rates from 2006 to 2010 ranged between 0.66 per 100,000 population and 1.15 per 100,000 population, with a total of 53, 471 cases reported. A bimodal distribution pattern for HFRS was observed in **China**, with the first peak occurring in spring and lasting from March to May, and a relatively shorter second peak in winter.

In a serological study conducted from May 1999 to November 2000, 13 of 115 patients with fever of unknown origin admitted to Siriraj Hospital in **Thailand,** were tested positive for hantavirus. These were the first recorded clinical cases of hantavirus infection in Thailand.[13]

In 2008, a cross-sectional study conducted to determine the prevalence of leptospirosis and hantavirus infections in **Sri Lanka** detected eight cases of hantavirus among 105 patients with suspected leptospirosis. Further enzyme-linked immunosorbent assay (ELISA) serotyping showed that the virus infecting the patients was a Thailand (THAIV) virus-related hantavirus.[14]

As of 2001, there were six human cases of hantavirus infection reported in **Malaysia**. The first case was detected in Singapore in 1985, but was suspected to be infected in Malaysia as the case had travelled to Malaysia prior to becoming ill. The second case was reported in 1987, and the third case was a man from Scotland who had worked in Malaysia for six months.[15] A study conducted in 2001 found three cases among 119 patients with chronic renal failure of unknown cause in a hospital in Kelantan. One of the cases had antibodies against both Hantaan (HTN) virus and Seoul (SEO) virus detected in the serum, and antibodies against the Sin Nombre (SN) virus was detected in the serum of the remaining two cases.[15]

Transmission

Rodents are predominantly found in rural areas which are conducive habitats.[16] Infected rodents transmit hantavirus in their urine, droppings, and saliva. Most humans get infected through inhalation of virus-contaminated aerosols of rodent excreta.[1] Transmission may also occur when broken skin or mucous membranes of the eyes, nose, and mouth are in direct contact with the infected substances. In addition, human may get infected from rodents' bites or through consumption of contaminated food.[17] The infectivity of hantavirus has been reported to persist in neutral solutions for several hours at 37^{0}C, for several days at lower temperature, and for up to two days in dried cell-culture medium.[18]

Norway rats (*Rattus norvegicus*) are commonly found in urban areas, which coincide with the detection of HFRS cases in city areas in several Asian countries such as China, Sri Lanka and Singapore.[17,19] In Germany, the proportion of HFRS cases detected among residents in urban counties of Baden-Württemberg state increased from 7% between January and April of 2007 to 25% during the same period in 2010. The cause of this increase was unknown, however several hypothesis were drawn including the influx of rodents into human habitats during extreme cold winter, increase in human activities in periurban areas, and basic shifts in the epidemiology of the virus in rodent population.[20]

Transmission of hantavirus among human is extremely rare. So far there have been no reported cases of human-to-human transmission in the U.S.[21] In a study on healthcare workers who had been exposed to patients infected with hantavirus, none showed evidence of infection or illness.[21] Infection through blood transfusion from a person who has previously been infected is also deemed unlikely.[21]

However, probable human-to-human transmission of Andes (AND) virus had been documented in Argentina in 2002.[22] Epidemiological investigation found that the 13 infected cases from four clusters were unlikely to have common environmental exposure(s) within each cluster; however, they were in close contact with the index cases.[22]

Seasonality

The transmission of hantavirus seems to occur in a seasonal cycle[10,12], with higher occurrence in spring than in fall.[23] A study conducted on rodents kept in outdoor enclosures found that the incidence of SN virus transmission in rodent peaked at the beginning of the breeding season which was typically between May and June.[24] On the other hand, there was no significant difference between the levels of viral transmission in enclosures with high rodent density and low rodent density. The results suggested

that seasonality might have a stronger influence on transmission dynamics than rodent population density.

Similarly, it has been observed that the number of human cases varies in a seasonal manner. In Belgium and France, an increase in human cases was found to be associated with a higher rodent population, which often occurred during the mast years. A mast year is a year in which vegetation produces a significant abundance of mast (fruit). This provides food for rodents and stoats, whose populations can explode. Seasonal variations in the number of human cases have also been observed in agricultural settings in Asia and Europe, where human exposure to rodents increases during the period of planting and harvesting of crops.[25]

Climate change

The first outbreak of HPS in the Four Corners of the U.S. was believed to be related to El Niño event. [26] Between 1992 and 1993, high rainfall was recorded in the area due to the effects of El Niño. This was followed by a 20-fold increase in the rodent population, and the outbreak in human occurred thereafter. This suggested that global climate change could significantly alter the dynamics of host–pathogen interaction.[23]

However, a study conducted in Sweden found no correlation between the occurrences of North Atlantic Oscillation (NAO) and the number of HFRS cases. In view of the conflicting results, researchers suggested a need to conduct long-term studies to better understand the effect of climate change on the prevalence of hantavirus infection in rodents and humans.

Clinical manifestation

HPS cases are mainly found in North and South America, while HFRS are usually detected in Europe and Asia. HPS is a severe and sometimes fatal respiratory disease in human, and is characterised by respiratory failure caused by accumulation of fluids in the lungs[27]. The main clinical manifestation of HPS includes fever, muscle aches and shortness of breath. Symptoms may develop between 1 and 5 weeks after exposure. The CFR of HPS can be as high as 50%.[28]The symptoms of HFRS usually develop within 1-2 weeks after exposure, but may take up to eight weeks with sudden onset of fever, lower back pain, bleeding manifestations, and kidney failure. [29] The severity of the disease depends on the type of virus that causes the infection, with the estimated mortality rate ranging from 5% to 15%.[28]

Diagnosis

The diagnosis of hantavirus infections is based on clinical and epidemiological information and laboratory tests. Clinical diagnosis of HFRS and HPS is difficult, as early symptoms such as fever, muscle aches, and fatigue can be easily confused with influenza or other diseases such as leptospirosis. A history of exposure to rodents is a strong indication of hantavirus infection.[30]

Laboratory confirmation is primarily based on serology, since the viraemic phase of the infection is short-termed. Levels of virus-specific antibodies increase rapidly and are detectable at the onset of diseases. Furthermore, serological assays are readily accessible to most hospitals. Viral RNA cannot be regularly detected in the blood or urine of hospitalised patients, although the virus has been shown to be detectable by polymerase chain reaction (PCR) during acute illness in research laboratories.[30, 4]

Treatment

Currently, there is no specific treatment or antiviral therapy for hantavirus infection. Patients

infected with HFRS and HPS are managed with supportive treatment.[29] Nevertheless, administration of intravenous ribavirin, an antiviral drug, during very early stage of the disease has been shown to improve recovery and reduce deaths associated with HFRS.[29]

To date, there is no WHO-approved vaccine available for the prevention of hantavirus infection.[31,32] However a few countries in Asia, including Democratic People's Republic of Korea (DPPK), the Republic of Korea (ROK), Japan and China have developed their own vaccines against HFRS.[31],[33]

Local situation

In Singapore, five sporadic cases of human infection with hantavirus have been reported between 1980s and 2010. The presence of hantavirus in commensal rodents and human were first reported locally in the 1980s. To determine the extent of hantavirus infection in Singapore, a sero-epidemiological survey was conducted on commensal rodents and four different diagnostic groups of patients between January 1985 and June 1986. Around 26% of the rodents captured were seropositive for hantavirus, and a hantavirus species, R36, was isolated from the captured Norway rats.[34] The same study demonstrated 8% IgG seropositivity in suspected cases of dengue haemorrhagic fever (DHF), 8% in non-A/ non-B hepatitis patients, 3% in suspected cases of leptospirosis, and 2% in acute nephritis patients. The suspected cases of DHF and leptospirosis were tested negative for the respective infections.[34]

Of the five cases reported in Singapore, two occurred in the 1980s, and the third case was reported in 1992 involving a ragman who presented with classical manifestations of HFRS.[35] HTN virus was detected in the serum of the third case through immunofluorescent assay (IFA).[36] The fourth and fifth cases were reported in 2010, involving a 41-year-old construction site supervisor and a 35-year-old information technology (IT) executive. [35]

Measures by public health agencies

Rodent control

Singapore is one of the busiest ports in Asia, rendering it both susceptible and vulnerable to the importation of infectious diseases through rodent infested maritime vessels. At our local sea ports, the Port Health Office under the National Environmental Agency (NEA) works together with the Maritime & Port Authority (MPA) to manage inward health clearance and quarantine of vessels. Their primary tasks are to control the arrival of vessels from plague-infected countries, vessels with human deaths or sickness on board, and vessels with high mortality rate among rodents. Such vessels must anchor at designated quarantine anchorage upon arrival for inspection.[37, 38]

Other than port health, NEA also controls and manages rodents in the city state.[39] NEA adopts a risk-based approach by targeting areas where the environment is conducive to the propagation of the rodent population.

Hantavirus is a notifiable zoonotic disease under Animals and Birds Act, administered by the Agri-Food and Veterinary Authority (AVA). Importers of animals including rodents as pets or for laboratory use are required to comply with a set of veterinary conditions.[40]

Human surveillance

Hantavirus is not a legally notifiable disease under the Infectious Disease Act (IDA) as the incidence of the disease in human has been low.[41] As the clinical presentation of the disease is non-specific, cases of hantavirus infection might have been missed or not reported in the past. The Ministry of Health (MOH) has implemented the Severe Illness and Death from Possible Infectious Diseases (SIDPIC) project in collaboration with the restructured hospitals, which focuses on investigation of unexplained deaths and critical illnesses with suspected infectious disease aetiology. The project serves as a surveillance programme for emerging infections caused by pathogens such as hantavirus.

Our local laboratories under NEA, Defence Science Organisation (DSO), and Singapore General Hospital (SGH) have the capabilities to detect hantavirus by PCR and/ or serology.

Risk assessment

Through seroprevalence studies, the local rodent population has been shown to be susceptible to hantavirus infection. Hence, the likelihood of human cases of hantavirus infection is possible, and this is reinforced by previous reports of sporadic local cases. However, the risk of an outbreak of hantavirus infection in Singapore is assessed to be low because (a) stringent rodent importation and control measures are in place, (b) the standard of environmental sanitation is high, and (c) the number of reported human cases is very low and sporadic, and human-to-human transmission of the disease is extremely rare. Surveillance of the disease through the SIDPIC programme facilitates early detection and appropriate management of human cases. In addition, good local field epidemiological capabilities, and strong collaboration amongst MOH, AVA and NEA would enable effective public health responses to any local outbreaks of hantavirus.

(Contributed by Public Health Intelligence Unit, Epidemiology & Disease Control Division, and Communicable Diseases Division, Ministry of Health)

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Virological surveillance of influenza-like illness in the community in Singapore, 2010-2013

Introduction

Influenza causes mild to severe illness and can lead to death. About 5% to 15% of the population worldwide are affected with upper respiratory tract infections (URTI) in seasonal influenza epidemics, resulting in about 3 to 5 million cases of severe illness, and between 250,000 and 500,000 deaths every year.[1] The considerable disease burden due to past influenza pandemics and the emergence of influenza A(H1N1)pdm09 virus in 2009 further underscore the importance of influenza surveillance.[2,3]

In Singapore, URTI was the top medical condition seen at government polyclinics and private general practitioner (GP) clinics based on the Primary Care Survey conducted by the Ministry of Health (MOH) in 2005 and 2010, and constituted 25% of all diagnoses in both years.[4] Seasonal influenza was associated with 8.3 deaths per 100,000 population based on a modelling study which used influenza virological data from 2004 to 2006.[5]

The MOH has a national surveillance programme for influenza, which includes virological surveillance to monitor the circulating viruses in Singapore. The purpose of our study was to describe the influenza activity in the community from 2010 to 2013 based on virological surveillance.

Materials and methods

As part of MOH's influenza virological surveillance, nasopharyngeal and/or throat swabs are taken from attendees at polyclinics and sentinel GP clinics with influenza-like illness (ILI).[6] The symptoms of ILI are fever with a temperature of at least 37.8°C, and cough or sore throat.

The National Public Health Laboratory and designated hospital laboratories carry out real-time reverse transcription polymerase chain reaction (RT-PCR) to detect influenza virus types and subtypes.

Results

During the four-year period from 2010 to 2013, a total of 13,858 samples were tested, of which 59.8% were taken from attendees at private GP clinics.

Approximately 33% of the samples tested were from children aged below 15 years, 19% from the age group of 15-24 years, 29% from the age group of 25-44 years, and 16% from the age group of 45-64 years. Samples from the elderly aged 65 years and older constituted about 3% of all ILI samples. The proportion of samples collected from the elderly with ILI increased from 2.6% in 2010 to 4.6% in 2013.

About 46.1% (6,389) of the samples tested positive for influenza during the study period. In the post-pandemic year of 2010, the influenza positivity was lowest in the elderly aged 65 years and older (*Table 1*). The annual trend of influenza positivity fluctuated across all age groups, with relatively lower influenza positivity observed in children and adolescents below the age of 15 years in the past 3-year period between 2011 and 2013.

Table 1

Outpatient attendees with ILI and proportion (%) tested positive for influenza by age group, 2010-2013

Age group (years)	2010		2011		2012		2013	
	No. of samples tested	% tested positive	No. of samples tested	% tested positive	No. of samples tested	% tested positive	No. of samples tested	% tested positive
Total*	7,038	49.7	2,885	40.5	2,119	46.0	1,816	41.6
0-14	2,342	49.0	888	34.2	664	40.1	530	34.9
15-24	1,385	53.0	544	41.5	368	44.3	333	36.0
25-44	1,984	50.0	821	44.0	625	51.0	513	49.5
45-64	966	47.5	480	45.6	357	50.1	339	45.4
65+	185	40.5	98	37.8	81	44.4	84	42.9

*Includes 271 samples with unknown age in the 4-year period.

Every year, bimodal peaks in the monthly influenza positivity were observed between May and July, and between December and January (*Fig. 3*). The highest monthly influenza positivity in each year ranged from 56.4% in January 2011 to 65.3% in December 2013.

The predominant virus subtype circulating in the middle of each year was consistently influenza A(H3N2), while influenza A(H1N1)pdm09 was the predominant virus subtype from December 2009 to January 2010, and from December 2010 to January 2011 (*Fig. 4*). Influenza A(H1N1)pdm09 and influenza A(H3N2) co-circulated in the community from December 2012 to January 2013. Influenza B was the predominant virus type circulating from December 2011 to February 2012.

After the 2009 pandemic, influenza A(H1N1) pdm09 virus continued to be the predominant circulating subtype in individuals aged 64 years and younger in 2010, while the elderly aged 65 years and older were mainly infected by influenza A(H3N2) virus (*Fig. 5*). Individuals aged 44 years and younger were still affected by influenza A(H1N1)pdm09 virus in 2011, while influenza A(H3N2) virus was the predominant influenza subtype in individuals aged 45 years and older. In 2012, there was a switch to influenza B virus as the predominant influenza type in all the age groups, with influenza A(H3N2) virus co-circulating in individuals aged 65 years and older. Influenza A(H3N2) was the predominant influenza subtype in all age groups in 2013.

Comments

Influenza viruses circulate throughout the year in Singapore, and there are typically two periods of higher influenza activity in the beginning and middle of the year. These two periods coincide with the

Figure 3
Monthly influenza positivity, January 2010 – December 2013

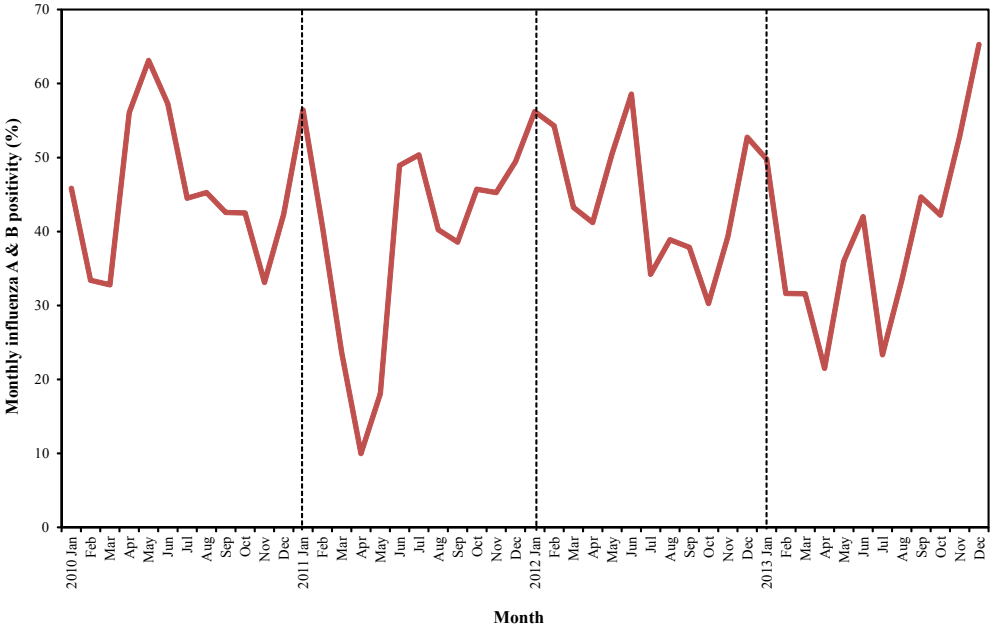


Figure 4
Monthly virus type/subtype distribution, January 2010 – December 2013

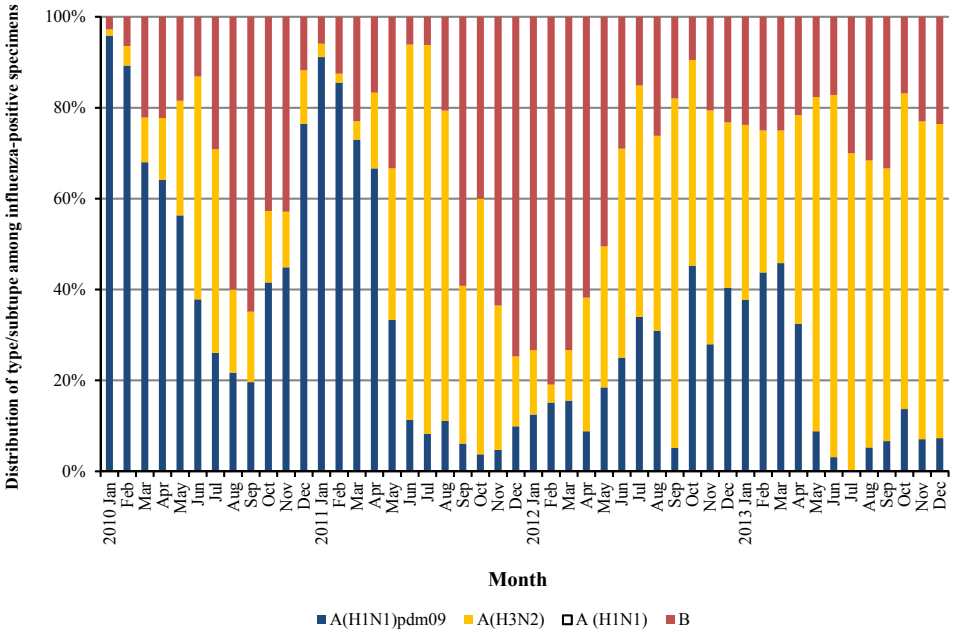
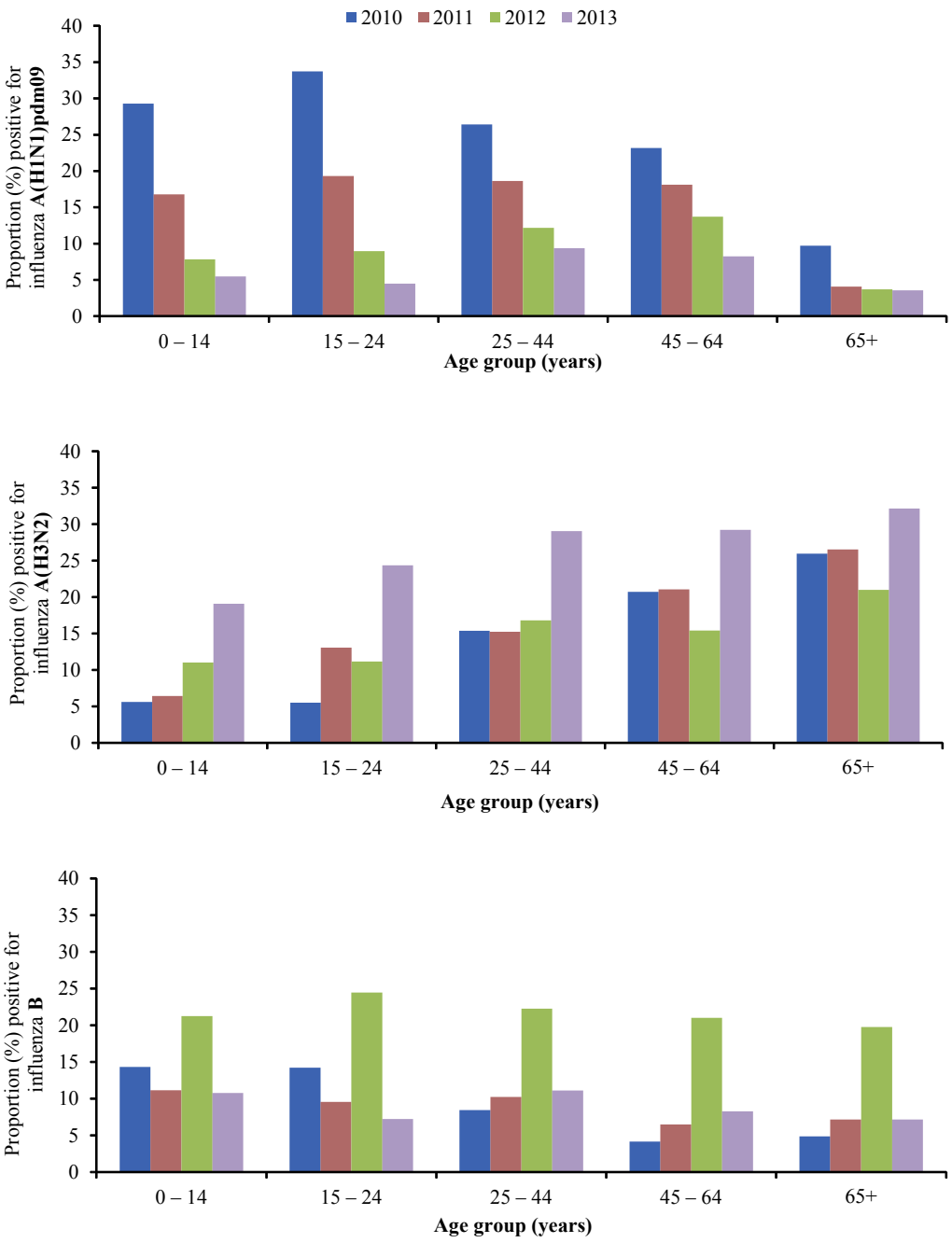


Figure 5
Age-specific influenza positivity (%) by virus type/subtype, 2010-2013



Northern and Southern Hemisphere winter seasons, respectively, when a rise in influenza activity in the temperate countries is observed. The bimodal pattern of influenza activity is also observed in other tropical and subtropical countries in South-East Asia, such as Indonesia, Myanmar, Thailand and Vietnam.[7-11]

One limitation of our study was the small number of samples taken from elderly outpatient attendees with ILI. Only 3% of the samples collected for virological surveillance in the four-year period were from the elderly aged 65 years and older. Based on statistical modelling studies, influenza-associated mortality rate and hospitalisation rate were found to be highest in the elderly.[12-15] Hence, there is a need to enhance influenza surveillance of the elderly for more precise estimation of influenza burden in this high-risk age group.

The monitoring of the circulating viruses in Singapore provides an indication of impending spikes in influenza activity. Identifying peak periods of influenza activity can help to facilitate planning and implementation of annual public health interventions to prevent and control influenza.[16,17] Annual public education campaigns by the Health Promotion Board are timed and rolled out in anticipation of higher level of influenza activity. The public is encouraged to practise hand hygiene and respiratory etiquette, and to seek treatment early if they have symptoms of ILI.[18] Individuals belonging to populations at higher risk of complications of influenza are encouraged to get vaccinated in order to protect themselves against influenza. With effect from 1 January 2014, persons at higher risk of developing influenza-related complications are allowed to use their Medisave for influenza vaccination.[19]

(Contributed by Lim C[1], Ang LW[1], Ma S[1], Cui L[2], James L[1], Lin RTP[2], Epidemiology & Disease Control Division[1], and National Public Health Laboratory[2], Ministry of Health, Singapore)

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Outbreak of gastroenterititis caused by *Salmonella* Enteriditis associated with the consumption of poached eggs from a restaurant in Singapore

Introduction

Salmonellosis is one of the most common food-borne infections worldwide[1]. An estimated 1.4 million cases of *Salmonella* infections are reported in the US yearly[2], while 1,499 cases of salmonellosis were reported in Singapore in 2012[3].

Salmonella Enteritidis is one of the most common serotypes worldwide, particularly in developed countries[4,5]. In Asia it has also emerged as the most common serotype in Japan, the Republic of Korea, Thailand[1] and Singapore[3].

We report the findings of our epidemiological, microbiological and environmental investigations of an outbreak of Salmonellosis, and highlight the importance of molecular typing in establishing the source of infection and its link to an asymptomatic food handler.

Notification of the outbreak

The Ministry of Health (MOH) was notified of nine incidents of gastroenteritis linked to consumption

of food in a restaurant from 10 to 18 Mar 2014. The implicated restaurant provided western cuisine for both lunch and dinner. The items served included soups, salads, pastas, and sandwiches. The restaurant also served eggs which were cooked in a variety of ways (sunny side-up, poached overeasy and scrambled) for lunch.

Methods

Epidemiological investigations

All the reported cases were interviewed and relevant clinical and epidemiological data such as age, gender, ethnicity, clinical symptoms, date of onset of symptoms, food items consumed and medical treatment sought were obtained.

A case was defined as a previously well individual who developed diarrhoea (more than 2 times in 24 hours) with/without fever after consuming food from the implicated restaurant from 9-11 Mar 2014.

Environmental investigations

A site visit was immediately made to the implicated restaurant to identify the source of infection and mode of transmission. The food preparation process was also reviewed with the restaurant management.

Microbiological investigations

Stools from the reported cases as well as food and environmental samples were taken for microbiological analysis (*Campylobacter, Salmonella, Staphylococcus aureus, Escherichia coli, rotavirus* and *norovirus)*. All implicated food handlers were referred to the National University Hospital and screened for enteropathogens.

Genotyping of *Salmonella* cultured from stool samples (determined by multiple-locus variable number of tandem repeat analysis, MLVA), was performed by the National Public Health Laboratory (NPHL). Seven variable-number tandem repeats (VNTR) loci selected for MLVA were amplified in a single multiplex PCR[6]. The PCR products obtained were then directly analysed using the QIAxcel High Resolution Kit, in combination with QIAxcel instruments.

Results

Epidemiological investigations

Based on the case definition, a total of 27 cases were identified (i.e. two cases from the first incident, five cases from the second incident, three cases from the third incident, five cases from the fourth incident, two cases from the fifth incident, four cases from the sixth incident, two cases from the seventh incident, two cases from the eighth incident and two cases from the last incident). The presenting symptoms were diarrhoea (100%), abdominal cramps (96.3%), nausea (92.6%), fever (85.2%) and vomiting (63.0%). Of these cases, eight were hospitalised (29.6%) while the rest sought outpatient treatment (70.4%).

All of the cases except two were Singaporean residents and 55.6% were males. All of them had consumed poached eggs from 1100 to 1600 hours on 9 Mar 2014 prior to their onset of symptoms. The onset of illness ranged from 2100 hours on 9 Mar 2014 to 0900 hours on 11 Mar 2014 (*Fig. 6*). The mean and median incubation periods were 14 hours and 11 hours, respectively, with a range from 7 to 41.5 hours.

Microbiological investigations

Three of 10 stool samples obtained from the cases were positive for *Salmonella Enteriditis*, MLVA type F (*Fig. 7*). Three of the nine food handlers from

Figure 6
Onset of gastrointestinal Illness of 27 reported cases associated with the consumption of poached eggs in a restaurant, 9-11 March 2014

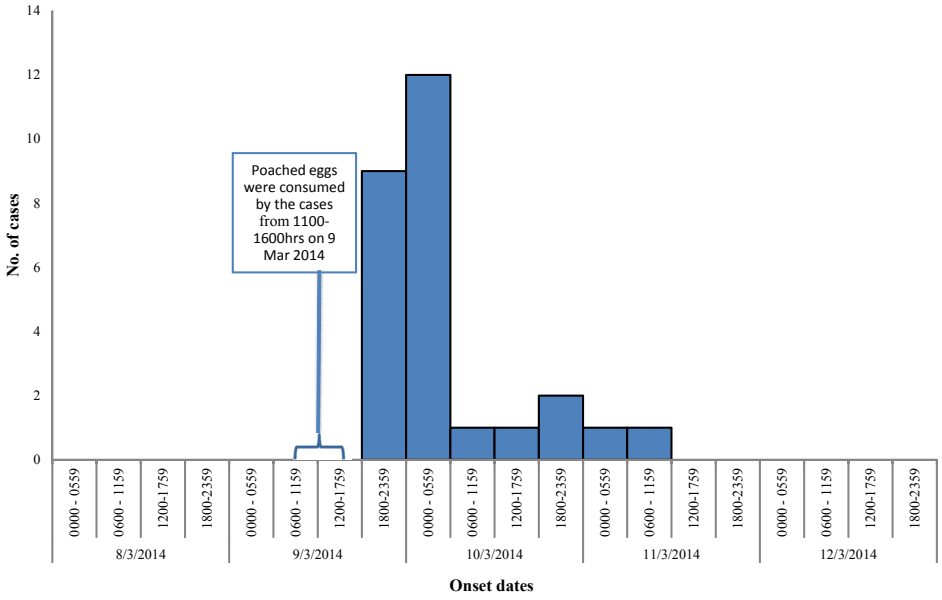
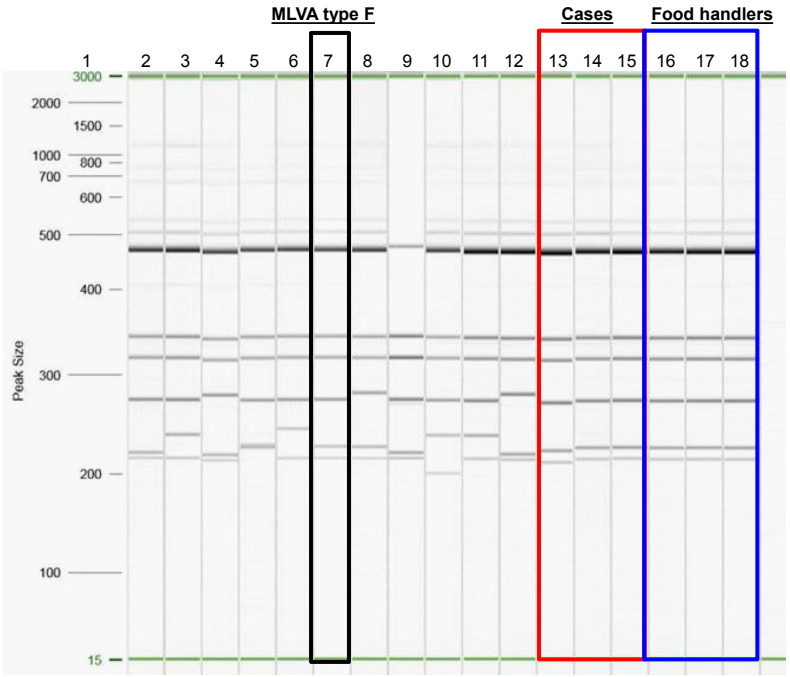


Figure 7
MLVA typing results of three *Salmonella*-positive cases and three asymptomatic *Salmonella*-positive food handlers



the implicated restaurant also tested positive for the same strain of *Salmonella Enteriditis*, MLVA type F.

Of the four food samples collected (salad, poached eggs, mayonnaise and raw eggs) for microbial analysis, the salad was found to have high total plate count (710,000 CFU/g; limit <100,000 CFU/g) and high total coliform count (460 MPN/g; limit <50 MPN/g).

Environmental investigations

The three food handlers were interviewed separately to gather more information of their duties. Following the interview, it was found that food handler 1 was in charge of preparation and cooking for most of the food items including the poached eggs. Although food handlers 2 and 3 were tested positive for *Salmonella Enteriditis*, their duties did not include the preparation of the eggs. Both food handlers also did not eat the poached eggs. Interestingly, food handler 3 only started work two days after the food poisoning incident on 9 Mar 2014 yet he was positive for the same strain of *Salmonella Enteriditis*. Both food handlers had however consumed food prepared by food handler 1, suggesting that they could have acquired the infection from food handler 1.

Food preparation process

On 7 Mar 2014, 900 eggs were delivered to the restaurant and stored in the chiller for use over the following three days, including the weekend. The restaurant usually sold the most number of eggs (about 300 eggs) on Sundays. These eggs were prepared in two batches. The first batch of 100 poached eggs was prepared on 8 Mar 2014 and used for orders from 0830 to 1200 hours on 9 Mar 2014. The second batch of 200 poached eggs was prepared on 9 Mar 2014 and used for orders from 1200-1630hours on the same day. The preparation process of the poached eggs is depicted in *Fig. 8*.

1.Preparation process of poached eggs

The preparation process of poached eggs served on 9 Mar 2014 was as summarised below:

- At 2000 hours on 8 Mar 2014, 100 eggs were placed into the oven at 65°C for 30-45 mins.
- The eggs were placed into a bowl of water and ice to stop the cooking process.
- The eggshells were removed and eggs were placed individually into a bowl. About 10-15 eggs were cooked in a pot of 70°C water with vinegar for 3-4 minutes.
- The poached eggs were then placed into a container of ice and water to stop the cooking process. About 30 eggs were placed into 1 container.
- The containers of eggs were stored in the chiller for use the next day.
- At 0800 hours on 9 Mar 2014, the remaining 200 eggs were prepared following the same procedures as above.
- Five containers of poached eggs (about 40 eggs each) were then kept in the chiller.

2. Preparation process of Hollandaise sauce

The preparation process of the hollandaise sauce is shown in *Fig. 9*. The sauce was drizzled over the poached eggs before serving.

Hygiene lapses

The following hygiene lapses were observed at the restaurant during the site visit:

Figure 8
Preparation process of poached eggs

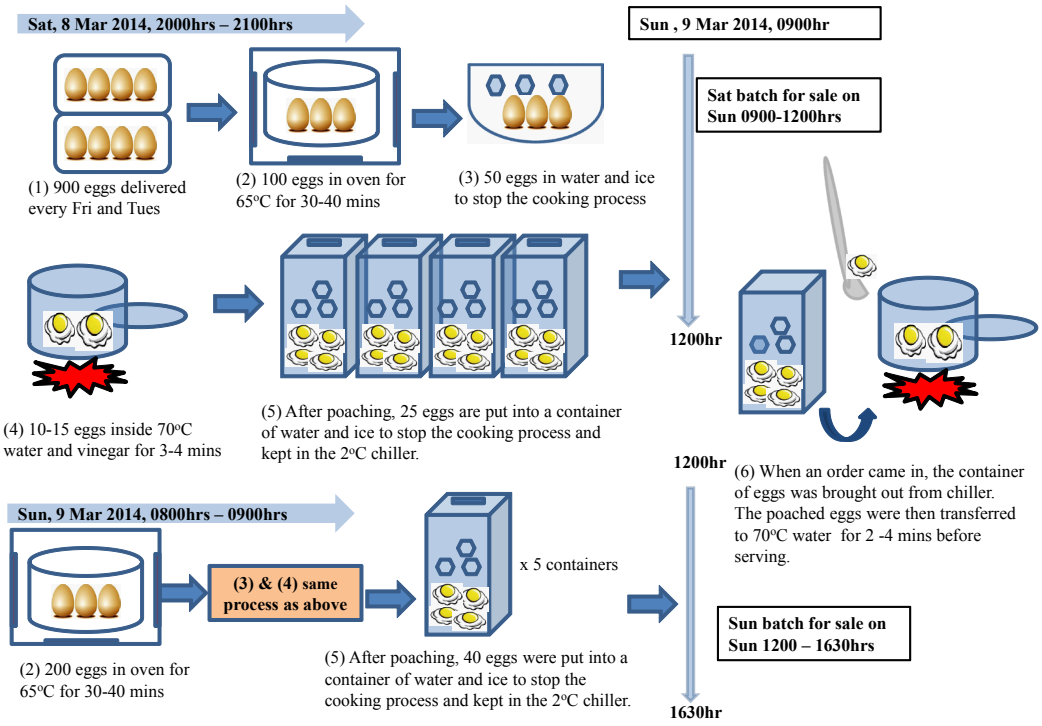
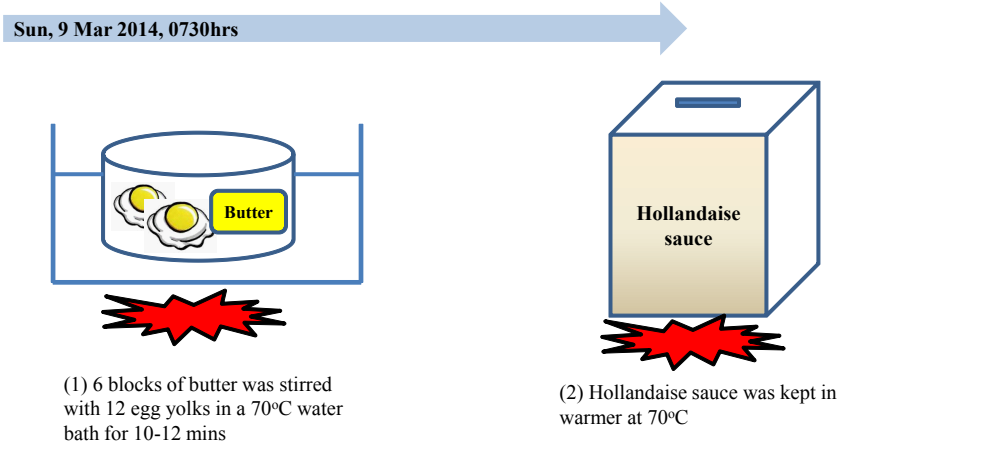


Figure 9
Preparation process of Hollandaise sauce



1) Improper storage of food (ready-to-eat fruits and egg mixture for scrambled eggs in the chiller were not covered)
2) Storage of food at incorrect temperature (opened tub of mayonnaise kept at room temperature instead of chiller)
3) Chest freezers not properly maintained (dirty gasket and ice formed at the gasket)
4) Expired bottle of sesame sauce found in the dry goods storage shelf.
5) Container of raw food (mushrooms) placed on top of chopping board for cooked food

Discussion

The epidemiological and clinical findings indicate that this was an outbreak of salmonellosis. The predominant reported symptoms (diarrhoea, abdominal cramps, nausea and fever) with a mean incubation period of 14 hours are compatible with the symptoms and known incubation period for *Salmonella* infection. This was further supported by the isolation of *Salmonella* Enteriditis from the stool samples of three cases.

This was a common source infection as poached eggs consumed at the implicated restaurant on 9 Mar 2014 was the only common food item among cases from the nine separate incidents. Moreover, the *Salmonella* bacteria isolated from 3 cases involved in separate incidents had similar MLVA type (*Salmonella* Enteritidis type F).

Salmonellosis is a bacterial disease characterized by acute enterocolitis, with sudden onset of abdominal pain, diarrhoea, nausea and vomiting. The incubation period is usually between 12 and 36 hours but it can range from 6 to 72 hours. Infection can arise from ingestion of the salmonella bacteria in food derived from infected animals or food that is contaminated by faeces of infected animals or humans[7]. Common implicated food items include raw or inadequately cooked poultry and eggs and dairy products, as well as processed meat products[7,8]. In Singapore, food-borne outbreaks of *Salmonella* Enteritidis have been associated with consumption of cream cakes[9], bread[10], and an egg-based pancake[11].

Shelled eggs can be contaminated by direct penetration of the eggshell from the colonised gut of an infected poultry or by direct contamination of the internal contents of the eggs by infected ovaries and oviducts[12]. As poached eggs were prepared without thorough cooking, any egg that was contaminated with *Salmonella* Enteritidis could contaminate an entire batch of pooled eggs, posing a risk to consumers. Although we were unable to rule out this hypothesis, it was thought to be unlikely as the affected incidents occurred from 1100 to 1600 hours suggesting that not one container but all five containers of poached eggs prepared for that day were affected. As all the eggs were poached in the same pot of water at 70 °C before they were put into five separate containers, contamination of the entire batch of eggs could only occur during poaching of the eggs at temperature of 70 °C. Again, this was unlikely.

One of the salmonella-positive food handlers, food handler 1, was involved in the preparation of the poached eggs. It was possible that he could have contaminated the poached eggs, especially when personal and food hygiene practices were not observed. This was supported by the observation made during the site visit, where he was continuously touching

the water in the container of poached eggs with unwashed bare hands. Further questioning revealed that the food handler was checking if the water was still cold as the container of poached eggs was left at ambient temperature until the eggs were sold out. During the interview, he also mentioned that he did not wear gloves during the preparation of the poached eggs, thus possibly coming into contact with the eggs with bare hands. Furthermore, the prolonged storage of the poached eggs at ambient temperature may also have promoted the proliferation of the bacteria. As poached eggs were only partially cooked, any contamination in the preparation process could result in food-borne illness.

Our investigation also revealed that the two food handlers (food handler 2 and 3) who did not consume the poached eggs also tested positive for the same MLVA type. This suggested that the two food handlers might have acquired *Salmonella* infection from a common source other than the poached eggs. Through our interviews with the two food handlers, we found out that both of them had consumed food prepared by food handler 1 on weekdays. Hence it was likely that both of them were infected through the food prepared by food handler 1. However, we are unable to ascertain conclusively on how contamination could have occurred. Infected food handlers can transmit *Salmonella* organisms to food ingredients if personal and food hygiene practices are not adhered[13-14].

The management of the implicated restaurant had been informed to rectify the hygiene lapses found and reminded to ensure food handlers observe good personal, environmental and food hygiene. The preparation of the poached eggs involved steps that could potentially lead to contamination of *Salmonella*. This included the use of ice and water to cool down ready-to-eat eggs as well as the practice of storing the eggs overnight for use the next day. Hence, the owner and chef of the restaurant were advised against such practices and to ensure that food items (especially eggs) that were cooked should be used for orders on the same day to minimize cross contamination and the growth of food-borne pathogens. The three infected food handlers were prohibited from preparing and handling food until they were cleared of food-borne pathogens.

(Contributed by Tow C, Png CK, Hishamuddin P, Ooi PL, Siti Zulaina MS, Koh YQM and La MV, Communicable Disease Division, Ministry of Health)

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Dengue and weather variables in Singapore

Weather variables are widely studied for their effects on indicating dengue incidence trends. However, these studies have been limited due to complex epidemiology of dengue, which involves dynamic interplay of multiple factors such as herd immunity within a population, distinct serotypes of the virus, environmental factors and intervention programmes.

We undertook a study to investigate the impact of weather factors on dengue in Singapore, considering the disease epidemiology and profile of virus serotypes. A Poisson regression combined with Distributed Lag Non-linear Model (DLNM) was used to evaluate and compare the impact of weekly absolute humidity (AH) and other weather factors (mean temperature, minimum temperature, maximum temperature, rainfall, relative humidity (RH) and wind speed) on dengue incidence from 2001-2009. The same analysis was also performed on three sub-periods, defined by predominant circulating serotypes. The performance of DLNM regression models were then evaluated through the Akaike's Information Criterion.

Findings

Whole period analysis

The Spearman rank correlation analysis, using time lagged weather data (0-20 weeks) showed that temperature (mean, maximum, minimum), AH (a composite index of mean temperature and relative humidity) and rainfall exhibited significant association with dengue incidence. On the other hand, no significant relationship was observed between dengue and wind speed, and RH. The correlation between AH and dengue incidence was the highest (its correlation coefficient was 0.234 with p-value < 0.05 at a 7-week lag) among all the weather variables studied. The second highest correlation was between mean temperature and dengue, with the lag period of 12 weeks and a corresponding correlation coefficient of 0.211 with

p-value <0.05. The correlation between rainfall and dengue incidence was, although significant, numerically quite small, about less than 0.15.

In general, a higher mean temperature was associated with a higher risk of dengue incidence but this observed relationship did not hold true when the mean temperature was higher than 27.8 degrees Celsius.

Sub-period analysis

To evaluate the coupling effect of weather factors as well as the impact of the dominant serotypes, further analyses were carried out on the three distinct sub-periods; namely, 2001-2003 (sub-period 1, dengue 2 dominant), 2004-2006 (sub-period 2, dengue 1 dominant) and 2007-2009 (sub-period 3, dengue 2 dominant). The impact of AH on dengue incidence in sub-period 1 and sub-period 2 was found to be similar to that observed in the entire period (2001-2009); i.e. increasing the AH generally increased the risk of dengue incidence. However, for sub-period 3, the effect of AH on dengue was not significant.

We also analysed the impact of mean temperature on dengue incidence. The effect of 0-9 weeks lag of mean temperature on dengue incidence in the three sub-periods was not consistent across the three sub-periods or with the pattern observed during the whole period. In sub-period 1, the impact of mean temperature on dengue was not significant when mean temperature was less than 27.8 degrees Celsius, while in sub-period 2, this effect turned out to be insignificant when the mean temperature was higher than 27.8 degrees Celsius. Interesting, the effect of mean temperature in sub-period 3 was an inverse curve.

Comments

As dengue virus transmission is through a human-to-mosquito-to-human cycle, the influence of meteorological factors on dengue is likely to be on mosquito populations and behaviours. In general, rain, temperature and RH have been found to be the most common weather variables associated with dengue incidence and outbreaks in other neighbouring countries. Rain provides more breeding habitats and opportunities for proliferation in the environment. There is also compelling evidence supporting the hypothesis that mosquito oviposition, development from mosquito larva to adults, biting rate and virus replication rate in mosquito are strongly enhanced at raised ambient temperatures. The percentage of hatched *Aedes aegypti* eggs was also found to be higher with the increase in RH.

Among the major meteorological variables, we found that AH had the best correlation with dengue incidence in Singapore. There was a moderate positive correlation between dengue and AH (correlation coefficient was 0.374; p<0.01). This correlation coefficient was relatively high compared with other weather factors. Besides the significant correlation coefficient, it was also noted that the peaks of AH were well synchronised with dengue peaks. Our modelling results suggest that AH may be a better indicator to predict dengue incidence.

Interestingly, rainfall, which had been found to be associated with dengue in other countries, did not seem to have much bearing on dengue cases in Singapore. This is consistent with the findings of the National Environment Agency which reported that typically about 70% of breeding habitats of *Aedes aegypti* were indoors, the most common being indoor ornamental containers and household articles where the impact of rainfall is likely to be limited.

In our study, the effect of AH on dengue was found to have an optimal maximum lag of 16 weeks, an interval which is consistent with an earlier study. The non-linear lag effect of weather predictors on dengue incidence has also been reported in many other studies. The lagged effect of dengue incidence could account for the length of life cycle as well as the host-vector-pathogen transmission cycle of vectors.

The effect of AH on dengue was more significant compared to mean temperature. Higher mean temperature corresponding to higher rate of dengue incidence was only found in sub-period 1 when the mean temperature was >27.8 degrees Celsius.

It is interesting to note that the impact of AH on the risk of dengue was prominent for the first 2 sub-periods but not significant in sub-period 3. Sub-period 3 was also markedly different when mean temperature was studied showing a reverse correlation when compared to sub-period 1. The inconsistent pattern in sub-period 3 was observed for both AH and mean temperature. A number of factors could have played a role in modulating the correlation between dengue trends and the weather parameters. First, the predominant virus involved in each sub-period was distinctly different. Second, there could be differing levels of relevant serotype-specific immunity in the population within each period. Third, there had also been a shift in control programme from a more reactive to preventive strategy and an increase of manpower from 250 in 2003 to 800 by 2010.

Conclusion

From the correlation and DLNM regression modelling analysis of the studied period, AH was found to be a better predictor for modelling dengue incidence than the other unique weather variables. Whilst mean temperature also showed significant correlation with dengue incidence, the relationship between AH or mean temperature and dengue incidence, however, varied in the three sub-periods. The shift in dominant serotypes and pre-emptive measures taken against dengue vectors since 2005 in Singapore may possibly explain the inconsistent weather-dengue patterns observed. Future studies on the impact of climate change on dengue need to take all other contributing factors into consideration in order to make meaningful public policy recommendations.

(Based on Xu H-Y, Fu X, Lee LKH et al. Statistical modelling reveals the effect of absolute humidity on dengue in Singapore. PLoS Negl Trop Dis 2014; 8(5): e2805.doi:10.1371/journal.pntd.0002805)

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