38th year of publication

Epidemiological News Bulletin

QUARTERLY

JANUARY - MARCH 2012 VOL. 38 NO. 1 A PUBLICATION OF THE MINISTRY OF HEALTH, SINGAPORE

CONTENTS

Suggested citation:
Ministry of Health, Singapore. [Article title]. Epidemiol News Bull [Year]; [Vol]:[inclusive page numbers]

MOH Weekly Infectious Diseases Bulletin
http://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html

ISSN 0218-0103

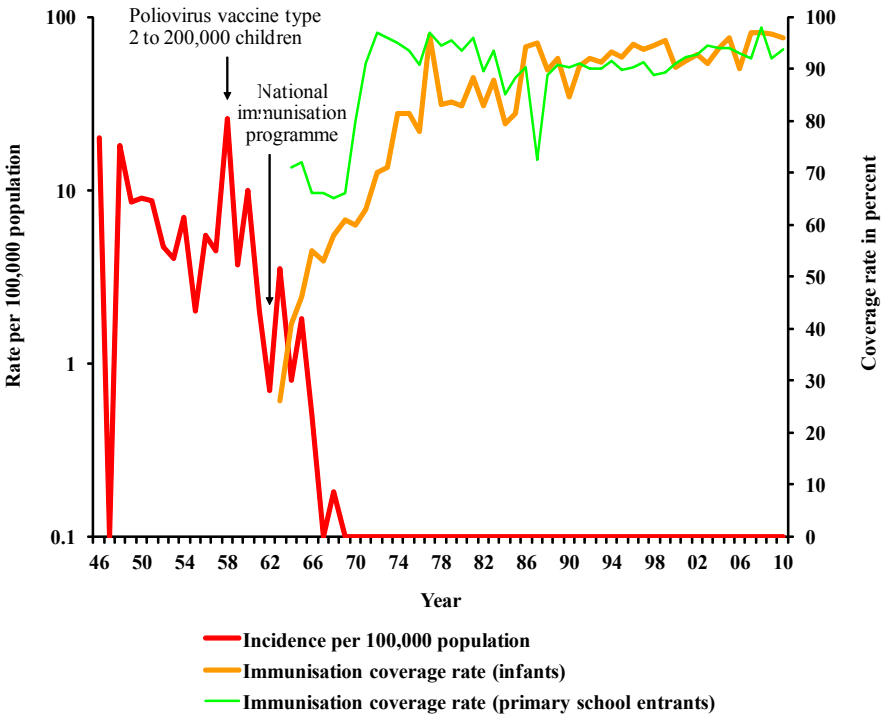
http://www.moh.gov.sg/content/moh_web/home/Publications/epidemiological_newsbulletin.html

Prevalence of antibody against poliovirus among children and adolescents in Singapore, 2008-2010

Poliomyelitis is the result of an enteroviral infection of the central nervous system leading to possible permanent paralysis and muscle atrophy, which most often involves deformity of legs.[1] In the 1950s, paralytic poliomyelitis was a major public health concern among children in Singapore with periodic occurrence of epidemics during the immediate post-war years.[2] To combat an epidemic involving 415 cases of paralytic poliomyelitis, immunisation against poliomyelitis on a mass scale using the oral polio vaccine (OPV) was first carried out in 1958.[3]

Childhood vaccinations represent effective strategies to protect against many important infectious diseases. Vaccination against poliomyelitis has been included in the National Childhood Immunisation Programme (NCIP) in Singapore since 1962. The primary course of three doses is given to infants aged 3, 4 and 5 months, while boosters are given at the ages of 18 months, 6-7 years, and 11-12 years. Both OPV and inactivated polio vaccine (IPV) are available for use in pre-school children in the public and private sectors. While OPV is used for the second and third boosters for school-going children who receive their polio vaccinations under the government-funded school health programme run by the School Health Services, Health Promotion Board, school-going children can choose to receive IPV at both the public and private sectors. The immunisation coverage for infants, pre-school and primary school children has been maintained at around 92% to 97% in the past decade.[4] The incidence of poliomyelitis had declined significantly since 1962 (*Fig. 1*). The last indigenous case was reported in 1978, and the last imported case was in 2006.

Figure 1
Incidence per 100,000 population from poliomyelitis and immunisation coverage rates in Singapore, 1946-2010



Between August 2008 and July 2010, we conducted a serological survey to estimate the prevalence of antibody against poliovirus among children and adolescents aged 1 to 17 years. This study is the most recent nationwide survey to assess the effectiveness of the poliomyelitis vaccination programme.

Subjects and methods

As part of the ongoing surveillance of infectious diseases in Singapore, the Ministry of Health (MOH) conducted a National Paediatric Seroprevalence Survey (NPSS) between August 2008 and July 2010 to gather information needed to evaluate and plan programmes to prevent and control infectious diseases among children in Singapore. This survey was conducted in accordance with Section 7 of the Infectious Diseases Act, which provides for the use of residual blood samples for public health surveillance. The study protocol was approved by the Institutional Review Board of the National University of Singapore.

The NPSS was carried out using residual blood samples collected prospectively from diagnostic laboratories in KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). These residual samples were from blood specimens that had been provided by patients earlier for routine biochemical investigations at KKH and NUH. Only Singapore citizens and permanent residents who were

ethnic Chinese, Malay and Indian aged between 1 and 17 years attending inpatient services or day surgery were included in the survey. Patients were excluded if they were known to be immunocompromised, on immunosupressive therapy, or diagnosed with mumps, measles, rubella, chickenpox, poliomyelitis, pertussis, diphtheria, hepatitis B, dengue, or hand, foot and mouth disease.

The National Immunisation Registry (NIR) of the Health Promotion Board monitors and tracks the immunisation coverage in the NCIP among children who are Singapore residents. Vaccination history records of the subjects from the NPSS were obtained from the NIR.

On the premise of an anticipated antibody prevalence of at least 96% in each of the age groups of 1–6 years, 7–12 years and 13–17 years, the minimum sample size required for each age group was 369, with a confidence level of 95% and an absolute precision of 2%. A total of 1,200 serum samples were collected, comprising 400 in each of the three age groups.

Laboratory method

Poliomyelitis IgG enzyme-linked immunosorbent assay (ELISA) kits (IBL-America, Minneapolis, MN, USA) were employed for the detection of human IgG antibodies against the three serotypes of poliovirus simultaneously. Briefly, diluted serum samples and standards were added into the microtiter plate wells coated with specific antigens. After incubation at room temperature for 1 hour, the plate was washed to remove unbound material. Anti-human-IgG peroxidase conjugate was then added, and incubated for 30 minutes followed by another wash step. Substrate (TMB) was then incubated with the sample for 20 minutes to induce color development. Stop solution was finally added to terminate the reaction, resulting in color change to yellow. The color intensity was measured spectrophotometrically at a wavelength of 450 nm by an ELISA reader. The concentration of the IgG antibodies was directly proportional to the intensity of the color, and was quantified using the standard curve calculated from the standards provided. The quantitative cut-off poliovirus IgG antibody value for seropositivity was 12 U/ml. The intra-assay coefficient of variation of the kit was assessed by a ten-fold determination of the weak positive control to less than 10%.

Data analyses

The 95% confidence intervals (CI) for binomial proportions were computed using Wilson's method.[5] The Fisher's exact test or Chi-square test was employed to compare the prevalence of poliovirus antibody by categorical variables. The Mantel-Haenszel Chi-square test for trend was used to evaluate differences between prevalence of poliovirus antibody among the three age groups. A p value of less than 0.05 was considered as significant.

Results

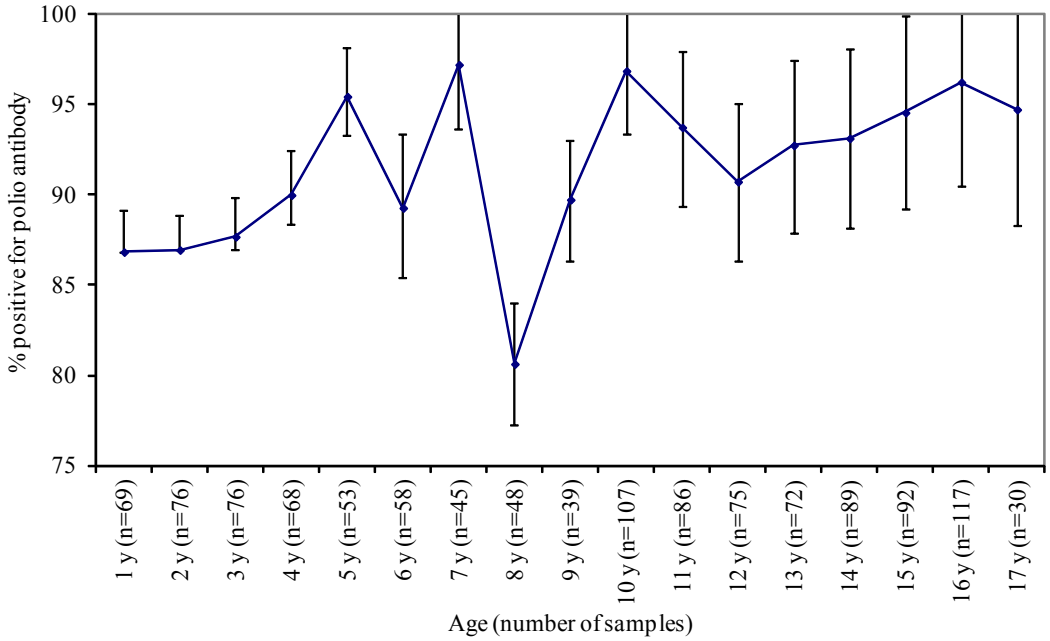
A high prevalence of poliovirus antibody of 92.3% (95% CI: 90.6—93.6%) was observed for the subjects aged 1-17 years. Increasing age was significantly associated with a higher prevalence of poliovirus antibody (test for trend, p=0.008). The prevalence in the age group of 1-6 years of 89.3% was significantly lower than that of the other two older age groups, while the prevalence in the age groups of 7–12 years and 13–17 years was similar at 93.3% and 94.3%, respectively (*Table 1*). The prevalence of poliovirus antibody by age hovered at about 90%, except the decrease observed at the age of 8 years (*Fig. 2*).

Table 1

Age-specific prevalence of poliovirus antibody (%) with 95% CI by gender and ethnic group

Demographics	Age group (years)			
	1 – 6 (n=400)	7 – 12 (n=400)	13 – 17 (n=400)	1 – 17 (n=1200)
All	89.3 (85.8—91.9)	93.3 (90.4—95.3)	94.3 (91.5—96.1)	92.3 (90.6—93.6)
Gender				
Male	88.6 (83.6—92.2)	93.4 (89.3—95.9)	91.7 (85.5—95.5)	91.2 (88.6—93.3)
Female	90.0 (84.9—93.5)	93.1 (88.3—96.0)	95.3 (92.2—97.3)	93.2 (90.9—94.9)
Ethnic group				
Chinese	89.0 (84.8—92.2)	92.6 (88.7—95.2)	93.1 (89.3—95.6)	91.5 (89.4—93.3)
Malays	87.4 (78.8—92.8)	94.3 (88.2—97.4)	97.9 (92.7.9—99.4)	93.4 (90.0—95.8)
Indians	95.0 (83.5—98.6)	94.6 (82.3—98.5)	93.3 (82.1—97.7)	94.3 (88.6—97.2)

Figure 2
Prevalence (%) of poliovirus antibody by age, with the bars indicating 95% confidence intervals



The prevalence of poliovirus antibody was 91.2% among males and 93.2% among females, with no statistical significance detected (p=0.234). The differences in the antibody levels among the three ethnic groups were also not statistically significant; 91.5% for Chinese, 93.4% for Malays, and 94.3% for Indians (p=0.395).

There were no records found in the NIR for 21 study subjects (1.8% of the total number). In addition to these 21 subjects with an unknown history of vaccination, NIR records showed no vaccination history against poliomyelitis for 3 subjects. In total, there were 24 subjects with an unknown or negative history of vaccination. The prevalence of antibody against poliovirus was 92.3% among 1176 subjects with history of vaccination, which was not statistically different from the seroprevalence of 91.7% among 24 subjects with an unknown or negative history of vaccination (p=0.709)

Comments

An estimated herd immunity of 80–86% is required to prevent transmission of poliovirus [6]. A seroepidemiological survey conducted in 1982-1984 revealed high levels of herd immunity in the local population with 94-97% possessing neutralising antibodies to poliovirus types 1 to 3.[7] Another survey was conducted in 1993 based on 600 serum specimens obtained from healthy children and adults between 6 months and over 40 years of age at designated government polyclinics.[8] A solid herd immunity of 98-99% with neutralising antibodies to all three types of poliovirus was maintained. There was no statistically significant difference in the immunity level against the three poliovirus types between genders or among the three major ethnic groups. In this latest survey conducted in 2008-2010, the high prevalence of poliovirus antibody again exceeded the herd immunity threshold range for transmission of poliovirus, which further confirms the success of Singapore's poliomyelitis vaccination programme in maintaining solid herd immunity against this disease in Singapore.

The seroepidemiological survey conducted in 1993 was based on the micro-neutralisation test using HEp-2 cells.[8] The titration for neutralising antibody against Sabin poliovirus types 1, 2 and 3 was carried out by the Department of Epidemiology, National Institute of Health, Tokyo, Japan. The antibody titre was expressed as the reciprocal of serum dilution that showed neutralisation, and a titre of 1:4 was considered seropositive. In the NPSS 2008-2010, commercial ELISA kits were used to measure IgG antibodies against all 3 poliovirus serotypes simultaneously. Although different laboratory methods were employed, the seroprevalence findings were similar in the two cohorts.

In the seroepidemiological study conducted in 1993, previous vaccination history was obtained from the participants who responded to a public announcement asking for volunteers to participate in the survey. About 86.8% had a history of vaccination against poliomyelitis; and of these 521 participants who had been vaccinated, their prevalence of antibody against all three poliovirus types ranged from 98.3% to 99.4%. These findings were similar to that of the NPSS 2008-2010.

Between 2001 and 2010, the immunisation coverage against poliomyelitis for the primary course of 3 doses was 95-97%, and that of the booster doses was 83-91% in children aged 2 years. The immunisation coverage of booster doses was 92-94% in school

children in the past decade. The evidence of solid herd immunity against poliomyelitis from the findings of the NPSS 2008-2010 corroborated the high immunisation coverage in the NCIP.

Poliomyelitis is a legally notifiable disease in Singapore under the Infectious Disease Act. There is an established surveillance system to ensure the early detection of any paralytic poliomyeltitis cases in the community to allow prompt prevention and control measures to be instituted. In December 1995, an acute flaccid paralysis (AFP) surveillance system was established to detect possible cases of poliomyelitis, as part of the requirements by the World Health Organization (WHO) for certification of poliomyelitis eradication in Singapore.[9] In December 1996, a National Committee for the Certification of Poliomyelitis Eradication was established, and the AFP surveillance system was enhanced to improve its sensitivity. On 29 October 2000, the WHO certified the Western Pacific Region, including Singapore, free of poliomyelitis.[10] This is the second WHO region to have achieved poliomyelitis-free status after the American Region.

Under the AFP surveillance system, all public acute care hospitals as well as paediatricians, internal medicine specialists and neurologists in private practice are required to notify MOH within 72 hours of diagnosis of all AFP cases under the age of 15 years, and all patients under the age of 15 years who are diagnosed with an 'at-risk' disease that could lead to AFP, regardless of whether AFP is present or not. This list of 'at-risk' diseases includes poliomyelitis, all forms of encephalitis, myelitis, acute infective polyneuritis, particularly Guillain-Barré syndrome (GBS), mononeuritis (not due to physical causes), and monoplegia. The submission of monthly returns, including a 'nil' return, was required. AFP surveillance can only be effective if clinicians perform the appropriate tests to rule out polio, and inform MOH promptly of all suspected cases so that control measures can be rapidly instituted.[11] All AFP cases under the age of 15 years should be treated as suspicious for polio until that diagnosis can be ruled out. In addition, MOH conducts periodic checks on all hospital discharges (through public and private hospitals' computer databases) for AFP cases as well as cases diagnosed with an 'at risk' disease. The National Polio Laboratory is required to notify MOH within 14 days of receipt of the samples or to provide preliminary results for viruses that require more time for typing.

The need to continue efforts to protect our local population from possible re-importation of poliomyelitis remains pertinent and relevant. There have been sporadic cases reported in other formerly polio-free countries, as a result of the importation of the virus by travellers. In 2010, while the WHO Western Pacific Region commemorated its ten years of polio-free status, there was the first importation of wild poliovirus (WPV) type 1 into the WHO European Region since it was declared polio-free in 2002. A large outbreak occurred in Tajikistan, following importation from India, resulting in 458 confirmed cases and 26 deaths with subsequent spread to at least three other countries in the region[12]. On 26 August 2011, the Ministry of Health, China, notified the WHO of the isolation of WPV type 1 in four cases in Xinjiang Uygur Autonomous Region of China.[13] Genetic sequencing indicated a 99% similarity with the WPV that caused an outbreak in Pakistan in 2009. These were the first wild-type polioviruses to be reported in China since 1999, following poliovirus importation from India. There has been no indigenous WPV transmission reported in China since 1994, and the country was certified poliomyelitis-free in 2000. As of 10 February

2012, China has reported 21 confirmed cases, including two deaths, with the onset of paralysis of the last case on 9 October 2011.[14]

The WHO officially removed India from the list of poliomyelitis-endemic countries on 25 February 2012. India has not had a case of paralytic poliomyelitis since 13 January 2011, and no recent environmental samples have identified WPV.[15] This reduces the number of poliomyelitis-endemic countries to a historical low of three: Afghanistan, Nigeria and Pakistan.[16] However, there is no room for complacency as poliovirus transmission continues in other parts of the world.[17]

In view of international travel and trade, there exists the risk of the introduction of poliomyelitis cases into Singapore, as evident by the last imported case from Nigeria in 2006. Therefore, it is imperative to ensure consistently high levels of immunisation coverage and immunity in the local population, and to maintain constant awareness and vigilance against poliomyelitis.

(Reported by Ang LW[1], Kita Y[1], Phoon MC[2], Tey SH[1], Cutter JL[1], James L,[1] Goh KT[1], and Chow VT[2], Ministry of Health[1] and National University of Singapore[2])

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Outbreaks of gastroenteritis caused by *Salmonella* Enteritidis linked to a bakery in Singapore

Introduction

Food-borne infections due to *Salmonella* are common. Common presentations for salmonellosis include acute enterocolitis with abrupt onset of headache, abdominal pain, diarrhoea, vomiting and nausea[1]. An estimated 1.4 million cases of *Salmonella* infections are reported annually in the United States[2], while 1480 cases of salmonellosis were reported in Singapore in 2010, of which, 300 were laboratory-confirmed *S.* Enteritidis[3]. Common sources of human salmonellosis are due to consumption of contaminated eggs and poultry meat while a wide range of domestic and wild animals may act as reservoir[3,4]. Food-borne outbreaks of *S.* Enteritidis have often been reported in bakery-related food products such as cream cakes[5] and bread[6].

Two outbreaks of *S.* Enteritidis were notified to the Ministry of Health (MOH) in Sep 2011. We describe the epidemiological, microbiological and environmental investigations of the outbreaks, and how the causative agent, source of infection and mode of transmission were determined. The importance of molecular typing in establishing the source of infection is highlighted.

Outbreak

On 21 Sep 2011, MOH was notified of eight cases of food poisoning. Their common link was the consumption of bread purchased from a bakery outlet located in Yishun estate. The next day, another three cases of food poisoning associated with bread consumption were reported. The bread was purchased from a different outlet of the same bakery located in Bedok estate.

Methods

Field investigations were carried out as soon as the notification was received. The cases were identified and their personal particulars such as age, gender, and ethnicity were recorded. Clinical signs and symptoms, date of bread consumption, date of onset of illness, the types of medical treatment sought and laboratory results of the hospitalised cases were obtained. The bakery outlets were inspected and food and environmental samples were taken for microbiological analysis (*Shigella, Campylobacter, Vibrio and Salmonella*). All food handlers were referred to the Communicable Disease Centre and screened for enteropathogens. A total of 12 food samples and two environmental swabs were collected at the Yishun outlet, and another seven food samples and three environmental swabs at the Bedok outlet. In addition, a total of 13 foodhandlers from the outlets were tested. Genotyping of *Salmonella* cultured from food and stool samples (determined by multiple-locus variable number of tandem repeat analysis, MLVA), were performed by the National Public Health Laboratory (NPHL).

A case was defined as a person who developed at least three episodes of watery diarrhoea after consuming bread from Yishun or Bedok bakery outlet from 17 – 18 Sep 2011.

Epidemiological findings

A total of 14 cases were identified - 11 cases linked to the Yishun outlet and 3 cases linked to the Bedok outlet. All of them had consumed omelette floss bread with or without ham prior to onset of symptoms.

Yishun bakery outlet

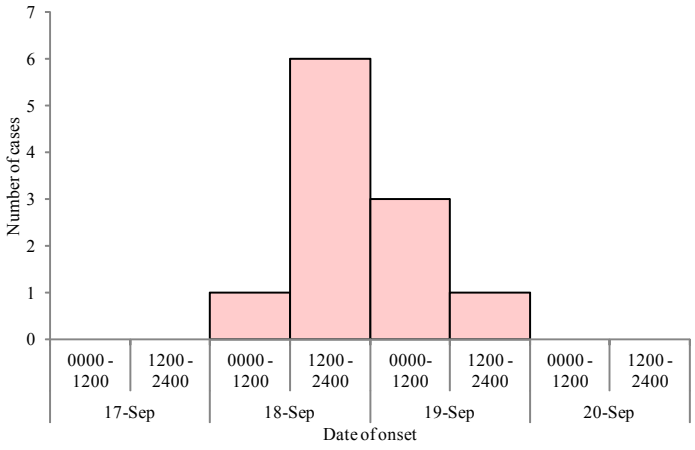
All the cases were Singaporean Chinese and 57.1% were female. The clinical features were watery diarrhoea (100%), fever (86%), abdominal pain (43%), and vomiting (36%). Seven (63.6%) cases were hospitalised, three (27.2%) sought outpatient treatment while the rest self-medicated. All recovered uneventfully.

The onset of illness was from 0900 hours on 18 Sep 2011 to 0900 hours on 19 Sep 2011 (*Fig. 3*). The mean and median incubation periods were 10 and 8 hours, respectively, with a range from 3.5 – 24 hours. Of the seven stool samples collected from the hospitalised cases, five (71.4%) were positive for *Salmonella* Enteritidis, MLVA type B, while the rest were negative for any bacterial food poisoning pathogens.

Of the 12 food samples collected at the Yishun outlet, two (ham and spicy chicken floss), were positive for *Salmonella* Enteritidis, with identical MLVA type B, while *S.* Richmond was isolated from another two food samples (mayonnaise and egg & ham bread). Two swabs (one from the open wounds on the left hand of a food handler and the other from a chopping board) as well as the stool samples of all the implicated food handlers were tested negative for bacterial food poisoning pathogens.

The ingredients of the omelette floss bread consisted of dough, egg, sliced ham, sliced cheese, mayonnaise and non-spicy chicken floss. All the ingredients were ordered from designated suppliers, except the dough and mayonnaise which were prepared in-house. The production process involved forming of the dough, baking of dough, making the mayonnaise, frying the omelette with ham, assembling the omelette bread, slicing the omelette bread and lastly, topping the final product with chicken floss. This whole preparation process started from 5 a.m. and was completed before 10 a.m. on the same day.

Figure 3
Onset of illness of 11 reported food poisoning cases linked to a bakery outlet at Yishun, 18 – 19 Sep 2011



The final product was then placed in a plastic container prior to display for sale. All leftover bakery items were discarded at the end of each day when the outlet closed at 10 p.m..

The preparation and manufacture of omelette floss bread up to the time of display at the counter are depicted in *Fig. 4*.

Bedok bakery outlet

All three cases were Singaporean Chinese and one of them was a female. The clinical features were watery diarrhoea (100%) and fever (100%). One (33.3%) case was hospitalised while the rest self-medicated. All recovered uneventfully.

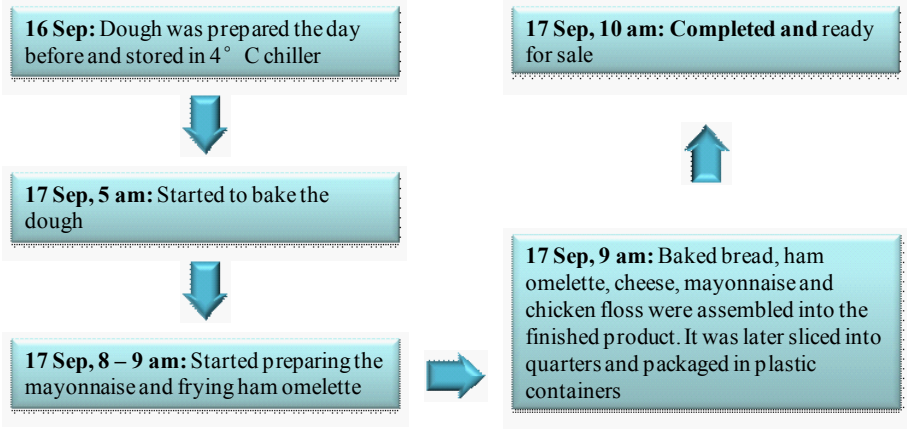
The onset of illness was from 0800 hours on 18 Sep 2011 to 1000 hours on 19 Sep 2011 (*Fig. 5*). The mean and median incubation periods were 19 and 24 hours, respectively, with a range from 10 - 24 hours. One stool sample collected from the hospitalised case was positive for *Salmonella* Enteritidis, MLVA type C.

Seven food samples and three environmental swabs were negative for bacterial food poisoning pathogens. One of the seven food handlers was tested positive for *Salmonella* group C and *Plesiomonas shigelloides*. This positive food handler reported that he had diarrhoea on 23 Sep 2011, the same day he was screened, but claimed that he was well on, and prior to, 17 Sep 2011. The implicated food item was also an omelette floss bread produced in-house at Bedok on 17 Sep 2011. However, no hygiene lapses were observed in this bakery outlet.

Discussion

These two outbreaks of bread-associated gastroenteritis showed clinical and epidemiological features consistent with salmonellosis (predominant clinical symptoms of fever and diarrhoea and an incubation period of 12 – 36 hours). The causative agent was *Salmonella* Enteritidis, MLVA type B for the Yishun outlet, and *Salmonella* Enteritidis, MLVA type C for the Bedok outlet. The implicated food item for both outbreaks was omelette floss bread. In the Yishun outbreak, *Salmonella* Enteritidis of the same genotype (MLVA type B) was detected in ham, one of the ingredients for the bread, as well as in the stool samples of the

Figure 4
Preparation and manufacture process of omelette floss bread



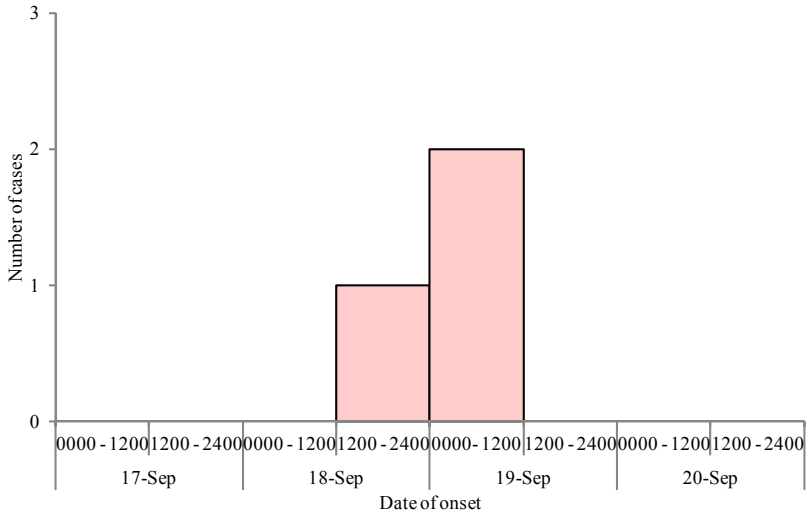
hospitalised cases, confirming the source of infection. The outbreak linked to the Bedok outlet of the bakery was likely to be caused by *Salmonella* Enteritidis, MLVA type C which was isolated from the hospitalised case. As the *Salmonella* organisms found in the stool samples of an infected food handler at this outlet and the hospitalised case are different, it is unlikely that this food handler was the source of infection.

Salmonella is commonly found in poultry and eggs. While the exact mechanisms for bacterial contamination of the omelette floss bread produced on 17 Sep 2011 in the Yishun outlet are uncertain, cross-contamination at the bakery during preparation could have occurred, as *S.* Enteritidis with identical MLVA type was detected in both uncooked ham and cooked spicy chicken floss. During our investigations, we uncovered hygiene lapses which were conducive to cross contamination, such as use of bare hands or the same disposable gloves to handle both raw and cooked food. There was also improper storage of raw food. In addition, the temperature gauge of the chillers was faulty.

Although the two incidents were linked temporally, they are unlikely to be linked to a common source outbreak, as the genotypes of *Salmonella* Enteritidis were different. Although the implicated food item was similar, they were prepared at two different outlets. Furthermore, even though the individual ingredients of the omelette floss bread were provided by the same supplier to the two outlets, we do not believe that there was an upstream source of contamination in the ingredients, as our national surveillance system did not detect any other cases that might be epidemiologically linked to these outbreaks (we would have expected more cases to appear given that the same batch of ingredients was used to prepare food over a period of time).

The bakery was directed to ensure a tighter supervision of food preparation, storage and handling for both outlets.

Figure 5
Onset of illness of 3 reported food poisoning cases linked to a bakery outlet at Bedok, 18 – 19 Sep 2011



(Contributed by Tien WS, Toh HY, Hishamuddin P and Tay J, Communicable Diseases Division, Ministry of Health)

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Surveillance of scarlet fever in Singapore

Introduction

Scarlet fever (SF) is a form of streptococcal disease caused by the bacterium *Streptococcus pyogenes,* group A streptococcus (GAS), and is transmitted through inhalation of infected respiratory droplets or direct contact with an infected person.[1-4] Clinical symptoms of SF include sudden onset of fever, sore throat, headache, nausea, vomiting, abdominal pain, "strawberry" tongue, myalgia, malaise and rash. The incubation period ranges from one to four days and the disease usually affects children under the age of 18 years.[1-5] While SF is usually a mild illness, complications and deaths can occasionally occur.[1,2] The case fatality rate of SF has been reported to be as high as 3% in some parts of the world.[1] SF can be treated with antibiotics to prevent rare but serious complications such as rheumatic fever, pneumonia, otitis media and post-streptococcal glomerulonephritis.[1-5]

On 20 June 2011, the Hong Kong Centre for Health Protection issued an alert urging the public to maintain vigilance against SF because of a high level of SF activity that year.[6] As of 17 June 2011, a total of 419 cases of SF had been reported in Hong Kong.[6] This surpassed the annual number of cases recorded in the past decade and was more than 1.5 times that of the previous high of 235 cases for the whole of 2008.[6] A similar increase in the number of SF cases was also reported in mainland China and Macau which saw increases by 2.6 times and 4.7 times, respectively, when compared to the same period in the previous year.[7] The majority of cases were under 10 years of age and had mild symptoms.[6,7] As of 23 June 2011, two deaths in Hong Kong had been reported in a five-year-old boy and a seven-year-old girl.[8] Both cases had initially presented with clinical features of SF and subsequently developed toxic shock syndrome.[8] Institutional outbreaks had also been reported in kin-

dergartens, child care centres, schools and residential settings in Hong Kong.[6,9]

In view of the heightened level of SF activity in Hong Kong in 2011 and some indications of regional circulation in mainland China and Macau, there was a concern that children who travelled to these areas during the school holiday period in June 2011 may be at increased risk of infection. As such, the Ministry of Health (MOH) alerted all local hospitals and medical doctors on 24 June 2011 to step up vigilance against the disease to ensure early detection and treatment of cases. Childcare centres, kindergartens, schools, playgroups and enrichment centres were also advised by MOH to step up on hygiene measures and to be on the lookout for cases in children and staff returning from holidays in Hong Kong, Macau and mainland China. A health advisory and a list of frequently asked questions on SF were made available on the MOH website.

SF is not a notifiable disease in Singapore. In view of the concern of imported SF cases triggering a similar outbreak in Singapore, MOH implemented an active surveillance study on local SF cases between 29 June 2011 and 8 August 2011. The aim of the study was to gain insights into the epidemiological profile of SF cases in Singapore.

Method

The active surveillance involved Kandang Kerbau Women's and Children's Hospital and National University Hospital, the two public sector hospitals which manage paediatric cases. As part of this surveillance study, MOH asked both hospitals to inform the Communicable Diseases Division of the Ministry of clinically diagnosed and laboratory confirmed SF cases who were seen at the emergency departments, outpatient paediatric specialist clinics or admitted between 29 June and 8 August 2011.

A clinical case was defined as an individual with symptoms consistent with SF. A laboratory confirmed case was defined as an individual with symptoms consistent with SF and who was tested positive for GAS. Any SF case that required intensive care management was considered a severe case.

Epidemiological information was obtained from medical records of the cases with permission from the respective hospitals. Further analysis of GAS positive samples were done by *emm* typing which is a sequence-based method for classifying GAS (*S. pyogenes*) according to their M protein serotypes.

Results

Epidemiological profile

A total of 67 cases of SF were notified to MOH between 29 June 2011 and 8 August 2011. The majority (61%) were clinically diagnosed while the remaining cases were laboratory confirmed (*Fig. 6*). Of these cases, only four were hospitalised while the others were treated as outpatients. None of the hospitalised cases required intensive care management. All the cases recovered with treatment.

Apart from fever, which was present in all cases, the next most common presenting symptoms were sandpaper rash (79%) and sore throat (76%) (*Table 2*). About one-fifth presented with strawberry tongue.

The cases ranged from 1 year to 14 years of age. More than half of the cases were in the age group of 5-9 years (57%), while 31% were in the age group of 0-4 years and another 12% were in the age group of 10-14 years (*Fig. 7*). 70% were male. 91% were

Singapore residents while 9% were non-residents. The majority of the residents were Chinese (70%), followed by Malays (28%), and Indians (2%).

Of the 67 cases, 18% had a history of recent travel prior to onset of symptoms. Of the 12 cases with travel history, three cases had been to Hong

Figure 6
Weekly number of reported cases of SF

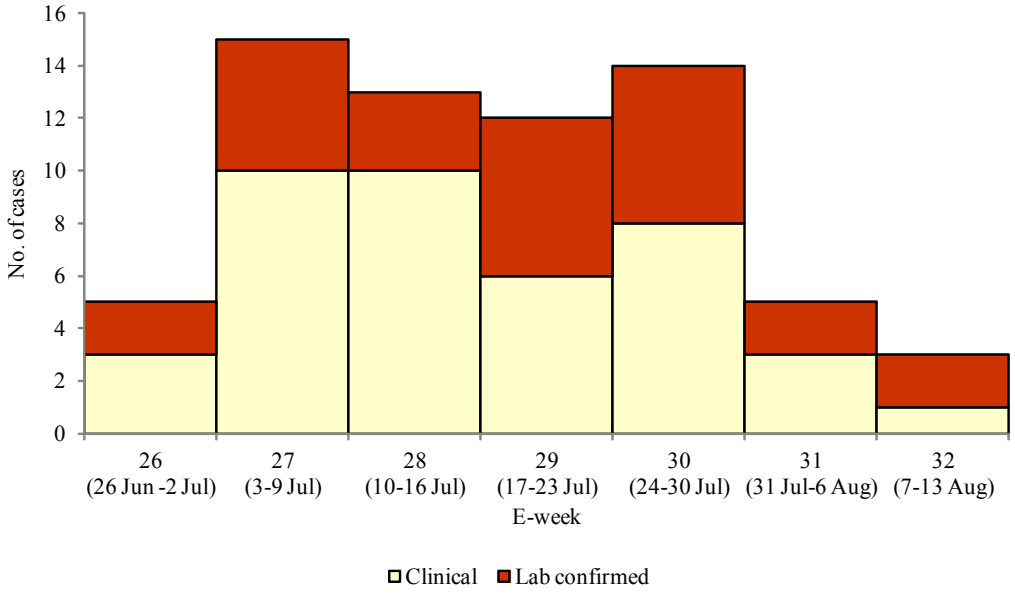
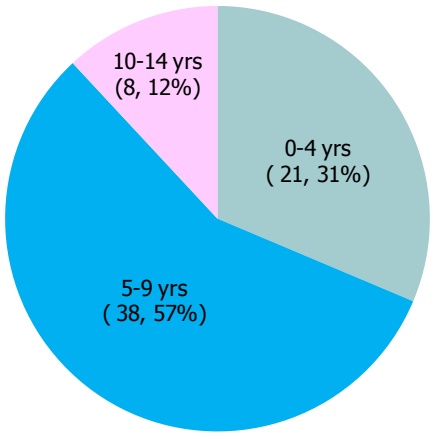


Table 2
Presenting symptoms of reported cases of SF*

Symptoms	No. of cases	%
Fever	67	100
Sandpaper rash	53	79
Sore throat	51	76
Cough	28	42
Vomiting	19	28
Strawberry tongue	13	19
Headache	5	7
Abdominal pain	4	6
Nausea	1	1

* Cases may have one or more presenting symptoms

Figure 7
Age group distribution of 67 SF cases



Kong but only one had developed symptoms on the day she returned to Singapore while the other two cases developed symptoms more than one week after returning to Singapore. All three cases were tested negative for GAS. Among the remaining nine cases with recent travel history, five cases had developed symptoms more than one week after returning to Singapore and they had travelled to Australia (two cases, tested GAS negative), India (one case, tested GAS negative), Saudi Arabia (one case, not tested) and Thailand (one case, tested GAS positive). The four cases with onset of symptoms within one week of returning to Singapore had travelled to Malaysia (three cases, one tested GAS negative; two not tested) and Vietnam (one case, not tested).

Laboratory investigations

Among the 67 notified cases, 52 cases (78%) had throat swab done. Of these 52 cases, 46% were positive for GAS. Seven cases were *emm*-typed and all belonged to *emm* type 12.

Comments

SF is not a legally notifiable disease in Singapore and the baseline number of SF cases is unknown. A weekly average of 10 cases was reported to MOH during the seven-week period of active surveillance. While four cases were hospitalised, none were severely ill. The majority of the cases (94%) were treated as outpatient, which indicated that the illness was mild and self-limiting.

All the seven cases that had been *emm* typed belonged to *emm*12, which was the predominant strain in Hong Kong and Taiwan.[8,10] It was unlikely that these cases had acquired the infection from Hong Kong as none had a travel history prior to onset of their symptoms. The two most common *emm* types circulating in Asia from 1990 to 2009 were *emm*1 and *emm*12.[11] Data on the common circulating *emm* types in Singapore is not available.

A limitation of the study was the likely under diagnosis of SF, as inapparent infections are common.[1] In addition, the study was confined to reporting at the tertiary clinical setting and the disease burden in the community could not be estimated.

Future studies could be undertaken to determine the baseline number of SF cases in Singapore, its severity and case fatality rates, and whether there are any potential implications to public health in Singapore.

(Contributed by Chua A[1], Ang LW[2], Tee N[3], Lin R[1], Hishamuddin P[1], Tay J[1] and Cutter J[1],
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Lymphadenitis following administration of BCG vaccine SSI®

In 2009, active surveillance and monitoring for vaccine adverse events (VAEs) related to influenza A H1N1 2009 vaccines in pregnant women and children was initiated by the Health Sciences Authority (HSA) in collaboration with the sentinel site at Kandang Kerbau Women's and Children's Hospital (KKH). This was subsequently expanded to include all VAEs following childhood immunisation. This active surveillance programme is different from the routine adverse drug reaction reporting system in that potential VAEs are identified from the patients' medical record and vaccination history when the patients are first admitted into the hospital.

In Singapore, *Bacillus Calmette-Guérin* (BCG) vaccine is routinely given to newborns as part of the national childhood immunisation schedule. Since June 2003, the BCG vaccine manufactured by Staten Serum Institute (SSI) is the sole BCG vaccine registered in Singapore. BCG Vaccine SSI® contains an attenuated strain of *Mycobacterium bovis* (BCG), Danish strain 1331.

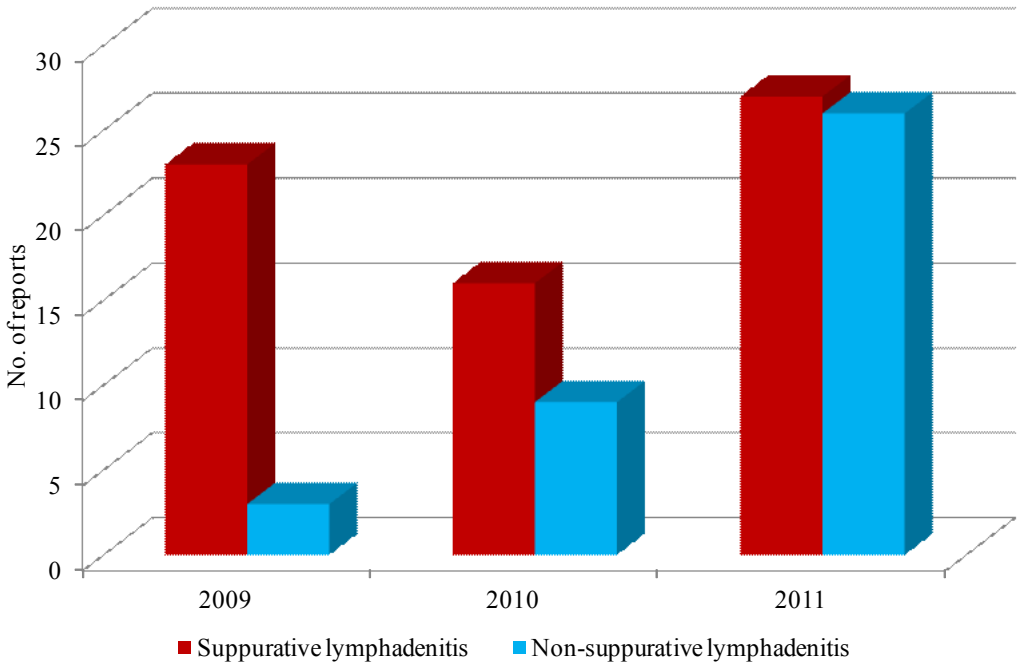
Local reports of BCG-associated lymphadenitis

In 2009, there were 26 reports of BCG-associated lymphadenitis of which 23 cases (88%) presented as suppurative lymphadenitis, defined as the presence of fluctuation on palpation or pus on aspiration, the presence of a sinus, or large lymph nodes adherent to skin with caseous lesions on excision.[1] Of these, 22 cases required surgical intervention such as excision or incision and drainage; one case was lost to follow-up.

In 2010, there were another 25 reports. Sixteen cases (64%) presented as suppurative lymphadenitis which required surgical intervention.

From January 2011 to October 2011, the reports of BCG-associated lymphadenitis increased to 53 (*Fig 8*). Twenty-seven (51%) of these cases presented as suppurative lymphadenitis, of which 25 cases required surgical excision or drainage. The other two cases resolved without requiring surgical intervention. The remaining 26 cases were non-suppurative cases. It should be noted that the figures for 2011 have yet to be finalised as many non-suppurative cases are currently under further observation to determine if the lymph nodes may eventually suppurate or resolve without surgery. The increase in the number of non-suppurative cases captured in the surveillance system could be partially due to the opening of a new specialist outpatient clinic at KKH in mid-2011

Figure 8
Reports of BCG-associated ymphadenitis, Singapore, January 2009 to October 2011



to specifically review paediatric referrals with mycobacterial infections including those with BCG-related complications through active case-finding.

Overseas reports of BCG-associated lymphadenitis

An increase in the number of reports of suspected BCG-associated suppurative lymphadenitis has also been identified in some countries such as Ireland and Latvia in recent years. However, the overall rate and pattern of VAEs remain consistent with the expected frequency of occurrence listed in the package insert of BCG Vaccine SSI®. HSA has been in contact with the regulatory agencies overseas to better understand the trend of BCG-associated lymphadenitis over the past few years observed in these countries and the possible factors that could have contributed to the increase. The interim finding was that the observed rate of lymphadenitis was likely to be multi-factorial.

Possible factors influencing the occurrence of BCG-associated lymphadenitis

Studies have revealed that the incidence of suppurative lymphadenitis is dependent on a number of factors including the strain of BCG vaccine and its constituents, host-related factors as well as administration techniques.[2]

Clustering of lymphadenitis in vaccination programmes are commonly associated with a change in vaccine strain, almost invariably to the Pasteur strain 1173P2 or Danish strain 1331. These strains are considered to be more reactogenic than others such as the Tokyo strain 172 and Glaxo strain 1077 and more likely to produce large ulcers at the inoculation site and suppurative lymphadenitis.[3-5] It has also been reported that for BCG vaccines in general, the risk of lymphadenitis after vaccination increases with the number of colony forming units (CFUs) in the vaccine.[3] Host-related factors such as serious immunodeficiency states like severe combined immunodeficiency (SCID) and acquired immune deficiency syndrome (AIDS) are also associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination.[2]

Intradermal administration technique[3] is also one of the determinants of the risk of lymphadenitis, and is most pronounced in infants aged under six months.[6] This is attributed to an increased risk of inadvertent subcutaneous injection for neonatal vaccination. It has been reported that the frequency of BCG-associated VAEs was lower when a papule was visible during the injection, reflecting that the injection was given intradermally.[7] Overdosing during intradermal BCG injection has also been found to increase the risk of VAEs including lymphadenitis, as some neonates receiving larger doses are more likely to overreact to the injection.[7]

Discussion

Based on the number of local reports received at KKH, the estimated local incidence rates for BCG-associated suppurative lymphadenitis with BCG Vaccine SSI® are 0.58/1,000, 0.43/1,000 and 0.96/1,000 for 2009, 2010 and 2011(up to October), respectively. From these figures, the cases of suppurative lymphadenitis appear to have doubled this

year, possibly attributed to the additional review of paediatric referrals with mycobacterial infections at the new specialist outpatient clinic at KKH.

The incidence of suppurative lymphadenitis observed locally this year is comparable to the background incidences reported in the literature. The European summary of product characteristics of BCG Vaccine SSI® states that regional lymph nodes larger than 1cm is infrequent (between 1/100 and 1/1000) and that suppurative lymphadenitis is rare (<1/1000). However, the reported incidence of these VAEs varies widely (from 1.9/1000 to 31/1000) in various studies.[7]

In view of the observed trend in the local incidences of suppurative lymphadenitis related to BCG vaccination, the Vigilance Branch, HSA, will continue to monitor the reports of lymphadenitis closely and review the data when the outcomes and doses administered for the year are finalised.

Intradermal administrative technique plays an important role in minimising BCG-associated complications such as suppurative lymphadentitis. This consideration is important when administering reactogenic vaccines such as the BCG Vaccine SSI®. More details on the administration of the BCG Vaccine SSI® are available on the package insert of the product.

It is also advisable for healthcare professionals to inform parents of possible suppurative lymphadenitis following vaccination so that early treatment can be sought. The median duration of symptoms prior to patient's presentation at the clinic is two months. Healthcare professionals are strongly encouraged to report all suspected VAEs with BCG Vaccine SSI® to the Vigilance Branch of HSA.

(Based on Reports of lymphadenitis following administration of BCG Vaccine SSI®. HSA Adverse Drug Reaction News 2011; 13: 1-2)

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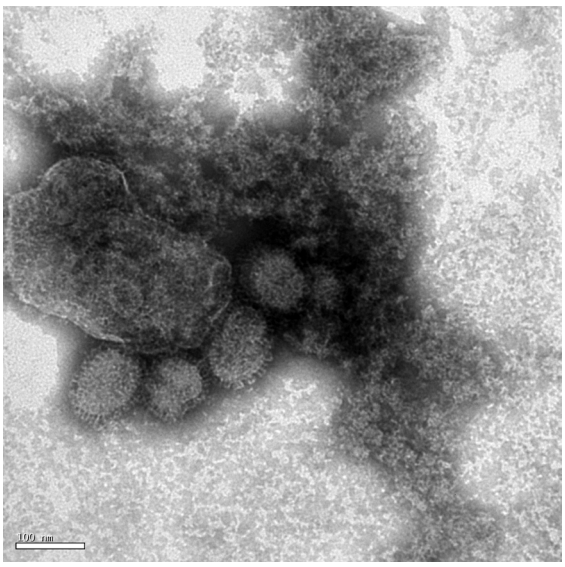
Influenza A/H3N2 virus particles obtained from virus isolation

This picture shows influenza A/H3N2 virus particles obtained from virus isolation. Culture supernatant was negatively stained with 2% phosphotungstic acid (PTA) and viewed using Jeol JEM-1400 electron microscope at 100kV with a magnification of 200,000 times.



Under electron microscope, influenza viruses look like small spheres (80 – 120 nm in diameter) with a distinctly visible membrane and numerous spikes made up of the receptor-binding protein hemagglutinin (HA) and neuraminidase (NA). HA spikes allow the influenza virus to bind and infect host cells. In addition to HA, other proteins such as neuraminidase (NA) are also anchored to the virus membrane and exposed on the surface of the virus particle. NA molecules are involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles to the surfaces of infected host cells. Thus, these proteins are targets for antiviral drugs. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. To date, up to 16 subtypes of HA and 9 subtypes of NA have been identified for influenza A.

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The Epidemiological News Bulletin is published quarterly by the Ministry of Health, Singapore

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