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Responding to emerging diseases: reducing the risks through understanding the mechanisms of emergence

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Over the past two decades, increasing concern and attention have been directed at the potential problems and threats associated with new and emerging diseases. This has been driven by fears arising from the rapid emergence, spread and public health impact of several recent outbreaks, such as the international spread of severe acute respiratory syndrome coronavirus (SARS-CoV) (2003), the potential of avian influenza H5N1 to emerge as a highly lethal pandemic as increasing numbers of human cases are reported (2003 and continuing), and the very rapid global spread of pandemic H1N1 influenza in 2009–2010. The emergence of SARS-CoV, in particular, demonstrated the considerable economic, political and psychological effects–in addition to the impact on public health–of an unexpected epidemic of a highly infectious, previously unknown agent in a highly connected and interdependent world. These examples clearly highlight the necessity and importance of global outbreak surveillance for the early detection and response to new potential threats. They also demonstrate clearly that these emergent diseases can move rapidly between countries and continents through infected travellers so that surveillance needs to be transparent and authorities made aware of international disease events elsewhere around the globe. Some of the specific threats to the Asian Pacific region have been reviewed elsewhere.[1–4]

So what do we mean by the term "emerging diseases," and how do they arise? The concept, definition and factors contributing to the emergence of disease threats were encapsulated in two reports from the US Institute of Medicine that defined the major issues and described the principal causes and mechanisms leading to infectious disease emergence, as well as discussing possible strategies for recognizing and counteracting the threats.[5,6] The most widely accepted definition describes emerging diseases as either new, previously unrecognized diseases that are appearing for the first time, or diseases which are known but which are increasing in incidence and/or geographic range. Examples of the former include Sin Nombre virus, which first came to light in 1993 as the cause of Hantavirus pulmonary syndrome in the Four Corners area of the United States of America, and Nipah virus, which was first isolated in 1999 as a cause of acute neurological disease in peninsular Malaysia. Examples of the latter include West Nile virus, which unexpectedly jumped from the Old World to emerge in the New World in 1999, and Chikungunya virus, which, with the help of a mutation making it more able to be transmitted by *Aedes albopictus* mosquitoes, spread from island nations in the south-western Indian Ocean to India in 2005–2006, and then jumped from south-western India to emerge in Italy in 2007. These examples re-enforce the importance of the movement of pathogens through either travel or trade (see below).

Many factors or combinations of factors contribute to disease emergence. They include population movements and the effect of urbanization; changes in land use such as deforestation and irrigated agriculture; increasing globalization of food, trade and commerce; increasing international travel; and changes in human behaviour such as intravenous drug use.[7–9] The development of new, more sensitive technologies can also provide improved detection and diagnostic procedures allowing a new dimension to pathogen discovery, thus detecting new or cryptic agents for known diseases.[10,11] Other factors that contribute to emergence are microbial mutation and selection and genetic re-assortment that can lead to the development of new genotypes of known diseases, as we see most frequently with influenza A and also in new patterns of antibiotic resistance. Finally, and sadly, known diseases can re-emerge if public health measures are reduced or decline because of complacency or apathy of individuals, communities or policy-makers, as exemplified by reduced vaccine coverage or childhood immunization programmes, or reduced vector control, or because of civil conflict. While all these factors described above are due to human activities, natural causes may also be important in emergence, such as climate change,

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floods, drought, famine and other natural disasters, and thus should not be forgotten or discounted.

While all these factors have been implicated in disease emergence, the importance of the increase in international travel and the globalization of trade cannot be over-emphasized. This includes the movement of infectious agents between countries and continents and the transportation of vector species to establish in new habitats and ecological niches far from their origins, resulting in countries and areas becoming receptive to exotic diseases. Highly successful examples of this are the Asian tiger mosquito, *Ae. albopictus*, which has become established in one or more sites on all continents, and the spread of West Nile and Chikungunya viruses between continents. It is probable that West Nile reached the New World through the transport of an infected mosquito on an aircraft to initiate the outbreak. Chikungunya may have been transported by a similar route or through viraemic travellers to India and Italy, but its ability to cause an outbreak in Italy was due to the earlier arrival and establishment of *Ae. albopictus* mosquitoes, probably transported to their new habitat through the medium of used car tyres on board cargo vessels.

At least four different patterns of disease emergence can be distinguished:

(1) new infectious agents as the etiological agents of known diseases, often detected because of the development of more sensitive techniques for detection, exemplified by the first description of human herpesvirus 8, the virus associated with Kaposi's sarcoma,[12] of human coronavirus NL63,[13] a new respiratory pathogen, and of Klassevirus 1,[14] a new agent causing childhood diarrhoea;

(2) known-agents of diseases that are increasing in incidence and/or geographic distribution, as seen with the spread of dengue, Japanese encephalitis and West Nile viruses;[15]

(3) new patterns of disease epidemiology or pathogenesis due to mutation or genetic reassortment, as exemplified by the generation of new strains of avian influenza,[16] and the severity of new genotypes of enterovirus 71 in the Asia-Pacific region;[17] and

(4) novel infectious agents as the cause of outbreaks/epidemics of new disease syndromes, as exemplified by SARS-CoV[18] and Nipah viruses,[19] neither of which had been observed previously.

Over the past two decades, approximately 75% of novel viruses have been zoonoses, with new viruses arising from ecological niches in wildlife and domestic animal populations. Indeed most of the diseases with pandemic potential fall into this category. Some examples of these are shown in **Table 1**, which also demonstrates that emerging diseases may arise anywhere in the world.

Table 1. **Examples of novel, emergent zoonotic virus diseases**

Year of isolation	Place of isolation	Virus	Reservoir/spillover host
1991	Venezuela	Guanarito virus[20]	Rodents
1992	Slovenia	Dobrava virus[21]	Rodents
1993	United States	Sin Nombre virus[22]	Rodents (*Peromyscus maniculatus*)
1994	Brisbane, Australia	Hendra virus[23]	Fruit bats (*Pteropus sp.*)/horses*
	Sao Paolo, Brazil	Sabia virus[24]	Rodents
1995	Florida, USA	Black Creek Canal virus[25]	Rodents
1996	Ballina, Australia	Australian bat lyssavirus[26]	Fruit and insectivorous bats
	Argentina	Andes virus[27]	Rodents
1997	Hong Kong (China)	Influenza H5N1[28]	Wild birds/domestic poultry*
	Menangle, Australia	Menangle virus[29]	Fruit bats
	Saudi Arabia	Alkhurma virus[30,31]	Camels and sheep†
1999	Peninsular Malaysia	Nipah virus[32,33]	Fruit bats/pigs*
2000	Peninsular Malaysia	Tioman virus[34]	Fruit bats
2002–2003	China, Hong Kong (China)	SARS coronovirus[35-38]	Bats/civets?*
2003–2004	Viet Nam, China	Influenza H5N1[39,40]	Wild birds/domestic poultry*
2007	Melbourne, Australia	Dandenong arenavirus[41]	Rodents?
	Peninsular Malaysia	Melaka virus[42]	Fruit bats?
	Uganda	Bundibugyo ebolavirus[43]	Fruit bats?/various animals (bush meat)*
2008	Lukasa, Zambia	Lujo virus[44]	Unidentified rodents
	Perak, Malaysia	Kampar virus[45]	Fruit bats?

* Spillover host; † Tick-borne

It is important to understand that although a disease may be new to us, it probably has been circulating in its own specific niche for a long time; we just haven't encountered it before. There have been many reports of zoonotic viruses described in wildlife, especially bats[46,47] and rodents.[48,49] In addition, many other viruses and other microbial agents have been described from wildlife in various parts of the world which have not yet been associated with human disease. Thus global surveillance for outbreaks of human diseases alone is insufficient to prepare for all eventualities, and a close watch needs to be maintained on animal diseases, in both domestic animals and wildlife. This need has given rise, in part, to the more holistic approach to surveillance, the concept of One Health,[50,51] in which close collaboration is strongly endorsed between human and veterinary medicine through which integrated surveillance should be a major goal.

Not all countries have the epidemiological or laboratory resources, or the public health infrastructure, to respond effectively to outbreaks of infectious diseases. For those countries and areas that seek assistance in verification and/or in response and control, the World Health Organization can act, in collaboration with a broad range of partner institutions around the world, together forming the Global Outbreak Alert and Response Network (GOARN), to mount rapid assistance through the provision of expertise and specific resources.

With the advent of the new International Health Regulations (IHR) (2005), there is a strong call for accountability in reporting possible new outbreaks with a potential for international spread. The purpose of the IHR (2005) is "to prevent, to protect against, control, and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade" (Article 2).[52] The accountability is linked to the national or local ability to detect and identify the etiology of possible risks to public health. There is a call to strengthen national capacity for surveillance and response and a requirement to alert the World Health Organization to any public health emergency of international concern. It is hoped that rapid, transparent surveillance procedures will provide an early global alert system to ensure that new outbreaks with a potential for international spread can be identified and controlled.

To ensure that countries have the core capacities to undertake effective preparedness planning, prevention, prompt detection, characterization, containment and control of emerging infectious diseases which could threaten national, regional and global security, the Western Pacific and South-East Asia Regional Offices of the World Health Organization developed *The Asia Pacific Strategy for Emerging Diseases* (APSED) as a road map to assist countries in their core capacity building.[53] Considerable progress has been made towards strengthening the core capacities needed to prevent, detect and respond to threats posed by emerging diseases in both regions, and a new five-year plan has been approved to continue the building of core capacity, especially with respect to reducing the risk through strengthening surveillance and thus providing early detection and rapid response to public health emergencies.

Surveillance, early detection and rapid response are certainly the keys to reducing the risks from emerging diseases. To achieve this, there is no doubt that the IHR (2005) will provide the scope and blueprint, but the pathways will require improved surveillance through a One Health collaboration and continued core capacity-building in epidemiology, laboratory capability, and other response components through the APSED workplan. However, to achieve a high level of surveillance and an ability to respond rapidly and effectively to infectious disease threats also requires a strong political commitment by policy-makers and governments, and by a cadre of well-trained and committed health workers in relevant disciplines.

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The Asia Pacific Strategy for Emerging Diseases – a strategy for regional health security

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Health security in the Asia Pacific region is continuously threatened by emerging diseases and public health emergencies. In recent years, the region has been an epicentre for many emerging diseases, resulting in substantial negative impacts on health, social and economic development. As the region is home to more than 50% of the world population, true global public health security depends to a large degree upon how successful this region is in developing and sustaining functional national and regional systems and capacities for managing emerging diseases and acute public health events and emergencies.

Tremendous efforts have been made by individual countries and the international community to confront emerging disease threats in recent years, but the need for a common regional strategic framework has been recognized by countries and areas in the Asia Pacific region, the World Health Organization, donors and partner agencies. To address this need, an updated Asia Pacific Strategy for Emerging Diseases, or APSED (2010), has been developed, aiming to strategically build sustainable national and regional capacities and partnerships to ensure public health security through preparedness planning, prevention, early detection and rapid response to emerging diseases and other public health emergencies. The Strategy calls for collective responsibility and actions to address the shared regional health security threat with a greater emphasis on preparedness-driven investments in health security. APSED (2010) serves as a road map to guide all countries and areas in the region towards meeting their core capacity requirements under the International Health Regulations (2005) to ensure regional and global health security.

A CONTINUING THREAT TO HEALTH SECURITY

Emerging diseases pose a continuing threat to health security. In recent years, the Asia Pacific region has been an epicentre for many emerging diseases (including re-emerging and epidemic-prone diseases) resulting in substantial negative impacts on health, social and economic development. Some of these diseases are severe acute respiratory syndrome (SARS); avian influenza A(H5N1); dengue; Nipah and Hendra viral diseases; leptospirosis; hand, food and mouth disease; and pandemic influenza A(H1N1) 2009.[1–4]

Although it is impossible to predict what, where, when and how new infectious diseases will emerge, we can be confident that emerging diseases and public health emergencies will continue to occur.[5,6] Factors driving disease emergence may include microbial adaption and evolution, increased international travel and trade, rapid urbanization, population growth, changes in human demographics and behaviour, climate change, continuous degradation of ecosystems, breakdown of public health measures and deficiencies in public health infrastructure (including inadequate sanitation).[7–10]

NEED FOR A COMMON STRATEGIC FRAMEWORK

Attempts to develop a global strategy for confronting emerging infectious disease threats were made more than a decade ago.[11] However, due to significant emerging disease outbreaks in recent years, more serious efforts have been made by countries and the international community to confront these threats. Many countries have invested in enhancing their fundamental public health surveillance and response systems. Various new programmes, projects and networks related to emerging diseases have also been initiated with the involvement of national governments, international organizations, development agencies, donors and partners (including the private sector) and academic or educational

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institutions. These efforts have helped improve the overall preparedness for emerging diseases in the region and globally.[12]

The experiences and lessons learnt from implementation of the original Asia Pacific Strategy for Emerging Diseases, or APSED (2005), and pandemic (H1N1) 2009 showed a clear need for harmonization, prioritization, coordination, collaboration and efficiency in addressing the common threats. Such a collective approach required an up-to-date, agreed upon strategic framework that is relevant to all countries, regions and international stakeholders. The World Health Organization (WHO), as the directing and coordinating agency for international health within the United Nations system, has played an essential role in developing such global and regional public health policies and strategies in consultation and collaboration with countries and areas, technical experts and partners. Global and regional strategies can be tailored for national use based on country and area needs and context.

WHO'S ROLE IN HEALTH SECURITY

WHO has the mandate to support countries and areas in strengthening national systems, to help develop capacity and to coordinate a global response to public health security threats, especially those of international concern. The substantially revised International Health Regulations, or IHR (2005), serve as a legal instrument to ensure global health security through a collective approach.[13] Global health security depends on all countries being well equipped to detect, assess, report and respond to any public health events that threaten health security. As infectious diseases do not respect national borders, there is recognition that no single country alone – no matter how capable, wealthy or technologically advanced – can prevent, detect and respond to all acute public health threats. Effective regional and international surveillance and response systems are vitally important to ensure health security for all. Within this collective defence system for health security, WHO has several comparative advantages, including its ability and mechanisms to work with countries and areas to develop health policies, strategies and standards and to connect global experts and technical resources through networks such as the National IHR Focal Points, the WHO Collaborating Centres, the Global Outbreak Alert and Response Network (GOARN) and the Global Influenza Surveillance Network.

STRATEGIC APPROACH AND PRIORITIES FOR REGIONAL ACTION

The Asia Pacific region is home to more than 50% of the world population, thus true global public health security depends to a large degree upon how successful the region is in building, strengthening and sustaining functional national and regional systems and capacities for managing all emerging diseases and acute public health events and emergencies.

In September 2005, for the first time, the Asia Pacific Strategy for Emerging Diseases, or APSED (2005), was developed to provide a common framework for the 48 countries and areas of the Asia Pacific region.[14] This strategy aims to strengthen national systems and capacities for combating emerging diseases. It is a three-in-one strategy to help countries: (1) strengthen the generic capacities for managing emerging diseases, (2) improve pandemic readiness, and (3) build up to meet the IHR core capacity requirements for surveillance and response. APSED (2005) identified five programme areas as priorities for national capacity-building, namely surveillance and response, laboratory, zoonoses, infection control and risk communication. Through the collective efforts of countries and areas, WHO and partners, considerable progress has been made in all five APSED (2005) capacity areas. For example, most countries have now established event-based surveillance systems to detect public health events including disease outbreaks. Trained rapid response teams (RRTs) are able to conduct field investigations quickly. The capacities of the national influenza centres have been significantly improved. These capacities were tested through a real-world global public health event – Pandemic (H1N1) 2009. The pandemic response clearly demonstrated the value of regional investment in capacity-building.[15]

The 2005 Strategy has been recently revised in response to requests from countries and areas following recent developments and evolving needs. The updated Strategy, now called the *Asia Pacific Strategy for Emerging Diseases (2010)*, also known as APSED (2010), was endorsed at the sixty-first Session of the Regional Committee for the Western Pacific in October 2010.[16] It builds on the experiences and accomplishments gained from implementing APSED (2005) and takes into account the key lessons learnt from the pandemic response, the needs expressed by countries and areas and the technical advice provided by experts during the intensive country and regional-level

consultations between July 2009 and October 2010. **Table 1** shows the similarities and differences between APSED (2005) and APSED (2010).

APSED (2010) aims to build sustainable national and regional capacities and partnerships to ensure public health security through preparedness planning, prevention, early detection and rapid response to emerging diseases and other public health emergencies. It calls for collective responsibilities and actions of countries and areas, WHO and partners to ensure a safer and more secure Region.

The 2010 Strategy has identified eight focus areas for prioritized technical and financial investment over the coming five or more years. These include: (1) surveillance, risk assessment and response; (2) laboratories; (3) zoonoses; (4) infection prevention and control; (5) risk communications; (6) public health emergency preparedness; (7) regional preparedness, alert and response; and (8) monitoring and evaluation.

The 2010 Strategy serves as a road map to guide all countries and areas in the region towards meeting their IHR core capacity requirements for ensuring regional and

Table 1. **Similarities and differences between APSED (2005) and APSED (2010)**

Area	APSED (2005)	APSED (2010)
Vision and goal	• Focus on addressing urgent need for managing emerging infectious diseases.	• Emphasis on collective responsibility for regional health security through addressing both emerging diseases and other acute public health emergencies.
Objectives	• Five interlinked objectives: → risk reduction → early detection → rapid response → effective preparedness → partnerships	• Five interlinked objectives: → risk reduction → early detection → rapid response → effective preparedness → partnerships
Focus areas	• Five programme areas: → surveillance and response → laboratory → zoonoses → infection control → risk communications	• Eight focus areas (original 5 + 3 new focus areas): → public health emergency preparedness (national) → regional preparedness, alert and response → monitoring and evaluation
Scope	• Emerging infectious diseases	• Emerging infectious diseases and beyond
Time frame	• 2006–2010	• 2011–2015
Process of development	• A top-down approach with various assessments and evaluations in supporting implementation and buiiiding on lessons from SARS.	• A bottom-up approach with intensive national and regional consultations and building on lessons from the influenza A(H1N1) 2009 pandemic.
Approach for implementation	• A step-by-step approach to ensure the minimum capacity components are in place. • A standard approach (less flexibility in implementing activities). • Focus on more resource-limited countries.	• Defining a clear vision for each focus area and stages towards the vision. • A non-standard approach (more flexibility in designing and implementing activities). • Continuing efforts for resource-limited countries, but also full participation of all countries and areas.

global health security. It endorses a common approach to surveillance, risk assessment and response for emerging diseases and related programmes such as food safety and health emergency preparedness and response.

CONCLUSIONS

Health security is a real and shared challenge requiring shared responsibility and collective actions. The anticipated benefits of APSED (2010) will be fully realized only if there is effective and coordinated implementation at both national and regional levels.

Conflict of interest:

None declared.

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A nationwide web-based automated system for outbreak early detection and rapid response in China

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Timely reporting, effective analyses and rapid distribution of surveillance data can assist in detecting the aberration of disease occurrence and further facilitate a timely response. In China, a new nationwide web-based automated system for outbreak detection and rapid response was developed in 2008. The China Infectious Disease Automated-alert and Response System (CIDARS) was developed by the Chinese Center for Disease Control and Prevention based on the surveillance data from the existing electronic National Notifiable Infectious Diseases Reporting Information System (NIDRIS) started in 2004. NIDRIS greatly improved the timeliness and completeness of data reporting with real-time reporting information via the Internet. CIDARS further facilitates the data analysis, aberration detection, signal dissemination, signal response and information communication needed by public health departments across the country. In CIDARS, three aberration detection methods are used to detect the unusual occurrence of 28 notifiable infectious diseases at the county level and transmit information either in real time or on a daily basis. The Internet, computers and mobile phones are used to accomplish rapid signal generation and dissemination, timely reporting and reviewing of the signal response results. CIDARS has been used nationwide since 2008; all Centers for Disease Control and Prevention (CDC) in China at the county, prefecture, provincial and national levels are involved in the system. It assists with early outbreak detection at the local level and prompts reporting of unusual disease occurrences or potential outbreaks to CDCs throughout the country.

Aberration of disease occurrence means the occurrence of cases is in excess of normal expectancy in a certain region. Early detection of the aberration of infectious disease occurrence and rapid control actions are prerequisites for preventing the spread of outbreaks and reducing the morbidity and death caused by diseases.

After China had an outbreak of severe acute respiratory syndrome (SARS) in 2003, the government took efforts to enhance the capacity of infectious disease surveillance and successfully built the innovative web-based Nationwide Notifiable Infectious Diseases Reporting Information System (NIDRIS) in 2004. It enabled all the health care institutes across the country to report in real time individual case information of notifiable infectious diseases by Internet.[1] This system shortened the interval between case diagnosis and case reporting to within one day on average.[2] However, enhancing the timeliness of data reporting is only the first step for outbreak monitoring and response. Effectively analysing and interpreting the large volume of reported data and rapidly distributing the results to the responders are also key components. Therefore, a tool was conceived to conduct automated and timely analyses and detection of aberration of infectious disease occurrence to facilitate a rapid response to outbreaks and to effectively communicate the outbreak information among Centers for Disease Control and Prevention (CDCs) in China. The universal availability of modern communication tools (such as computers, the Internet and mobile phones) in China also helped this idea to be realized.

In 2005, the China CDC, cooperating with the World Health Organization, initiated a national project to develop the China Infectious Disease Automated-alert and Response System (CIDARS). The system

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Table 1. **Type of aberration detection method for different infectious diseases**

Aberration detection methods	List of infectious diseases
1. Fixed-threshold detection method (FDM)	Type 1 diseases: plague, cholera, SARS, human avian influenza, poliomyelitis, pulmonary anthrax, diphtheria, filariasis, unexplained pneumonia
2. Temporal detection method (TDM)	Type 2 diseases: hepatitis A, hepatitis C, hepatitis E, measles, epidemic haemorrhagic fever, epidemic encephalitis B, dengue fever, bacillary and amoebic dysentery, typhoid and paratyphoid, epidemic cerebrospinal meningitis, scarlet fever, leptospirosis, malaria, influenza, epidemic mumps, rubella, acute haemorrhagic conjunctivitis, epidemic and endemic typhus, infectious diarrhoea (excluding cholera, dysentery, typhoid and paratyphoid)
3. Spatial detection method (SDM)	Type 2 diseases; same as TDM

was successfully implemented and began to operate nationwide in 2008. This paper introduces the design and development of CIDARS and reports the preliminary evaluation of the system's performance.

OVERVIEW OF NATIONAL NOTIFIABLE INFECTIOUS DISEASE REPORTING SYSTEM

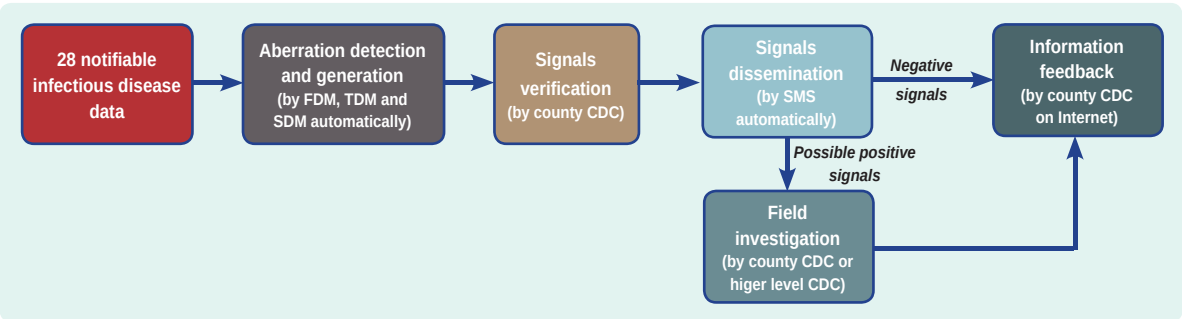
According to the Law of Prevention and Control of Infectious Disease in China, 39 infectious diseases are regulated as notifiable diseases. All cases of notifiable infectious diseases are diagnosed by clinicians using the uniform case definition issued by the Chinese Ministry of Health. A standard report form is used to collect patient's information, including name, gender, age, identification number, residential address, date of onset, date of diagnosis and diagnosis results. Since the implementation of NIDRIS in 2004, all notifiable infectious disease cases have been reported in real time directly from hospitals to the national infectious diseases surveillance database, located at the China CDC, Beijing, China.[1] NIDRIS covers all health care institutions across the country, including general hospitals, specialized hospitals, township and village clinics and private clinics. According to the annual report on disease surveillance in 2008, approximately 67 000 health institutions reported case information to NIDRIS and about 5 million infectious diseases cases were reported annually.[2]

DESIGN AND IMPLEMENTATION OF CIDARS

System description

CIDARS was developed based on the existing data from NIDRIS on 28 diseases (**Table 1**) that are outbreak-prone and require prompt action are included in the system. By integrating multiple aberration detection methods, CIDARS conducts real-time and daily analysis on the data and sends the abnormal signals to CDCs at the county level by short message service (SMS) using mobile phones. CDCs at national, provincial and city levels can also monitor the response process of each signal and provide timely technical guidance and support, if necessary. The system consists of four interconnected components: aberration detection, signal generation, signal dissemination and signal response information feedback (**Figure 1**). The unifying operational protocol of CIDARS on the workflow of these components was developed for the system users.

Figure 1. **Flow diagram of China Infectious Diseases Automated-alert and Response System (CIDARS)**



FDM - fixed-value detection method; TDM - temporal detection method; SDM - spatial detection method; SMS - short message service, possible positive signals - denoting a possible outbreak judged by county CDC staff after conducting signal verification; negative signals - not denoting a possible outbreak judged by country CDC staff after conducting signal verification.

Aberration detection

The three aberration detection methods were developed and applied in CIDARS in two stages. At the first stage, two aberration detection methods, the fixed-threshold detection method (FDM) and the temporal detection method (TDM), were developed in 2006. One year later, the third method, the spatial detection method (SDM), was added and integrated with the first two methods. The 28 diseases were classified into two types according to severity, incidence rate and importance. They were analysed with one of the three different aberration detection methods (**Table 1**). The three methods are briefly described as follows:

(1) Fixed-threshold detection method

Type 1 diseases, includes nine infectious diseases characterized with higher severity but lower incidence, and are analysed using FDM with the threshold of one fixed value.[3]

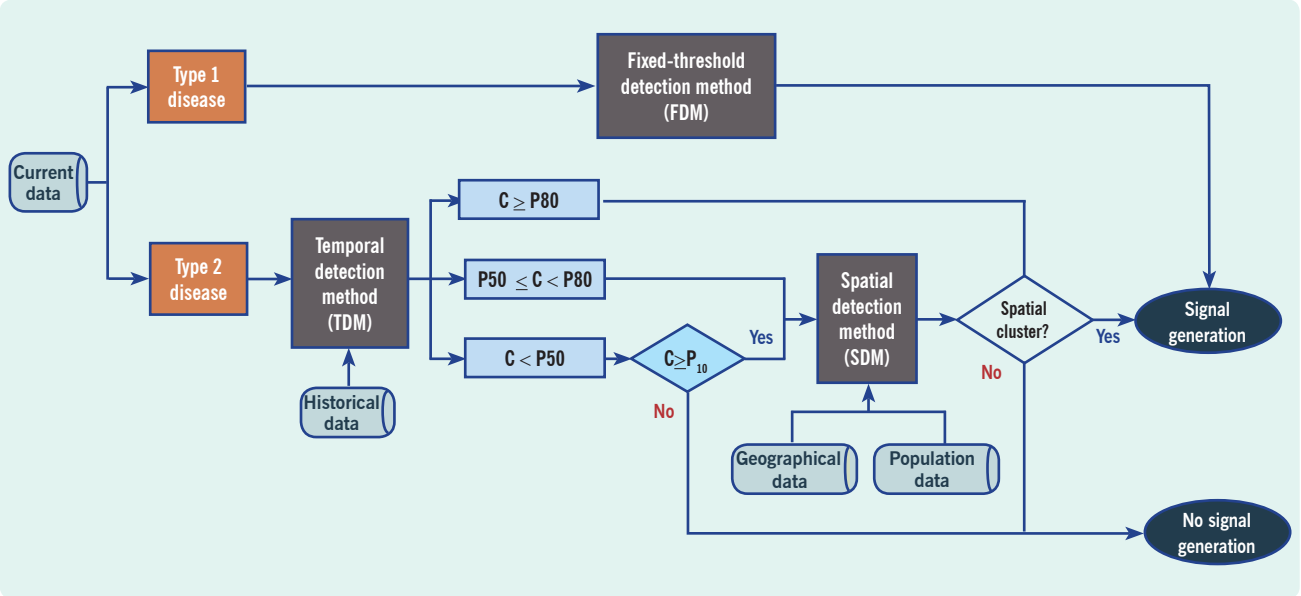
(2) Temporal detection method

For type 2 diseases (more common infectious diseases), the moving percentile method is used to detect aberration of disease occurrence by comparing the reported cases in the current observation period to that of the corresponding historical period at the county level. To account for the day-of-week effect and the stability of data, the most recent seven-day period is used as the current observation period and the previous three years as the historical period.[4,5] The number of cases in the current observation period is the sum of reported cases within the recent seven days. The corresponding historical period included, for each of the previous three years, the same seven-day period, the two preceding seven-day periods and the two following seven-day periods that resulted in 15 historical seven-day data blocks covering 105 days. We set the percentile of the 15 blocks of historical data as the indicator of potential aberration. The current observation period and historical data block are dynamically moved forward day by day.

(3) Spatial detection method

One SDM, the SaTScan method, is used to search for spatial clusters of the incidence of type 2 diseases. SaTScan is a freely available spatial, temporal and space-time data analysis platform.[6,7] This model is applied to the data at the township level. The population data required by SaTScan were obtained from the Chinese Bureau of Statistics, and the geographic data were from the Chinese Institute of Geographic Sciences and Natural Resources Research. When the incidence of disease in certain geographic areas (one town or more than one town) is significantly higher than that of other areas in the county, this area is categorized as spatial clustering.

Figure 2. **The aberration detection and signal generation technology road map of CIDARS**



C: the sum of the reported cases during the current seven-day period; P: the percentile of historical data. Type 1 diseases include plague, cholera, SARS, human avian influenza, poliomyelitis, pulmonary anthrax, diptheria, filariasis, and unexplained pneumonia. Type 2 diseases include hepatitis A, hepatitis C, hepatitis E, measles, epidemic haemorrhagic fever, epidemic encephalitis B, dengue fever, bacillary and amoebic dysentery, typhoid and paratyphoid, epidemic cerebrospinal meningitis, scarlet fever, leptospirosis, malaria, influenza, epidemic mumps, rubella, acute haemorrhagic conjunctivitis, epidemic and endemic typhus, infectious diarrhoea (excluding cholera, dysentery, typhoid and paratyphoid).

Signal generation

Whether or not to generate a signal depends on the calculated results of these three aberration detection methods. The rules of signal generation are (**Figure 2**):

1. For type 1 diseases, the signal is immediately generated once one case is reported to NIDRIS.

2. For type 2 diseases, the generation of a signal is decided by the calculated results of both TDM and SDM, both of which are operated with certain logic sequence (**Figure 2**) and are conducted once a day at 24:00. The signal is finally generated when any one of the following requirements are met after the calculation process of TDM and SDM where C is the sum of cases during the current seven-day period and P is the percentile of the historical data:

- TDM: $C \geq P80$;
- TDM: $C \geq P50$ and $C < P80$, and SDM showing spatial clustering;
- TDM: $C < P50$ and $C \geq P10$, and SDM showing spatial clustering.

Signal dissemination

At least two epidemiologists in every CDC are designated to automatically receive the signals on their mobile phones by the SMS system located at the China CDC, Beijing, China. For type 1 diseases, the signal is distributed in real time, and for type 2 diseases the signal is released at 08:00 once a day.

Signal response and information feedback

The signal response process includes two steps: signal verification and field investigation. The initial verification is conducted by epidemiologists in local CDCs by reviewing the reported cases in NIDRIS, completing a general assessment of information from other surveillance sources or directly contacting the reporting agencies. If the signal denoted one suspected outbreak after the initial verification, this signal would be determined as a possible positive signal, otherwise this signal would be determined as a negative signal. It is estimated that the verification of one negative signal may take about 10 minutes for one professional epidemiologist. Once a possible positive signal is determined, field investigation is conducted to confirm whether an outbreak is occurring.

The information on the signal verification and field investigation is fed back into CIDARS by local epidemiologists, so that the epidemiologists at the CDCs can actively monitor the outcome of signal verification and the evolvement of the outbreak.

ROLES OF SYSTEM USERS

China CDC took responsibility for the system design, development and maintenance as well as monitoring severe outbreaks. CDCs at provincial and prefecture levels took charge of the system's user management within their administrative areas, daily reviewing and following up on the signals response process. All CDCs at the county level are responsible for receiving and responding to the signals, and promptly feeding the response results into CIDARS.

PRELIMINARY RESULTS

During the period 1 July 2008 to 30 June 2010, 221 counties from 10 provinces were selected to conduct the initial evaluation on CIDARS. For type 1 diseases, 308 signals were generated, involving nine diseases, 69 (22.4%) of which were identified as possible positive signals that triggered further field investigation, with nine cholera outbreaks confirmed. For type 2 diseases, 100 629 signals were triggered, including 19 infectious diseases, with about 4.4 signals per county per week on average. Among these, 1371 signals (1.36%) were verified as possible positive signals, and 167 outbreaks were finally confirmed by conducting field investigation. Generally, the percentage of possible positive signals to all signals of the respiratory diseases group (2.78%) was higher than that of zoonoses and vectorborne diseases group (1.95%) and food and waterborne diseases group (0.24%).

DISCUSSION

The development and application of CIDARS was one significant activity to enhance the capacity of early outbreak detection and rapid response in China. It has been integrated into the routine work of outbreak monitoring and response for all of China's CDCs.

Compared to the manual analysis of surveillance data and reporting unusual information level by level, as done in the past in China, CIDARS greatly shortens the frequency of surveillance data analysis and that of outbreak communication among different CDCs. It also

lessens the workload of data collating and analysing for epidemiologists to a great extent. The web-based system was developed and is maintained by the national CDC. The local CDCs only need to use their existing mobile phones, a computer and the Internet to receive and review the signals and transmit information. No new equipment was needed, which reduced the cost for local users.

Many outbreak early warning systems disseminate the signal by e-mail which may make it hard to confirm that the information is received successfully and in a timely manner.[3,8,9] CIDARS uses an SMS platform and designates the specific mobile phones to receive the signal by short text message; the system automatically gets a confirming message which ensures accurate and timely dissemination. As opposed to some systems using only one-sided generation and distribution of the information, CIDARS has a good feedback function for processing signal responses and results to facilitate outbreak response cooperation and assistance, if necessary.

From the initial evaluation of the system, we found that CIDARS can quickly generate abnormal signals and effectively assist in the early detection and confirmation of some disease outbreaks, including both type 1 and type 2 diseases. However, the percentage of possible positive signals of all signals in CIDARS seems to be a little low. As we know, a low percentage of positive signals is a common deficiency facing many similar outbreak early warning systems.[3,10–12] The percentage of possible positive signals varied among the respiratory, zoonotic and vectorborne, and food and waterborne disease groups, which demonstrated that different algorithms need to be considered based on the epidemiological characteristics of the disease.

Although CIDARS is a powerful and sophisticated system, one challenge is to maintain normal operations of the system. Advanced computers with high-powered data calculation ability, the stability of Internet access as well as a professional system maintenance team are necessary. There are currently more than 6000 system users which raises the challenge of user management and training as staff turnover occurs.

One limitation of CIDARS is that it is hard to detect the outbreaks before the cases are diagnosed and reported by clinicians because the system is based on the notifiable infectious disease surveillance data. Therefore, CIDARS sometimes may be less timely and sensitive than some other outbreak detection systems using data on pre-diagnosis of cases in hospitals, media reports or school absenteeism. In addition, many negative signals are currently generated by CIDARS, causing unnecessary signal response for local staff.

Some improvements to CIDARS should be considered in the future. More flexible and reasonable algorithms and parameters for aberration detection should be developed and calibrated for the different characteristics of particular diseases and various needs of different areas in order to improve the performance of outbreak detection. New diseases could be added into the system by local users to address priorities in a particular jurisdiction. Finally, more systematic evaluations of the performance of the system should be conducted, especially on the feedback from users.

Competing interests

None declared.

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Evaluating influenza disease burden during the 2008–2009 and 2009–2010 influenza seasons in Mongolia

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It is critical to monitor the incidence and clinical characteristics of influenza and its associated hospitalization to understand influenza disease burden. A disease burden study can inform the prioritization of a public health response. However, little is known about the epidemiology and disease burden of influenza in developing countries, including Mongolia. Thus we performed prospective data and sample collection from patients who visited outpatient clinics with influenza-like illness (ILI) and hospitalized patients with severe acute respiratory infections (SARI) in two sites of Mongolia, Baganuur District of Ulaanbaatar and Selenghe Province, from 2008 to 2010. In total, we examined 350 ILI cases during the 2008–2009 influenza epidemic period and 1723 ILI cases during the 2009–2010 influenza epidemic period.

We observed the highest ILI incidence per 1000 population in the one to four year age group in Baganuur and in the under one year age group in Selenghe during both periods. Thirteen SARI cases were positive for seasonal influenza A(H1N1) during the 2008–2009 season and 17 SARI cases were positive for pandemic influenza A(H1N1) 2009 during the 2009–2010 season. Among these cases, 84.6% and 58.8% were children under five years of age, respectively, during the 2008–2009 and 2009–2010 seasons. Taken together, children, especially children under five years, had higher influenza infection incidence and hospitalization rate in Mongolia. Although mortality impact also should be considered, we believe that our findings can be useful in formulating an influenza control strategy during influenza epidemic periods in Mongolia.

Influenza is a common vaccine-preventable viral infection that is characterized by a sudden onset of fever, headache, myalgia, malaise, non-productive cough, sore throat and rhinitis. Influenza can cause severe disease or death in the very young, the elderly and people with underlying medical conditions. In developed countries with temperate climates, annual seasonal epidemics usually occur in winter or early spring and often result in dramatic increases in cases, hospitalizations and deaths. The methods used to estimate disease burden, especially mortality impact, have been well established in developed countries and several such study results have been published.[1–5] On the other hand, much less is known about the burden of influenza in developing countries. Monitoring the incidence and clinical characteristics of influenza and hospitalization due to influenza is critical in understanding the influenza disease burden in the population and guiding prevention and control strategies.

Mongolia is a landlocked, middle-income country in north-eastern Asia. Mongolia's total land area is 1 566 600 km^2 and its population density was 1.7 people per square kilometre in 2008. The average annual rainfall is low (200–220 mm) with the heaviest rainfall between June and August. In 2008, the total population of Mongolia was estimated to be 2 694 955, with 27.6% of the population under 15 years of age, 68.3% in the 15–64 year age group and 4.1% aged 65 years and older.

Little is known about the influenza disease burden in Mongolia.[6–8] Therefore, we performed prospective data and sample collection from patients who visited outpatient clinics with influenza-like illness (ILI) and hospitalized patients with severe acute respiratory infections (SARI) to define the epidemiology and disease burden of influenza in Mongolia.

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Figure 1. **Map of study sites in Mongolia**

METHODS

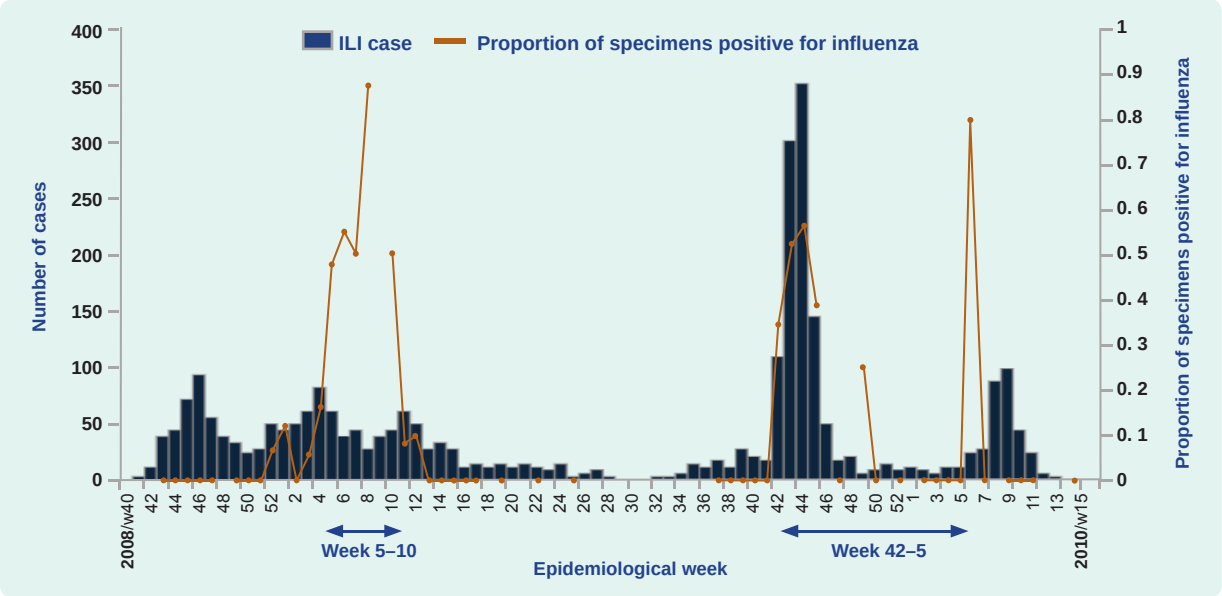
We selected the study population and conducted health care facility-based surveillance to monitor the incidence of ILI and hospitalization with SARI during the 2008–2009 and 2009–2010 influenza seasons. Two study sites were chosen. One site was Baganuur District, a district of Ulaanbaatar, the capital of Mongolia, located 130 km east of the city centre with a population of 25 875. The other study site was Selenghe Province, located 300 km north of Ulaanbaatar at the border to the Russian Federation with a population of 21 460 (**Figure 1**). Age distribution nationwide and at the two study sites were comparable (**Table 1**). Each site has one hospital and four family group practices (outpatient clinics), and all the residents receive free medical care. All the patients with ILI who visited these health care facilities as well as patients who were hospitalized with a diagnosis of SARI were enrolled in this study.

An ILI case was defined as a person with sudden onset of fever (>38.0 °C) and cough or sore throat in the absence of other diagnoses. A SARI case was defined as a person with ILI who developed shortness of breath or difficulty breathing and required hospital admission. Nasopharyngeal swabs were collected for virological testing from patients who met the case definitions of ILI or SARI and whose onset of symptoms were within 72 hours. We collected a maximum of 20 swabs per week from each study site. The specimens were transported to and tested at the National Influenza Center, National Center of Communicable Diseases laboratory in Ulaanbaatar. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) was used to detect influenza

Table 1. **Population by age group**

	Nationwide	Baganuur	Selenghe
0–11 months	64 074 (2%)	671 (3%)	356 (2%)
1–4 years	197 046 (7%)	1 721 (7%)	1 392 (6%)
5–9 years	231 309 (9%)	2 180 (8%)	1 919 (9%)
10–14 years	251 864 (9%)	2 528 (10%)	1 952 (9%)
15–24 years	579 274 (22%)	5 911 (23%)	4 609 (21%)
25–44 years	860 574 (32%)	8 101 (31%)	6 830 (32%)
45–64 years	401 437 (15%)	3 700 (14%)	3 591 (17%)
≥ 65 years	109 377 (4%)	1 063 (4%)	811 (4%)
Total	**2 694 955**	**25 875**	**21 460**

Figure 2. **Epidemiological curve of ILI cases and the proportion of specimens positive for influenza in Baganuur**



A(H1N1), A(H3N2) and B with specific primers following the protocol provided by the Centers for Disease Control and Prevention in the United States of America. In addition, after the first pandemic influenza A(H1N1) 2009 case was confirmed in Mongolia (October 2009), pandemic influenza A(H1N1) 2009 virus was also detected by using real-time RT-PCR.[9] The proportion of specimens positive for influenza virus was calculated for each week. For each influenza season, we defined the influenza epidemic period starting from the week when the proportion of specimens positive for influenza first reached 20% and ending when it fell below 20%. Information on demographic characteristics; medical history, including underlying medical conditions; influenza immunization status; clinical course and treatment with antiviral medications was collected from every case by using a standardized questionnaire. The government census data in 2008 were used for estimating population-based proportion. Data were entered into a Microsoft Access database (Microsoft, WA, USA) and statistical analyses were conducted using SPSS version 18.1 (IBM, IL, USA).

Figure 3. **Epidemiological curve of ILI cases and the proportion of specimens positive for influenza in Selenghe**

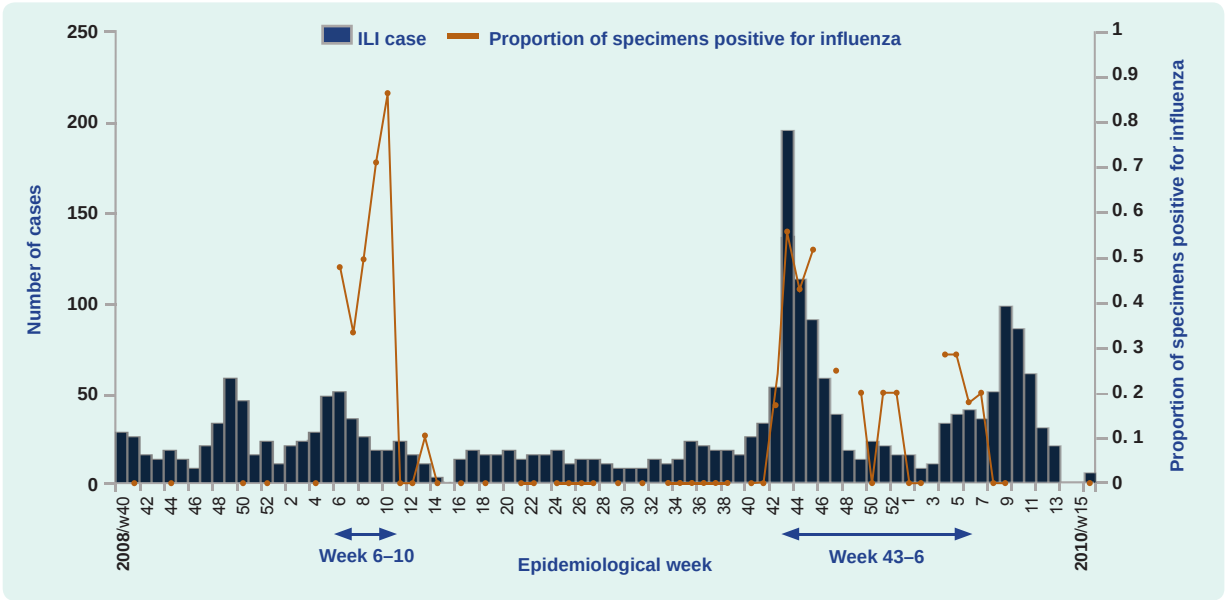


Table 2. **Number of ILI cases and incidence per 1000 population in Baganuur during the two influenza epidemic periods**

Age group	2008–2009 influenza period Week 5, 2009–week 10, 2009 (6 weeks)		2009–2010 influenza period Week 42, 2009–week 5, 2010 (17 weeks)	
	Number of ILI cases	Incidence per 1000 population	Number of ILI cases	Incidence per 1000 population
0–11 months	18	2.7	54	8.0
1–4 years	79	4.6	221	12.8
5–9 years	55	2.5	177	8.1
10–14 years	25	1.0	194	7.7
15–24 years	23	0.4	160	2.7
25–44 years	17	0.2	164	2.0
45–64 years	5	0.1	71	1.9
≥ 65 years	3	0.3	25	2.4
Total	**225**	**0.9**	**1 066**	**4.1**

RESULTS

This study was conducted from 1 October 2008 to 18 April 2010. In total, 128 samples (17%) out of 733 collected samples in Baganuur District and 93 samples (18%) out of 510 collected samples in Selenghe Province were positive for either seasonal influenza A(H1N1) or pandemic influenza A(H1N1) 2009 viruses (**Figures 2, 3**). Influenza A(H3N2) and B viruses were not detected during the study period. There were several weeks during the pandemic in which we could not collect samples due to limited laboratory capacity. The influenza epidemic period of the 2008–2009 season in Baganuur ran from week five of 2009 through week 10 of 2009 (six weeks) and that of the 2009–2010 season ran from week 42 of 2009 though week five of 2010 (17 weeks) (**Figure 2**). Similarly, the influenza epidemic period of the 2008–2009 season in Selenghe ran from week six of 2009 through week 10 of 2009 (five weeks) and that of the 2009–2010 season ran from week 43 of 2009 through week six of 2010 (17 weeks) (**Figure 3**). We observed the demographic characteristics of ILI cases during these influenza epidemic periods.

Influenza-like illness at each site

In Baganuur, 225 ILI cases were enrolled during the 2008–2009 influenza epidemic period and 1066 ILI cases during the 2009–2010 influenza epidemic period (**Table 2**). The median age of cases was six years (range two months–81 years) during the 2008–2009 period and 12 years (range 22 days–85 years) during the 2009–2010 period. There was no difference in the male-to-female ratio between the two periods (0.9). One hundred and seventy-seven ILI cases (78.7%) during the 2008–2009 period and 646 cases (60.6%) during the 2009–2010 period were younger than 15 years of age. On the other hand, three cases (1.3%) during the 2008–2009 period and 25 cases (2.3%) during the 2009–2010 period were 65 years of age or older (**Table 2**). ILI incidence per 1000 population

Table 3. **Number of ILI cases and incidence per 1000 population in Selenghe during the two influenza epidemic periods**

Age group	2008–2009 influenza period Week 6, 2009–week 10, 2009 (5 weeks)		2009–2010 influenza period Week 43, 2009–week 6, 2010 (17 weeks)	
	Number of ILI cases	Incidence per 1000 population	Number of ILI cases	Incidence per 1000 population
0–11 months	13	3.7	78	21.9
1–4 years	39	2.8	157	11.3
5–9 years	26	1.4	108	5.6
10–14 years	20	1.0	82	4.2
15–24 years	14	0.3	112	2.4
25–44 years	9	0.1	92	1.3
45–64 years	4	0.1	22	0.6
≥ 65 years	0	0.0	6	0.7
Total	**125**	**0.6**	**657**	**3.1**

Table 4. **Result of samples collected from SARI cases**

	2008–2009 season	2009–2010 season
Seasonal influenza A(H1N1)	13	0
Pandemic influenza A(H1N1) 2009	0	17
Negative	96	39
Total sample tested	**109**	**56**

by each age group is shown in **Table 2**. The highest incidence was seen in the one to four year age group during both influenza epidemic periods. The ratio of ILI incidence between the 2008–2009 and 2009–2010 periods was highest (14.2) among the 45–64 year age group.

In Selenghe, 125 ILI cases were enrolled during the 2008–2009 influenza epidemic period and 657 ILI cases during the 2009–2010 influenza epidemic period (**Table 3**). The median age was seven years (range one month–63 years) during the 2008–2009 period and eight years (range 23 days–78 years) during the 2009–2010 period. The male-to-female ratio was 0.6 and 0.9 for the 2008–2009 and 2009–2010 periods, respectively, indicating more females presented with ILI during the 2008–2009 period. Ninety-eight ILI cases (78.4%) during the 2008–2009 period and 425 ILI cases (64.7%) during the 2009–2010 period were younger than 15 years of age. On the other hand, no case during the 2008–2009 period and six cases (0.9%) during the 2009–2010 period were 65 years of age or older (**Table 3**). ILI incidence per 1000 population by each age group is shown in **Table 3**.

Table 5. **Age distribution of SARI cases confirmed with influenza virus**

	2008–2009 season	2009–2010 season
0–11 months	4	1
1–4 years	7	9
5–9 years	1	0
10–14 years	0	3
15–24 years	1	4
25–44 years	0	0
45–64 years	0	0
≥ 65 years	0	0
Total	**13**	**17**

The highest incidence was seen in children under one year old during both influenza epidemic periods. The ratio of ILI incidence between the 2008–2009 and 2009–2010 periods was highest (10.2) among the 25–44 year age group.

Severe acute respiratory infections with influenza

In total, 165 SARI cases were tested for influenza during the study period. Thirteen cases were positive for seasonal influenza A(H1N1) virus during the 2008–2009 season, and 17 cases were positive for pandemic influenza A(H1N1) 2009 virus during the 2009–2010 season (**Table 4**). Further analysis was focused on those influenza-positive cases. The median age of SARI cases during the 2008–2009 season was one year (range one month–20 years) while that of the 2009–2010 season was four years (range six months–22 years). Among SARI cases, 84.6% and 58.8% were younger than five years of age during the 2008–2009 and 2009–2010 seasons, respectively (**Table 5**).

Table 6. **Characteristics of influenza-positive SARI cases and their clinical course**

	2008–2009 season (*n* = 13)	2009–2010 season (*n* = 17)
Median age (range)	1 year (1 month–20 years)	4 years (6 months–22 years)
Male-to-female ratio	0.9	0.8
Underlying medical conditions	2 cases	3 cases
Antiviral treatment	0 cases	5 cases
Oxygen supply	0 cases	3 cases
Ventilation support	1 case	0 cases
Mean duration between onset and admission	5.5 days	5.2 days
Mean hospitalization period	7.2 days	5.8 days

The characteristics of influenza-positive SARI cases and their clinical course are shown in **Table 6**. SARI patients during the pandemic period were more likely to be older and female. Two (15.4%) patients during the 2008–2009 season and four (23.5%) patients during the 2009–2010 season had underlying medical conditions. None of the hospitalized patients had influenza vaccination in either season. Mean duration between onset of illness to admission was similar for the two seasons. Five out of 17 cases (29.4%) were administered antiviral treatments during the 2009–2010 season, while none was given during the 2008–2009 season. Three cases received oxygen supply during the 2009–2010 season, and ventilation support was provided to one case during the 2008–2009 season. The mean length of hospital stay was longer during the 2008–2009 season compared with the 2009–2010 season (7.2 days versus 5.8 days). No fatal case was observed during either season.

DISCUSSION

In temperate countries, influenza activity has a clear seasonality. Mongolia is located in a temperate zone of north-eastern Asia and therefore has clear seasonal patterns of influenza, as evidenced through national influenza surveillance.[7] However, no apparent excess mortality was estimated by using the Serfling model.[10] This may partly be because the elderly population, which occupies a major part of influenza excess mortality, is smaller in developing countries. Therefore, in this study, we conducted prospective surveillance and sample collection to define the influenza disease burden by focusing on outpatient visits with ILI and hospitalized patients with SARI.

In this study, we estimated ILI incidence in the 2008–2009 and 2009–2010 seasons and also characterized SARI cases. The highest ILI incidence was seen in children younger than five years of age and the same was seen among the influenza A(H1N1) positive SARI cases. Similar findings were observed in another influenza epidemiological study.[11] The first confirmed case of pandemic influenza A(H1N1) 2009 virus in Mongolia was reported on 12 October 2009. Though the highest ILI incidence was observed among children younger than five years of age in both influenza epidemic periods, the ratio of ILI incidence between the 2008–2009 and 2009–2010 periods was highest among the age groups of 45–64 years (14.2) in Baganuur and 25–44 years (10.2) in Selenghe. This indicated that ILI incidence among the adult population was elevated compared with the previous season. This might be due to the larger susceptible population that could result in a higher number of ILI, but it could also be due to the change of health-seeking behaviour because of the publicity during the 2009–2010 influenza epidemic period when the pandemic influenza A(H1N1) 2009 virus was the dominant strain. Although very few vaccinations were administrated in these seasons and antiviral treatment was only administered during the pandemic period, no death was recorded and the number of confirmed SARI cases remained stable during the study period. Lower ILI incidence in the elderly population may explain why the severity of SARI due to influenza was low in Mongolia; however, we definitely need further studies since the size of registered SARI cases was small.

There are several limitations in our study. Because of limited laboratory capacity, especially during the pandemic period, we could not collect samples for certain weeks from all the ILI and SARI cases, which potentially led to an underestimation in the analysis. Because we defined the influenza epidemic periods from limited laboratory results and defined a cut-off point at 20% of influenza-positive proportion, we might have shortened the influenza epidemic periods and in turn underestimated the ILI cases. In spite of these limitations, the proportion of specimens positive for influenza in our study were 17% in Baganuur and 18% in Selenghe, which is compatible with other studies showing 10%–19%.[12–14]

We observed the highest incidence of ILI among children, especially children under five years of age; the highest proportion of SARI was also observed in this age group. Other infections such as respiratory syncytial virus and rhinovirus can also cause ILI in this age group, so it is necessary to examine other pathogens with influenza-negative samples for more clear disease burden estimation. We believe our findings can lead to awareness among parents who have young children with high potential to be affected with influenza infection. This awareness will encourage individuals in Mongolia to adopt non-pharmaceutical interventions (e.g. hand hygiene) during the influenza epidemic period. However, to reveal a more accurate disease burden of influenza in Mongolia and to develop intervention strategies such as a vaccination programme, further studies in urban areas and with more severe patients are necessary to observe the severity of influenza infection.

Conflicts of Interest:

None declared.

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An outbreak of gastroenteritis caused by *Salmonella enterica* serotype Enteritidis traced to cream cakes

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Introduction: This paper describes the epidemiological, microbiological and environmental investigations conducted during an outbreak of *Salmonella* gastroenteritis in Singapore.

Methods: A case-control study was undertaken to identify the vehicle of transmission. Microbiological testing was performed on faecal, food and environmental samples. Isolates of *Salmonella* were further characterized by phage typing and ribotyping.

Results: There were 216 gastroenteritis cases reported from 20 November to 4 December 2007. The causative agent was identified as *Salmonella enterica* subspecies *enterica* serotype Enteritidis for 14 out of 20 cases tested. The vehicle of transmission was traced to cream cakes produced by a bakery and sold at its retail outlets ($P < 0.001$, OR = 143.00, 95% CI = 27.23–759.10). More than two-thirds of the 40 *Salmonella* strains isolated from hospitalized cases, food samples and asymptomatic food handlers were of phage type 1; the others reacted but did not conform to any phage type. The phage types correlated well with their unique antibiograms. The ribotype patterns of 22 selected isolates tested were highly similar, indicating genetic relatedness. The dendrogram of the strains from the outbreak showed distinct clustering and correlation compared to the non-outbreak strains, confirming a common source of infection.

Discussion: The cream cakes were likely contaminated by one of the ingredients used in the icing. Cross-contamination down the production line and subsequent storage of cakes at ambient temperatures for a prolonged period before consumption could have contributed to the outbreak.

Salmonella enterica subspecies enterica serotype Enteritidis (*Salmonella* Enteritidis) is one of the most common *Salmonella* serotypes worldwide, particularly in developed countries.[1] Its increasing incidence in the United Kingdom and the United States of America in the 1980s was mainly attributed to consumption of raw or undercooked contaminated poultry, hen eggs and egg-containing products.[2,3] In Asia, *Salmonella* Enteritidis has also emerged as the most common human serotype in Japan, the Republic of Korea and Thailand.[4] In Singapore, it accounted for 62.2% of human non-typhoidal salmonelloses in 2007.[5] The vehicles of transmission identified in a few reported localized outbreaks included luncheon pork[6] and an egg-based Malay pancake.[7]

We undertook extensive epidemiological, microbiological and environmental investigations during an outbreak of *Salmonella* gastroenteritis in November and December 2007 in Singapore to determine the causative agent, source of infection and mode of transmission.

The outbreak

On 23 November 2007, the Singapore Ministry of Health was notified of an outbreak of food poisoning involving 15 people who developed illness within 48 hours after attending a birthday celebration. In the following weeks, other clusters of cases were reported from different parts of Singapore. Preliminary investigation showed that most of the cases had consumed cream cakes purchased from various retail outlets that were franchisees of a large and well known local bakery. No other type of cake or bakery products was implicated.

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In view of the unusual occurrences of gastroenteritis suspected to be linked to the bakery and with onset of symptoms since 20 November, outbreak control measures were concurrently implemented while epidemiological investigations were in progress. The public was educated and alerted to the outbreak through the media and advised to discard all bakery products purchased from the implicated retail outlets. Joint actions were taken by the Singapore Ministry of Health; the Agri-Food & Veterinary Authority of Singapore, the licensing authority of the bakery; and the National Environment Agency, the licensing authority of the retail outlets. The bakery was ordered to recall all cream cakes from distribution and sale on 30 November 2007. Production of cream cakes ceased on 3 December followed by other bakery products on the next day. Both the bakery and retail outlets were subsequently closed on 4 December and 5 December, respectively, for thorough cleaning and disinfecting. The last case reported onset of illness on 4 December.

METHODS

Epidemiological investigations

All cases reporting symptoms consistent with the case definition between 20 November and 8 December were interviewed and relevant clinical and epidemiological data such as age, sex, ethnicity, clinical symptoms, date of onset of illness, food items eaten 72 hours before onset of illness, food establishments visited and medical treatment sought were obtained. A case reported during this period was defined as a person who developed diarrhoea (two or more liquid stools per day) and one or more of the following symptoms: nausea, vomiting or abdominal cramps. Contact tracing was also conducted to search for unreported cases.

A case-control study was initiated to determine the specific vehicle(s) of transmission. We made an attempt to obtain more epidemiological information from the first 60 consecutive cases that fit our case definition and from about 100 controls. Interviews were conducted using a set of structured questionnaires to find out what food had been consumed 72 hours before onset of illness and who had contact with pets or family members with history of diarrhoea within the last seven days. Controls consisted of apparently healthy individuals with no recent travel history or gastrointestinal symptoms during the previous two weeks. They were asked similar questions covering the period within three weeks of onset of illness of the reported cases.

Differences in proportions between cases and controls were compared using χ^2 test or Fisher's exact test. To quantify the extent of risk, odds ratio and its 95% confidence interval were also derived. All calculations were performed using SPSS version 15 (SPSS Inc., Chicago, IL). A P value of < 0.05 was considered to be statistically significant in a two-tailed test.

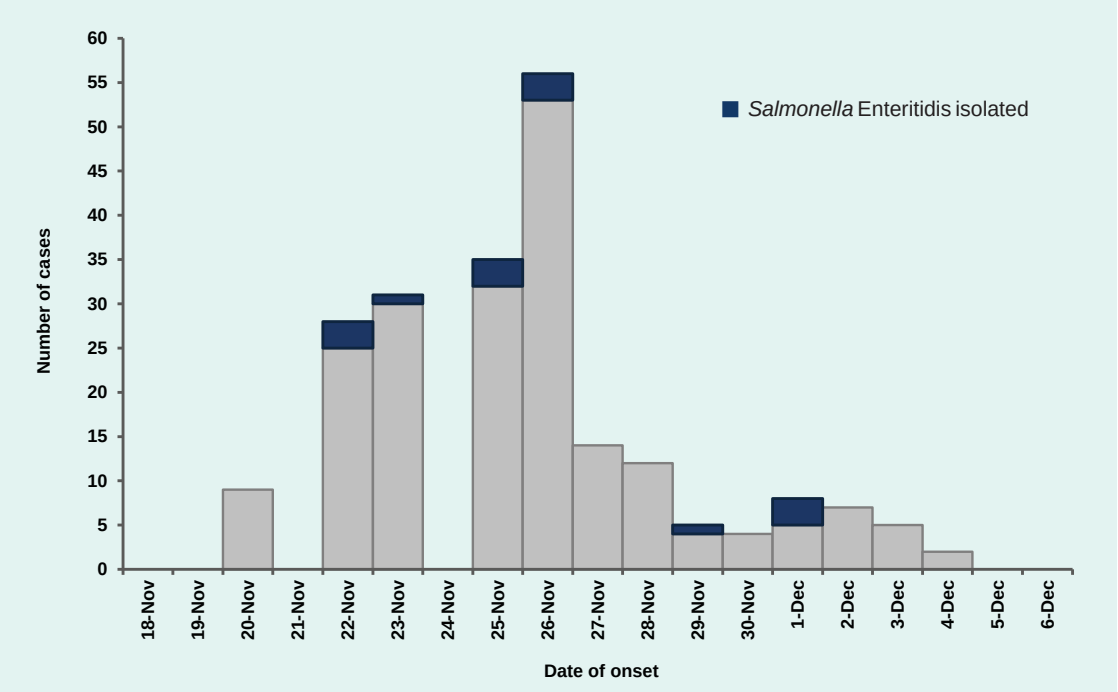
Microbiological investigations

All food handlers and staff in the bakery, including delivery men, cleaners and staff in the 38 retail outlets were referred for a medical examination that included testing of stool samples for enteric pathogens. Raw ingredients, food samples and environmental swabs were sent for microbiological analyses.

The methods for the culture of *Salmonella* and other bacterial enteropathogens from stools and food samples have been described in previous outbreak investigations.[6] Fresh 24-hour *Salmonella* isolates grown on blood agar plates were serotyped by slide agglutination with antisera obtained from Statens Serum Insitut of Copenhagen, Denmark.[8] Isolates of *Salmonella* Enteritidis were further analysed by biotyping (antimicrobial susceptibility testing), phage typing and molecular typing (ribotyping). Antimicrobial susceptibility testing was performed using a disk diffusion method on Mueller Hinton agar and Clinical and Laboratory Standards Institute interpretive criteria,[9] while phage typing was carried out by the method of Ward et al.[10]

Automated ribotyping was performed with isolates from the cases, food samples and food handlers in the outbreak, as well as isolates not related to the outbreak (food samples and ATCC type strain). Automated ribotyping was performed with the RiboPrinter microbial characterization system (RP) (Qualicon, Inc., DuPont, Wilmington, DL). The isolates were cultured on blood agar consisting of trypticase soy agar and 5% sheep blood (BBL Microbiology Systems, Cockeysville, MD) and incubated overnight at 35 °C. Colonies were picked from individual culture plates, placed in tubes containing lysis buffer, heat treated and loaded into the RP. Within the RP, bacterial DNA digestion was accomplished with 50μL of *Pst*I at 40 U/μL (Roche Diagnostics GmbH, Mannheim, Germany) and 50μL of SphI at 40 U/μL (Roche Diagnostics GmbH, Mannheim, Germany). The substitute restriction

Figure 1. **Onset of symptoms of 216 gastroenteritis cases linked to consumption of cream cakes, 20 November to 4 December, 2007**



enzyme protocol in which digestion takes place at 37 °C for two hours was used. The Riboprint pattern for each isolate was then compared to the patterns generated for the other isolates. Interpretation of the ribotype patterns was aided by use of the software BioNumerics 2.5 (Applied Maths, Sint-Martens-Latem, Belgium) and the use of an import script provided by DuPont-Qualicon to import the patterns into BioNumerics. Clustering was performed by using the unweighted pair-group method with arithmetic averages based on Pearson correlation (global pattern comparison). A dendrogram was constructed with the BionNumerics software. Clustering was performed by using a 1% optimization parameter and a 1% band position tolerance.

Environmental investigations

Site visits were made to the suspected bakery and its retail outlets to identify the possible sources and causes of contamination. The entire production process in the bakery from the purchase of raw ingredients to distribution in the retail outlets was thoroughly reviewed with the management.

The investigations were carried out in accordance with the Infectious Diseases Act of Singapore.

RESULTS

Epidemiological investigation

A total of 39 reports of food poisoning occurring either singly or in small clusters involving 216 people that met the case definition were reported, with onset of illness between 20 November and 4 December 2007 (**Figure 1**). The main presenting symptoms were diarrhoea (96%), fever (63%), vomiting (60%) and headache (16%). Their ages ranged from one year to 78 years (median age, 29 years) with no gender difference. Among the major ethnic groups in Singapore, Chinese comprised 70.4% of the cases; Malays, 27.3%; and others, 2.3%. Of the reported cases, 18 (8.3%) were hospitalized while the rest either sought outpatient treatment or self-medicated.

Of the first 60 cases contacted 53 agreed to participate. We attempted to enrol approximately 100 controls however only 39 agreed to participate. Results of the case-control study based on 54 cases and 39 controls implicated cream cakes from the suspected bakery ($P < 0.001$, OR = 143.00, 95% CI = 27.23–759.10) as the vehicle of transmission (**Table 1**). No other food items or risk factors were implicated. The median incubation period based on

Table 1. **Results of case-control analysis in an outbreak of gastroenteritis, November–December 2007**

Food items and risk factors	Cases (*n*=54)			Controls (*n*=39)			*P* value	Odds ratio	95% confidence interval
	Exposed	Not exposed	% exposed	Exposed	Not exposed	% exposed			
Cream cakes*	52	2	96.3	6	33	15.4	<0.001	143.00	27.23–751.10
Poultry	20	34	37.0	27	12	69.2	0.003	0.26	0.11–0.63
Dairy products	9	45	16.7	25	14	64.1	<0.001	0.11	0.04–0.30
Eggs	6	48	11.1	23	16	59.0	<0.001	0.09	0.03–0.25
Contact with family members with gastroenteritis	11	43	20.4	9	30	23.1	0.754	0.85	0.32–2.31
Contact with pets	10	44	18.5	5	34	12.8	0.573	1.545	0.48–4.95

* Purchased from suspected confectionary and its retail outlets

the interval between consumption of the implicated food item and onset of illness was 12.3 hours (range: 3–139 hours).

Microbiological investigations

A total of 428 faecal specimens from cases (20), and food handlers (176) and retail outlet staff from the bakery (232) were tested for bacterial enteropathogens. *Salmonella* Enteritidis was isolated from 14 (70%) of 20 cases. Six (3.4%) of 176 food handlers and staff from the bakery and four (1.7%) of 232 staff from the retail outlets also tested positive for *Salmonella* Enteritidis. Three other food handlers (two from the factory, one from a retail outlet) were positive for *Salmonella* Group C and another food handler (from another retail outlet) for *Salmonella* Group E.

Seventy raw ingredients, 25 semi-processed products and five ready-to-serve products from the factory were tested. Of these 100 samples, 12 semi-processed products and ready-to-serve products (whole hazelnuts from an opened container, one truffle chocolate cream specimen, two chocolate cream specimens and eight hazelnut paste specimens taken from different opened tubs) tested positive for *Salmonella* Enteritidis. One food sample showed high bacterial count (Standard Plate Count = 160 000 000 cfu/gm) and another tested positive for *Bacillus cereus.* Of 23 ready-to-serve products from nine of 38 retail outlets, eight cake samples from five of the outlets also tested positive for *Salmonella* Enteritidis with a concomitant high bacterial count (Standard Plate Count = 4 300 000 cfu/gm). Of two cake remnants provided by the cases, one was positive for *Salmonella* Enteritidis and the other for *Salmonella* Group C.

All the environmental swabs were negative for *Salmonella*. A raw egg sample taken from the house of one hospitalized case and raw and liquid eggs obtained from the supplier of the bakery were negative for *Salmonella*.

Phage typing results of isolates from the food handlers, food samples and cases showed 27 (67.5%) out of 40 isolates were of phage type 1 and 13 (32.5%) were isolates that reacted but did not conform (RDNC) (**Table 2**). The phage type correlated well with the antibiogram results, with the strains within each phage type having a unique antibiogram. *Salmonella* Enteritidis of both phage type 1 and RDNC isolates were sensitive to ampicillin, chloramphenicol, ceftriaxone and ciprofloxacin and resistant to nalidixic acid. *Salmonella* Enteritidis phage type 1, however, was resistant to sulphamethoxazole/ trimethoprim while that of RDNC isolates were sensitive to it.

Ribotyping using *Pst*I and *Sph*I restriction enzymes for restriction of DNA showed that the ribotype patterns obtained were highly similar between isolates, indicative of direct genetic relatedness between the isolates even though they are of a different phage type (**Figure 2**). The dendrogram from the cluster analysis showed the distinct clustering and correlation of the *Salmonella* Enteritidis isolates from the outbreak as compared to the non-outbreak strains (**Figure 3**).

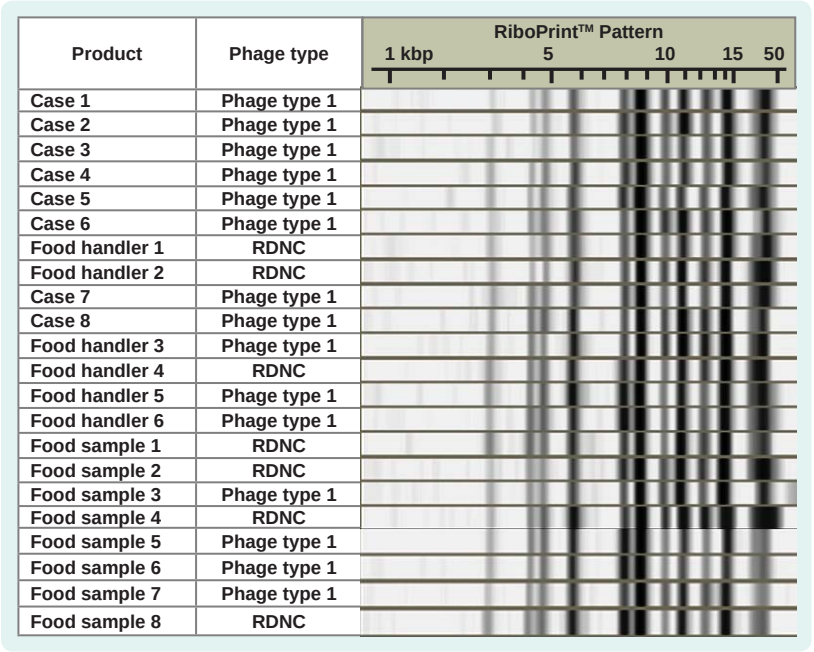
Environmental investigation

Semi-processed products and ready-to-serve food items were not adequately separated. Utensils and working surfaces were also not cleaned and disinfected thoroughly and regularly. High-risk food ingredients

Table 2. **Results of phage typing of isolates of *Salmonella* Enteritidis**

Source		Number of isolates analysed	Number of phage type 1 isolates (%)	Number of RDNC isolates (%)
Food handlers	Factory	6	3 (50.0)	3 (50.0)
	Outlets	3	2 (66.7)	1 (33.3)
Food samples	Factory	9	6 (66.7)	3 (33.3)
	Outlets	8	4 (50.0)	4 (50.0)
	Remnant	1	1 (100.0)	0 (0.0)
Cases		13	11 (84.6)	2 (15.4)
Total		**40**	**27 (67.5)**	**13 (32.5)**

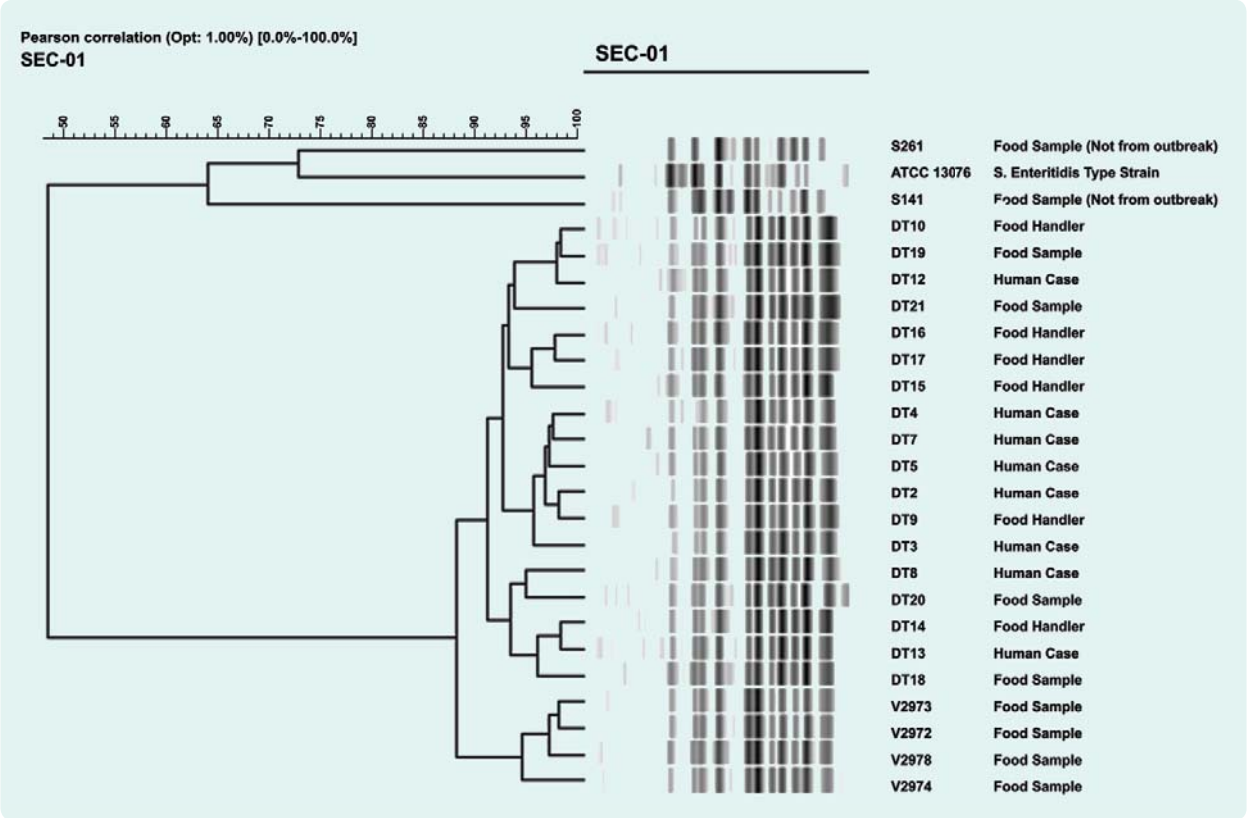
Figure 2. **Results of phage typing and ribotyping of *Salmonella* Enteritidis isolates from eight cases, six food handlers and eight food samples**



such as cream produced in bulk quantity were left at ambient temperatures for prolonged periods. Moreover, the final ready-to-serve products were not immediately kept in refrigerators with temperature display to prevent bacterial growth. No irregularities in personal and food hygiene among the food handlers were observed during the site visits. None of the staff reported recent history of gastrointestinal illness.

Butter cream was a key ingredient used to make the cream cakes. It was processed in-house, unlike the production of other types of cakes in which ready-to-add packaged fresh cream was used. The butter cream was made from butter, sugar syrup that had been boiled at high temperature (120 °C) and half-whisked egg whites. The egg whites were manually separated from the whole eggs by the production staff who claimed that they were properly gloved during the process. After being cracked and their contents separated, these eggs were pooled in the kitchen and held at room temperature. Other ingredients such as chocolate paste or hazelnut paste were subsequently mixed with the butter cream to form chocolate cream or hazelnut cream, respectively. The butter cream was prepared in bulk quantity for use over two production days. The prepared creams were stored at room temperature in the production area. The prepared creams were used to sandwich the chocolate sponge bases that had been baked in the oven. The final product was then decorated. The cakes and other bakery products were delivered from the bakery to 38 retail outlets around the island in well maintained refrigerated trucks in accordance to specified schedules.

Figure 3. **Dendrogram of *Salmonella* Enteritidis isolates using automated ribotyping**



The cakes at the retail outlets were displayed for sale in well maintained refrigerated showcases.

DISCUSSION

This outbreak was the largest common source outbreak of gastroenteritis caused by *Salmonella enterica* subspecies *enterica* serotype Enteritidis in Singapore. The epidemiological evidence implicating cream cake as the vehicle of transmission was supported by microbiological and molecular findings. *Salmonella* serotype Enteritidis was isolated from cases, food samples and food handlers. More than two-thirds of the isolates belonged to phage type 1, and the others reacted, but did not conform to any phage type. Although the phage type correlated well with the antibiogram findings, with the strains within each phage type having a unique antibiogram, the ribotype patterns among the isolates (phage type 1 and RDNC) were highly similar, indicating genetic relatedness. Moreover, the dendrogram of the *Salmonella* Enteritidis isolates from the outbreak showed distinct clustering and correlation compared to the non-outbreak strains. The multiple laboratory methods enabled us to discriminate the *Salmonella* strains isolated from various sources and link the outbreak to a common source.[11,12]

Cakes, ice cream and other bakery products (e.g. custards) are known vehicles of transmission of *Salmonella* Enteritidis and ingredients made from raw eggs provide a potential source of contamination.[13–17] Ingredients made from raw eggs provide a potential source of contamination In this outbreak, egg white manually separated from raw egg yolks was one of the ingredients of the butter cream processed in-house for the icing of cream cakes. The eggs were not pasteurized or heated to a high temperature, unlike other ingredients of the icing. The exact mechanism by which the implicated cake was contaminated remained unclear. We could not rule out the possibility of introduction of *Salmonella* Enteritidis via a particular batch of eggs sent to the bakery before the outbreak, although egg samples taken from the supplier were negative. Ready-to-serve cream cakes, kept in the open preparation area uncovered at ambient temperatures in the bakery for at least two hours before distribution by refrigerated trucks to the retail outlets, could have led to further multiplication of *Salmonella* to high infective doses.

The asymptomatic food handlers who tested positive for *Salmonella* Enteritidis could have been infected during preparation, handling or consumption of

contaminated cream cakes during the outbreak. Some of these workers at the bakery were routinely assigned to break the eggs to obtain the egg white or taste-test the quality of the ingredients, while others claimed to have eaten the implicated cakes. Infected food handlers can transmit *Salmonella* organisms to food ingredients, work surfaces and utensils, if personal and food hygiene practices are insufficiently observed.[18–21] *Salmonella* Enteritidis has been recovered from fingers following the breaking of intact shell eggs artificially contaminated with the enteropathogen, with some organisms surviving hand-washing with soap and hot water.[21]

Cross-contamination of utensils, equipment and work surfaces could have also occurred as the layout of the cake production area was such that semi-processed products and ready-to-serve food items were not adequately segregated. *Salmonella* can survive in the environment for several days.[22] Cross-contamination down the production line could also have caused the food products and whole hazelnuts (opened packet) to be contaminated.

There were several limitations in the epidemiological investigations of this outbreak. In the case-control study, the number of controls was too few as some who were identified refused to participate in the interview. This resulted in the wide confidence intervals of the implicated food item. Also, the questionnaires did not include other food items that either used raw eggs as an ingredient or were manufactured by other bakeries, even though it was unlikely that any of these food items would be the vehicle of transmission, and the respondents had difficulty recalling all the food items consumed. Furthermore, we did not know the shelf life of the cream cakes, batch numbers and the quantities manufactured, which could have been used to explain, to some extent, the transmission of infection.

We had no evidence to implicate raw eggs used for the icing as the source of infection, as no *Salmonella* could be isolated from the samples tested. Thus, we could not explain how the semi-processed and ready-to-serve products became contaminated in the factory. The hazelnuts could have been contaminated at the source since they did not undergo heat treatment in the bakery. However, a trace back investigation was not conducted. Additionally, detailed information regarding poultry flocks and eggs was not available. Lastly, in this outbreak, less than 10% of the reported cases had their stools examined for *Salmonella* organisms as most of them either self-medicated or were treated as outpatients.

Notification of cases from this outbreak was based on both reports of food poisoning and routine reporting of infections with *Salmonella*. In view of several local outbreaks that were caused by *Salmonella*, reporting of *Salmonella* in Singapore was subsequently made mandatory in 2009. This will enable more rapid and targeted epidemiological investigations into common source foodborne outbreaks of salmonellosis.

This outbreak highlighted the importance of prompt notifications of food poisoning incidents by clinicians, clinical laboratories and the public. As soon as the vehicle of transmission was suspected, the public was quickly alerted and immediate action taken to recall and destroy the implicated products and temporarily halt production, as in other reported outbreaks.[23] The availability of routine molecular typing techniques in outbreak settings would facilitate tracing the source of infection and confirming epidemiological linkages of the *Salmonella* strains isolated from humans, food, animals and the environment. The incident also served as a good reminder to all food handlers to constantly observe proper personal and food hygiene practices. Food manufacturers are also advised to use only pasteurized eggs for food products that do not undergo severe heat treatment.

Note:

This article is based on a report from Communicable Disease Surveillance in Singapore, 2007. Reference: Outbreak of Salmonellosis traced to consumption of cream cakes, Communicable Disease Surveillance in Singapore, 2007, Singapore: Ministry of Health; 2008. Available from: http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Reports/2008/Special%20Feature.pdf.

Conflicts of Interest

None declared.

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Western Pacific Surveillance and Response Instructions to Authors

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To create a platform for sharing information to improve surveillance of and response to public health events in the Western Pacific Region.

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- To produce a web-based publication on surveillance and response activities in the region that has high exposure and is freely accessible.
- To promote information sharing on experiences and lessons learnt in surveillance and response for public health events in the Western Pacific Region and globally.
- To build capacity in communicating epidemiological findings in the Western Pacific Region.
- To highlight new and relevant technical or guidance documents and meeting reports published by the World Health Organization, Western Pacific Regional Office.

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