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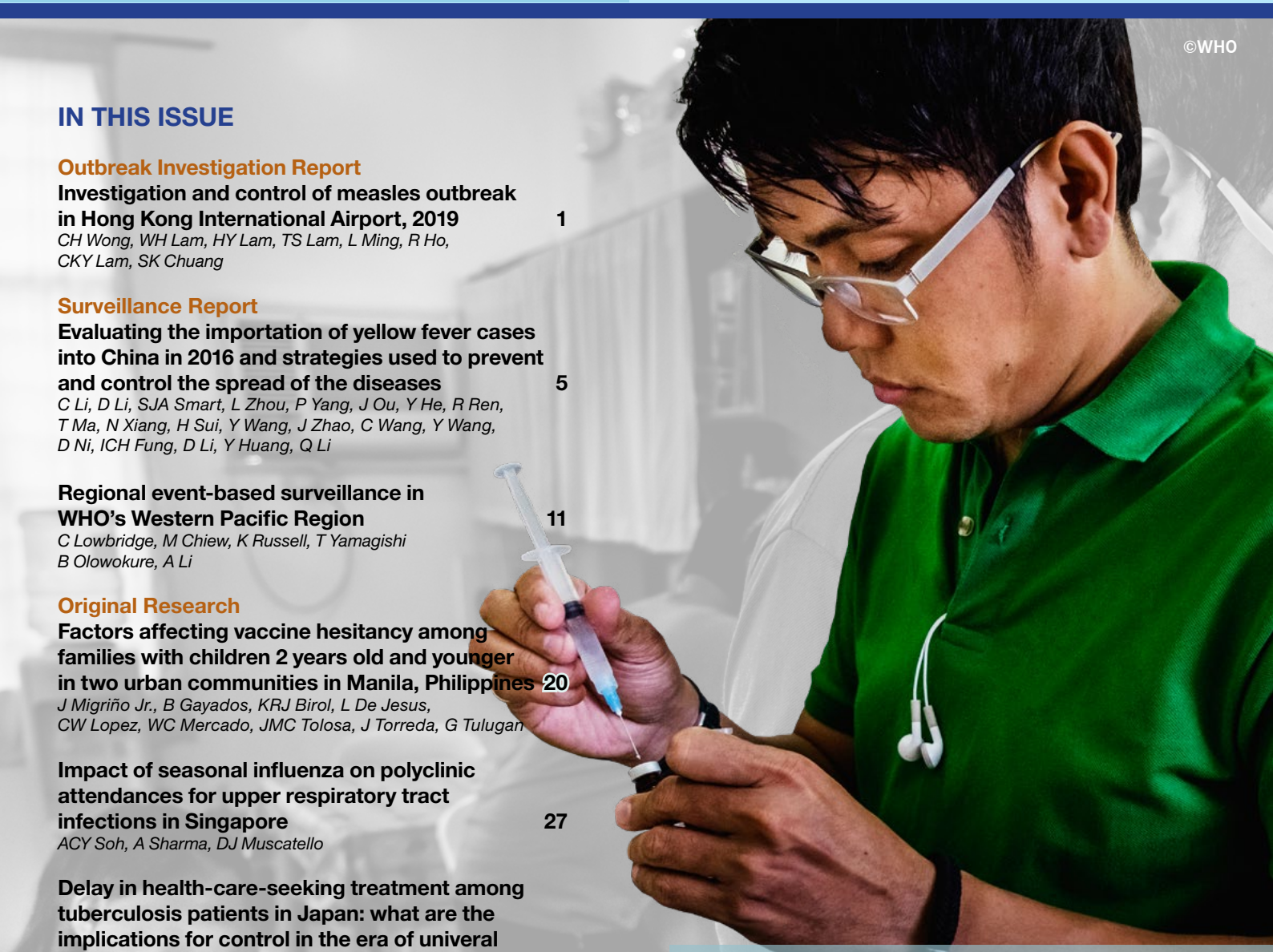

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Western Pacific Surveillance and Response

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Investigation and control of a measles outbreak at the Hong Kong International Airport, 2019

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Introduction: Hong Kong SAR (China) achieved measles elimination status in 2016, and the incidence of measles infection had been low over the past few years. However, the Centre for Health Protection (CHP) at the Department of Health was notified on 22 March 2019 of an outbreak of three cases of measles infection among workers at the Hong Kong International Airport (HKIA).

Methods: We reviewed notifications of measles received by CHP from 1 January to 17 May 2019. We defined a confirmed case of measles as having laboratory evidence of measles infection. All confirmed cases among airport workers or those with epidemiological information suggesting they had been infected by contact with airport workers were included in the review. We described the epidemiological features and reviewed the control measures against the outbreak.

Results: We identified 33 cases, 29 of which were among airport workers. They comprised 22 men and 11 women, aged 20–49 years (median 25 years). The majority of people with confirmed measles presented with fever and rash. All required hospitalization. None developed complications. Control measures, including enhanced environmental hygiene and improved ventilation at HKIA and vaccinations for the airport community, were implemented. Vaccinations were provided to 8501 eligible airport workers, and the outbreak was declared over on 17 May 2019.

Discussion: Early recognition of the outbreak and prompt control measures, especially targeted vaccination of the exposed population, effectively controlled the outbreak in just two weeks.

Hong Kong SAR (China) achieved measles elimination in 2016. The annual number of measles cases had remained at a very low level since then, with nine, four and 15 cases recorded in 2016, 2017 and 2018, respectively. In 2019, amid worldwide increases in measles incidence, especially in the Philippines, the Centre for Health Protection (CHP) of the Department of Health of Hong Kong SAR (China) also recorded an upsurge of measles cases (73 cases as of 17 May 2019), including a major outbreak at the Hong Kong International Airport (HKIA).

HKIA occupies 1255 hectares on Lantau Island. It is one of the world's largest and busiest airports, connecting 120 airlines to over 220 destinations worldwide and handling about 75 million passengers in 2018. It has more than 73 000 workers. CHP was notified on 22 March 2019 of an outbreak of three cases among HKIA workers, and an epidemiological investigation was initiated.

METHODS

Case definition

For this investigation, we defined a laboratory-confirmed case of measles as a person having any of the following: (1) a positive serological test for measles virus IgM antibody; (2) a fourfold or greater increase in the measles antibody (IgG) titre; (3) the isolation of measles virus from a clinical specimen; or (4) a positive reverse transcription-polymerase chain reaction (RT–PCR) for measles virus in a clinical specimen, with any of the four occurring between 11 February and 17 May 2019.

Typical measles was defined as a patient with laboratory-confirmed measles who presented with fever, rash and at least one of the three "C"s (cough, coryza or conjunctivitis). Patients with laboratory-confirmed measles who did not have signs or symptoms satisfying the

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definition of typical measles were classified as having modified measles.

Study period and case selection

The earliest recorded confirmed measles patient among the HKIA workers had an onset of rash on 4 March 2019. In an effort to identify any other epidemiologically linked measles cases, we reviewed all measles cases notified to CHP from 1 January to 17 May 2019. All cases among the HKIA workers were included in the HKIA outbreak investigation. Patients with epidemiological information suggesting that they were infected or contracted the disease from an airport worker were considered to be epidemiologically linked to the HKIA outbreak.

We conducted an epidemiological investigation for every measles case. We reviewed the clinical records and interviewed patients for demographic information and their clinical course, travel history, exposure and contact history. We investigated the local movements of all patients during the incubation and communicable periods, attempting to postulate the transmission chain of the outbreak. We also reviewed CHP records for the timing and type of control measures implemented during the outbreak.

Ethics statement

Ethics approval was not required as this was an emergency response case.

RESULTS

The cases

We identified 29 cases among airport workers in the HKIA outbreak and four cases epidemiologically linked to the outbreak (one airport visitor, one traveller and two health-care workers with nosocomial exposure to an airport case). These 33 cases comprised 22 men and 11 women, aged 20–49 years (median 25 years). Two thirds (22/33) of the patients were aged 20–29 years. The first patient had an onset of rash on 4 March 2019, and the last patient had an onset of rash on 5 April 2019 (**Fig. 1**). The vast majority had rash (33, 100%) and fever (31, 93.9%). Their clinical courses were mild and none developed complications. All were isolated in a hospital until the end of the communicable period (four days after the onset of rash). All respiratory specimens from the 33 patients tested positive for measles virus by polymerase chain reaction (PCR) and belonged to genotype B3.

The measles vaccination history of the 33 patients showed that 12 (36%) had a documented record of at least two doses of measles-containing vaccine, 19 (58%) had no officially documented history of vaccination, and two (6%) were unvaccinated. Among the 33 cases, 23 (70%) were born in Hong Kong SAR (China) and 10 (30%) were not born locally.

Fifteen cases (45%) were classified as typical measles, and 18 (55%) were modified measles. Nine (50%) patients among the 18 modified measles cases and three (20%) among the 15 typical measles cases had received two or more doses of measles-containing vaccine.

Most (27/29) of the affected airport workers did not know each other and could not recall any direct contact with other affected individuals. We identified at least three sub-clusters of this outbreak, with separate sources of infection affecting 32 of the 33 cases. Each of the suspected sources was responsible for two generations of infection and affected one to seven people in each generation (**Fig. 2**). For one case, the source could not be determined.

Outbreak response

The measles outbreak at HKIA was confirmed on 22 March 2019 when three measles cases were notified to CHP and an initial epidemiological investigation revealed that the affected individuals were all airport workers who likely contracted measles at work. An outbreak response team was formed on the same day to carry out in-depth epidemiological investigations and formulate targeted control measures. An onsite investigation was conducted with experts in microbiology and field epidemiology. HKIA management was advised to improve ventilation by increasing the intake of fresh air and increasing the number of alcohol-based hand-rub dispensers in the airport. Press releases alerted the public to the measles outbreak and provided information about prevention and control measures.

Immediately after the outbreak was identified, measles-mumps-rubella (MMR) vaccinations were offered to airport workers without presumptive measles immunity,

Fig. 1. **Epidemic curve of measles cases linked to the HKIA outbreak, 2019 (by date of rash onset)**

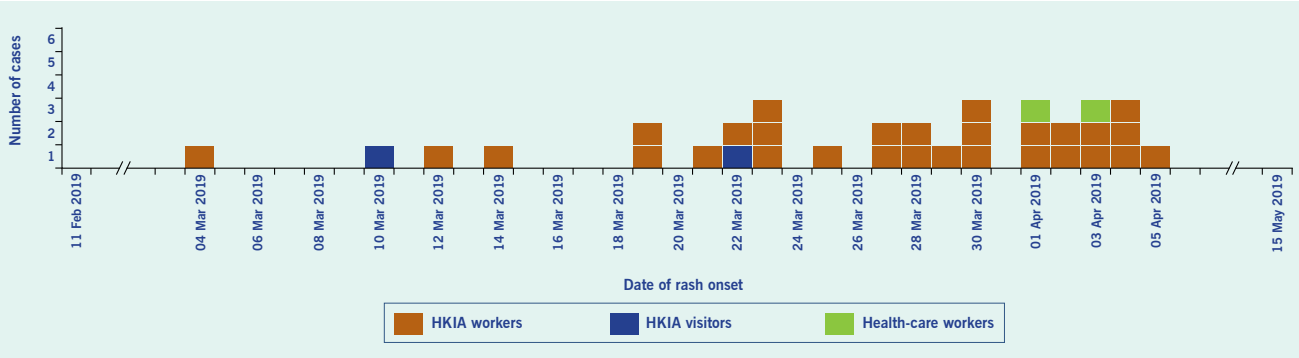
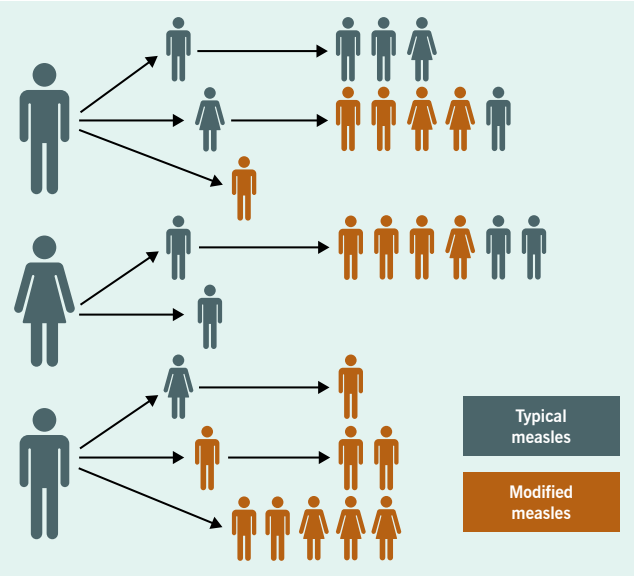


Fig. 2. **Transmission chain of the HKIA outbreak (n = 32)**



for example, those without a history of vaccination, as an outbreak control measure. Vaccination stations were set up at the airport, and medical teams, including doctors and nurses, were deployed to conduct onsite vaccinations. Between 22 March and 17 May 2019, MMR vaccinations were provided to 8501 airport workers.

The outbreak was declared over on 17 May after two incubation periods (42 days) passed since 5 April 2019, the date when the last case visited HKIA.

DISCUSSION

This was the first major outbreak recorded in Hong Kong SAR (China) since the certification of the elimination of measles in 2016. Outbreaks among workers in airports have been reported previously elsewhere, for example, in Kansai, Japan, in 2016, affecting 34 individuals (including 32 airport staff members and two health-care workers) and Taoyuan International Airport in Taiwan (China) in 2018.[1,2] Heavy traffic flows, crowded environments that include international travellers and the recent upsurge in measles cases worldwide put airport workers at higher risk than the general population of having contact with travellers infected with measles. The airport's recirculating ventilation design and crowded environments in certain places, such as changing rooms, might have contributed to the transmission of measles among the HKIA workers who shared the same air space but might not have close interaction with one another. Measles virus can live up to two hours in airspace where an infected person has coughed or sneezed.[3] Susceptible individuals may become infected by breathing contaminated air and/or touching contaminated environments.

More than half of the cases (55%) in this outbreak were classified as modified measles, which is considered to have lower transmission potential.[4] This is consistent with our observation that most of the patients who gave rise to secondary cases presented with clinically typical measles.

Primary vaccine failure occurs in some recipients of measles-containing vaccine, with about 5% of people who received two doses of measles vaccines not developing immunity after vaccination.[5] One study has suggested that in the post-elimination era, when there is lack of boosting of immunity from exposure of wild-type measles, the duration of immunity among vaccinated individuals may not last.[6] Moreover, recent studies also supported the presence of secondary vaccine failure, in which waning immunity in adults who received two doses of measles-containing vaccine was observed.[7,8] Among the

33 affected individuals, two thirds (22/33) were 20–29 years old, and more than half (12/22) of them had a documented history of having previously received two or more doses of measles-containing vaccine. Further analysis of the IgM and IgG results from blood specimens taken within 72 hours of rash onset could provide more information on the proportion of cases with potential secondary vaccine failure.

This outbreak lasted for a month, from 4 March, when the first patient had an onset of rash, to 5 April, when the last patient had an onset of rash, and the outbreak was halted after two generations of transmission. We believe that early recognition of the outbreak and prompt implementation of control measures, especially the aggressive vaccination campaign targeted at airport staff, effectively prevented further spread of the disease and swiftly controlled the outbreak in about two weeks – from the identification of the outbreak on 22 March to 5 April, when the last affected individual visited HKIA.

One limitation of this report is the fact that our analysis of the transmission was retrospective, based on self-reported local movement history provided by the patients. Such reporting is subject to recall error and might not reflect the actual transmission chain. Because of the mild clinical course of the cases, other undiagnosed measles cases likely existed but were not detected, which may underestimate the actual outbreak size.

It is possible that other people may have been infected through this outbreak and travelled outside of Hong Kong SAR (China) and, therefore, would not have been included in this study. Cross-border communication of measles outbreaks involving other airports might have provided data to plug the loophole and better reflect the actual outbreak situation.

CONCLUSIONS

Measles remains a public health threat, even in areas where measles has been eliminated. We demonstrated that early recognition of an outbreak and prompt control measures, especially vaccination for a potentially exposed population, can quickly control measles outbreaks.

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Conflicts of interest

None

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None

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Evaluating the importation of yellow fever cases into China in 2016 and strategies used to prevent and control the spread of the disease

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During the yellow fever epidemic in Angola in 2016, cases of yellow fever were reported in China for the first time. The 11 cases, all Chinese nationals returning from Angola, were identified in March and April 2016, one to two weeks after the peak of the Angolan epidemic. One patient died; the other 10 cases recovered after treatment. This paper reviews the epidemiological characteristics of the 11 yellow fever cases imported into China. It examines case detection and disease control and surveillance, and presents recommendations for further action to prevent additional importation of yellow fever into China.

The 2016 yellow fever outbreak in Angola led to renewed attention to this often-fatal disease. Of the 4306 suspected cases reported, 376 individuals died (mortality rate, 8.7%).[1] The outbreak was declared to have been one of the largest and most challenging yellow fever outbreaks in recent years by the World Health Organization (WHO), in part because of its international spread to other countries, including China.

Yellow fever is a zoonotic disease that is endemic in tropical regions of Africa and South America. It is caused by the yellow fever virus, an arbovirus that belongs to the *Flavivirus* genus.[2] The virus is transmitted between humans, or from monkeys to humans, through the bite of infected mosquitoes belonging to the *Aedes* and *Haemogogus* genera, respectively. Yellow fever causes an estimated 30 000 deaths each year, most of which are in Africa, where more than 500 million people are at risk for yellow fever.[3] An additional 400 million people in Central and South America are also at risk.[3] Though *Aedes aegypti* mosquitoes are found in China (primarily in Fujian Province) and other parts of Asia, yellow fever had never, before 2016, been reported in China or any other part of Asia.

In 2015, more than 200 000 Chinese nationals were working or conducting business in Angola.[4] According to the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ), dozens of the Chinese nationals in Angola contracted yellow fever during the 2016 outbreak, resulting in eight deaths in Angola.[5] Facing the possibility of an imported yellow fever epidemic, China developed a national yellow fever control and prevention protocol,[6] and took steps to strengthen surveillance at airports and health-care facilities and to implement emergency vector surveillance. Despite these efforts, 11 Chinese nationals who were infected during the outbreak in Angola imported yellow fever into China in 2016.

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Considering frequent travel, labour relationships, and close trade with endemic countries in South America and Africa, China faces a continued risk of yellow fever importation. Therefore, the purpose of this paper is to examine China's response to the importation of its first yellow fever cases, particularly the emergency response, as well as case detection and disease surveillance and control.

METHODS

We obtained and analysed data collected as part of China's emergency response. The following paragraphs describe the steps taken to identify and document the imported cases of yellow fever and to collect demographic and epidemiological data, as well as clinical information.

Case definition

Suspected cases of yellow fever were identified by clinicians based on clinical manifestations consistent with yellow fever, which included fever, jaundice, liver and kidney dysfunction, vomiting, and bleeding, as well as epidemiological history (i.e. history of travel or residence in the last 14 days before symptom onset). Confirmed cases were defined as suspected cases that tested positive for yellow fever virus using nucleic acid testing.[6]

Case discovery

Yellow fever cases imported into China were either discovered by AQSIQ staff during point-of-entry screening or later reported by treating health-care providers. Febrile passengers passing through the point of entry were identified via temperature screening and were transported to the hospital for diagnosis and treatment. Travellers with mild or moderate symptoms that had not been detected by entry screening were identified by health-care providers in hospitals while seeking medical care. Clinicians identified and documented symptoms consistent with yellow fever to identify suspected cases. When a suspected case of yellow fever needed to be confirmed, patient blood samples were sent to the provincial Center for Disease Control and Prevention (CDC) for laboratory testing by real-time reverse transcriptase polymerase chain reaction (rRT–PCR).[7] All information was reported to the local health administrative departments after disease confirmation.[8]

Data collection

Once a suspected case was diagnosed by a laboratory, the provincial CDC conducted a field investigation to collect demographic and epidemiological information (including travel history, i.e. the dates of arrival in Angola and return to China and yellow fever vaccination status) and clinical information (including symptoms, time of symptom onset and date of hospital visit).

Vector surveillance

Routine surveillance of *Aedes* density has been conducted in China for many years. According to the surveillance protocol,[9] all provinces are classified into three groups (high, middle and low) depending on the level of risk of mosquito-borne disease transmission. In high-risk areas, surveillance is conducted throughout the year. In middle- and low-risk areas, surveillance is conducted from May to November and from June to September. After each of the imported cases of yellow fever was identified, emergency monitoring was conducted to measure the mosquito density within a radius of 200 metres of the patient's residence. The Breteau Index (BI) was calculated to determine the number of positive containers per 100 households inspected.[9]

Ethics approval and consent to participate

The case information was collected according to the regulations of the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases as a part of the emergency response, which was exempted from ethics approval and consent to participate.

RESULTS

Case characteristics

A total of 11 cases of yellow fever were reported in China, all imported from Angola. All were Chinese nationals living in Luanda, the capital of Angola, at the time of the outbreak. Seven cases were residents of Fujian Province, two of Jiangsu Province, and one each of Zhejiang Province and Sichuan Province. All cases were identified in weeks 11 to 15 of 2016, approximately one to two weeks after the peak of the Angolan epidemic. The patient age range was 18–52 years (median: 42 years). Eight were male, and three were female. Eight were retailers, and

Table 1. **Demographic characteristics of imported cases of yellow fever**

Case no.	Sex	Age (years)	Date of symptom onset	Reporting region	Location at time of diagnosis	Vaccination status	Reporting institution	Notes	Data source
1	M	32	8 March 2016	Beijing	Beijing	Not vaccinated before symptom onset	AQSIQ	Died of the disease	10,19–21
2	M	46	5 March 2016	Shanghai	Shanghai	Unknown	AQSIQ		22
3	M	44	9 March 2016	Beijing	Beijing	Not vaccinated before travel to Angola	AQSIQ		10,23
4	M	44	11 March 2016	Beijing	Beijing	Not vaccinated before travel to Angola	AQSIQ		10,23
5	M	50	6 March 2016	Beijing	Beijing	Not vaccinated before travel to Angola	AQSIQ	Received treatments in multiple hospitals in Angola from 6 to 16 March 2016	10,24
6	F	42	11 March 2016	Fujian	Fuzhou	Not vaccinated before travel to Angola. Vaccinated in Angola on 7 March 2016, 3 days before symptom onset.	Medical Institution		10,25
7	M	42	17 March 2016	Fujian	Fuzhou	Vaccinated 7 days before symptom onset	Medical Institution		10,26
8	F	36	15 March 2016	Fujian	Fuzhou	Vaccinated 5 years before symptom onset	Medical Institution		10,26
9	F	53	13 March 2016	Fujian	Fuzhou	Vaccinated 1 day before symptom onset	Medical Institution		10,26
10	M	18	12 March 2016	Fujian	Fuzhou	Vaccinated 10 days before symptom onset	Medical Institution		10,27
11	M	29	5 April 2016	Beijing	Beijing	Vaccinated 10 months before symptom onset	AQSIQ	Sought medical care at a local hospital in Angola	10,11

AQSIQ, General Administration of Quality Supervision, Inspection and Quarantine.

three were labourers. Ten reported having been bitten by a mosquito at least six days before symptom onset; the other patient (case no. 2) was unsure if he had been bitten. Six patients reported having received yellow fever vaccinations. Case nos. 6, 7, 9 and 10 were vaccinated less than 14 days before system onset. Case no. 8 was vaccinated in China five years before symptom onset, and Case no. 11 was vaccinated in Namibia 10 months before the onset of illness (**Table 1**).[10]

Case detection

Ten cases received medical treatment in Luanda but were not diagnosed with yellow fever; the other case, having only mild symptoms, did not seek medical treatment before returning to China. Seven cases returned to China through the Beijing Capital International Airport; the other four entered through Shanghai. Six cases were reported within the city of entry, and five were eventually reported in Fujian Province, where they had sought medical care. Of the six cases discovered by AQSIQ, two cases with mild illness self-declared their symptoms at the time of entry (**Table 1**).

Disease control and surveillance

The Chinese Government took steps to strengthen surveillance at airports and health-care facilities and implemented emergency vector surveillance in an attempt to prevent further cases of yellow fever. Specifically, the Government intensified multisectoral coordination and collaboration; strengthened surveillance, vector monitoring and risk assessment; enhanced clinical management of yellow fever cases; conducted vector control activities; carried out public risk communication activities; and deployed a medical team to Angola to provide yellow fever vaccination to unvaccinated Chinese nationals.[11]

DISCUSSION

We describe the 11 cases of imported yellow fever in China, most of which were discovered within two weeks after the peak of the outbreak in Angola in 2016. After the outbreak in Angola was announced, China quickly released a protocol for yellow fever prevention and control.[6] At the same time, AQSIQ, in the hope of preventing yellow fever from entering China, issued an announce-

ment that included instructions for screening travellers and checking vaccination certificates.[12]

Several strategies were implemented to control the spread of yellow fever in China. First, all travellers from Angola were required to present yellow fever vaccination certificates. Those without a certificate were isolated at the point of entry or their place of residence for six days. Second, all travellers from affected countries were screened upon entry. Anyone who self-declared or who was suspected of having yellow fever was isolated at the entry point. There, AQSIQ staff administered an epidemiological survey and collected blood samples for testing. Third, travellers from Angola and other epidemic countries were required to perform self-health monitoring for six days after entering China. If suspicious symptoms occurred, the affected traveller was asked to report to a health-care provider, disclose their travel history and receive prompt treatment. Additionally, aircraft, containers and other cargo from the epidemic countries were targeted for mosquito control. It was also recommended that persons travelling to Angola and other epidemic countries should be vaccinated again for yellow fever before departure from China. For the imported yellow fever cases, emergent monitoring of mosquito-borne vectors was also performed.

Areas recommended for improvement include epidemic information sharing, risk warning and health education for Chinese nationals in Angola and other yellow fever-endemic countries. According to our investigation, Chinese nationals in Angola are generally employees sent by private companies or individual business people, primarily from Fuqing City in Fujian Province. More than 200 000 Chinese nationals live and work outside China,[3] so timely health-related communication between health officials, companies and overseas workers could help protect China's expatriate population from public health threats in their countries of temporary residence. Overseas workers in Angola should have received a yellow fever vaccination before their departure from China. Information about the yellow fever epidemic, if received from their companies or Chinese health officials, might have encouraged personal prevention measures such as mosquito-avoidance precautions. Information on travellers with yellow fever, especially those who returned to China for treatment, should have been reported by the employing companies to the Chinese embassy or Government, which would have provided valuable information for disease prevention. Required vaccination and improved communication are also crucial for individual business people who are travelling to yellow fever-endemic countries. All inbound passengers should be required to present proof of vaccination if they are arriving from yellow fever-endemic countries. Health education materials (e.g. videos, posters, warning signs, brochures and text messages) could be provided at the points of entry by inspection and quarantine officials to encourage inbound passengers to self-declare symptoms of a potential communicable disease.[13]

Additional strategies have been identified and are recommended for reducing the risk of importation and spread of infectious diseases in China. For instance, China could strengthen regulations and legislation to put an end to the fabrication of false yellow fever vaccination certificates, a practice used to circumvent the vaccination regulations of the International Health Regulations, or IHR (2005). Globally, governments, including that of China, could ensure their citizens receive yellow fever vaccination when travelling to countries that recommend it, could tighten border controls to ensure incoming visitors from yellow fever-endemic countries have proof of vaccination and could make public policies a priority in the prevention of diseases among travellers.[14]

The active period for the *Aedes aegypti* mosquito in Fujian Province was reported to be from May to October in 2016.[15] However, the result of emergency monitoring (BI: 15) indicated continued transmission risk of mosquito-borne diseases after the peak period. Thus, the public should be educated to eliminate containers that can hold water in which mosquitoes may breed.

Risk of disease importation

Due to frequent travel and close trade with yellow fever-endemic countries in Africa and South America, China faces a continued risk of yellow fever importation as travel volume has increased. Travel patterns to and from yellow fever-endemic regions in relation to China indicate that Angola sends the second-highest number of travellers into China and also receives the second-highest number of Chinese visitors.[14] During the years 2010–2030, tourist arrivals in Asia and the Pacific are expected to increase by 331 million, bringing the total number of tourists to about 535 million in 2030. With this increase in travel, there will be a concomitant increase in the importation of infectious diseases. Due to the presence of the urban mosquito vector, *Aedes aegypti*, among large unvacci-

nated populations, 1.8 billion people in Asia were put at risk for yellow fever by international travellers during the 2016 outbreak.[14] In Angola, by September 2016, near the end of the 2016 yellow fever outbreak, 884 laboratory-confirmed cases of yellow fever had been reported, with 373 deaths. The confirmed cases of yellow fever in China were the first-ever cases to be imported into Asia.[14]

In 2012, a total of 475 761 air passengers travelled to China from yellow fever-endemic countries. Of those, 195 291 travelled from the South American countries of Argentina, Brazil, Columbia and Venezuela, and 104 854 travelled from the African countries of Angola, Ethiopia, Ghana and Nigeria. During that same year, 466 832 air passengers from China travelled to yellow fever-endemic countries. The importation of yellow fever from endemic countries by unvaccinated Chinese workers is a serious concern, as they are apparently able to circumvent the mandated IHR (2005) regulations that require proof of vaccination for entry into China from certain yellow fever-endemic countries, including Angola.[14]

Vaccinations

Finally, although yellow fever is a vaccine-preventable disease, the vaccination rate of yellow fever in Chinese nationals in Angola is estimated to be very low.[16] Vaccinations should be required for all Chinese nationals going to or returning from countries where yellow fever is endemic, as per the WHO recommendations.[11] This would protect Chinese citizens who are residing in countries such as Angola and Brazil, where the risk of contracting yellow fever is substantial.

The WHO risk assessment report of yellow fever infection in non-immunized travellers underlined the need to reinforce the implementation of yellow fever vaccination requirements and highlighted the risk of international spread of the disease through non-immunized travellers.[11] A safe and effective vaccine for yellow fever has been available for more than 50 years. The licensed, live attenuated yellow fever vaccine produces immunization within 10 days and has a long duration of immunity. However, it is in short supply, with only about 80 million doses produced annually. An estimated half a million doses of the vaccine would be needed annually to cover the Chinese population travelling to yellow fever-endemic countries. Yellow fever 17D vaccine is manufactured in China for the domestic market and therefore is available, although the supply is limited.[12]

Routine vaccination for children living in countries at risk for yellow fever is also recommended by WHO.[3] The vaccine confers long-term protection (10 years or more, possibly lifelong) within 10 days for more than 90–95% of individuals who receive the vaccine. Within 30 days after vaccination, 99% of those immunized develop immunity. A single dose is likely to provide lifelong immunity. The yellow fever vaccination certificate is now valid for the duration of the life of the person vaccinated.[17]

Among the 11 cases, there were two cases with vaccination failure. Although vaccination failure for yellow fever is unusual, some studies showed up to 26% seronegativity in vaccines after mass immunization campaigns.[18] External factors such as improper cold chain handling, storage and administration may be the cause of failure.

In conclusion, we have described the first-ever importation of yellow fever cases in China, discussed the methods used for case detection and prevention of imported infectious disease, and provided several recommendations for disease prevention and control. Experiences gained from the response to imported yellow fever cases in 2016 can be used to protect Chinese travellers from yellow fever and to prevent new importations of the disease.

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Regional event-based surveillance in WHO's Western Pacific Region

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In the World Health Organization's Western Pacific Region, event-based surveillance has been conducted for more than a decade to rapidly detect and assess public health events. This report describes the establishment and evolution of the Western Pacific Region's event-based surveillance system and presents an analysis of public health events in the Region. Between July 2008 and June 2017, a total of 2396 events were reported in the Western Pacific Region, an average of 266 events per year. Infectious diseases in humans and animals accounted for the largest proportion of events recorded during this period (73%, 1743 events). Maintaining and strengthening this well-established system is critical to support the rapid detection, assessment and response to public health events to sustain regional health security.

The early detection of public health events is critical to the implementation of rapid response measures to mitigate health, social and economic impacts. The effective detection and response to health emergencies is a key priority for the World Health Organization (WHO) and mandated to WHO under the International Health Regulations, IHR (2005).[1,2] The early detection of risks to public health is an important component of this, particularly in the context of today's interconnected global community, in which even public health risks that originate in remote parts of the world may have an increased risk of spread.[3,4] No single country can undertake the task of regional surveillance and risk assessment. WHO, however, is well positioned to carry out this task. Public health surveillance is an essential component of WHO's role in health emergencies, enabling the early detection, assessment and response to public health events, whether their impact is at the national, regional or global level. WHO works collaboratively with ministries of health, national public health agencies and other international organizations, for example, World Organisation for Animal Health (OIE) and Food and Agriculture Organization of the United Nations (FAO).

Event-based surveillance (EBS) is the organized and rapid capture of information about events that are a potential risk to public health.[5] This information can be obtained through official or unofficial channels. Information from unofficial channels is usually unverified and non-standardized, being taken from sources such as media reports or community reporting. EBS reports require verification and then assessment before being used for public health purposes. Indicator-based surveillance is the consistent and systematic collection, monitoring, analysis and reporting of reliable data on diseases, syndromes and conditions from established, predominantly health-system-based formal sources, such as registers of notifiable diseases or syndromic surveillance systems.[5]

For more than a decade, the Asia Pacific Strategy for Emerging Diseases (APSED)[6] has guided Member States in the Western Pacific Region as a common framework for building the core capacities described in IHR (2005).[2] The Strategy includes a focus on regional preparedness, alerts and responses, which acknowledges and highlights the importance of both EBS and indicator-based surveillance to detect public health emergencies and gather information for risk assessment and public health decision-making. The Western Pacific Region's surveillance system therefore uses multiple sources of information, both event-based and indicator-based, for risk assessment and decision-making for responses.[6]

While there have been various progress reports related to EBS as part of APSED implementation, existing WHO regional event detection, verification and risk assessment systems are not well described. This paper describes the Western Pacific Region's surveillance

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and risk assessment system, in addition to presenting an analysis of events detected by the system between July 2008 and June 2017.

The evolution of event-based surveillance in the Western Pacific Region

2004–2005

In 2004, WHO's Regional Office for the Western Pacific established a regional system for EBS, then known as rumour surveillance, following the first major emerging infectious disease outbreak of the 21st century: severe acute respiratory syndrome (known as SARS). This system was established with financial support from the Government of Japan to maintain one Field Epidemiology Training Programme (FETP) fellow to serve as a rumour surveillance officer, scanning media sources for rumours of potential public health risks daily. The major focus was infectious disease–related events.

2006–2015

The IHR were implemented to prevent, protect against, control and provide a public health response to the international spread of disease.[2] The IHR were revised in 2005, becoming the IHR (2005), and an obligation was added requiring State Parties to notify WHO of events that may constitute a public health emergency of international concern. IHR (2005) authorized WHO to seek verification from State Parties of unofficial reports of public health events. In addition, it established a network of national IHR focal points in Member States and IHR contact points within WHO to facilitate urgent reporting and communication about public health events.[2] The implementation of IHR (2005) led to a more systematic and formalized approach to rumour surveillance.[2] The Regional Office for the Western Pacific further strengthened event detection by building regional capacity, and it expanded its regional Field Epidemiology Fellowship Programme to include fellows and alumni of the FETP or the modified FETP (FET) from additional countries. The scope of event detection and assessments has also been expanded to cover more food safety and disaster events, including those caused by natural hazards, such as earthquakes and typhoons. In 2008, for the first time, the Regional Office published A Guide to Establishing Event-based Surveillance.[5]

2016 to the present

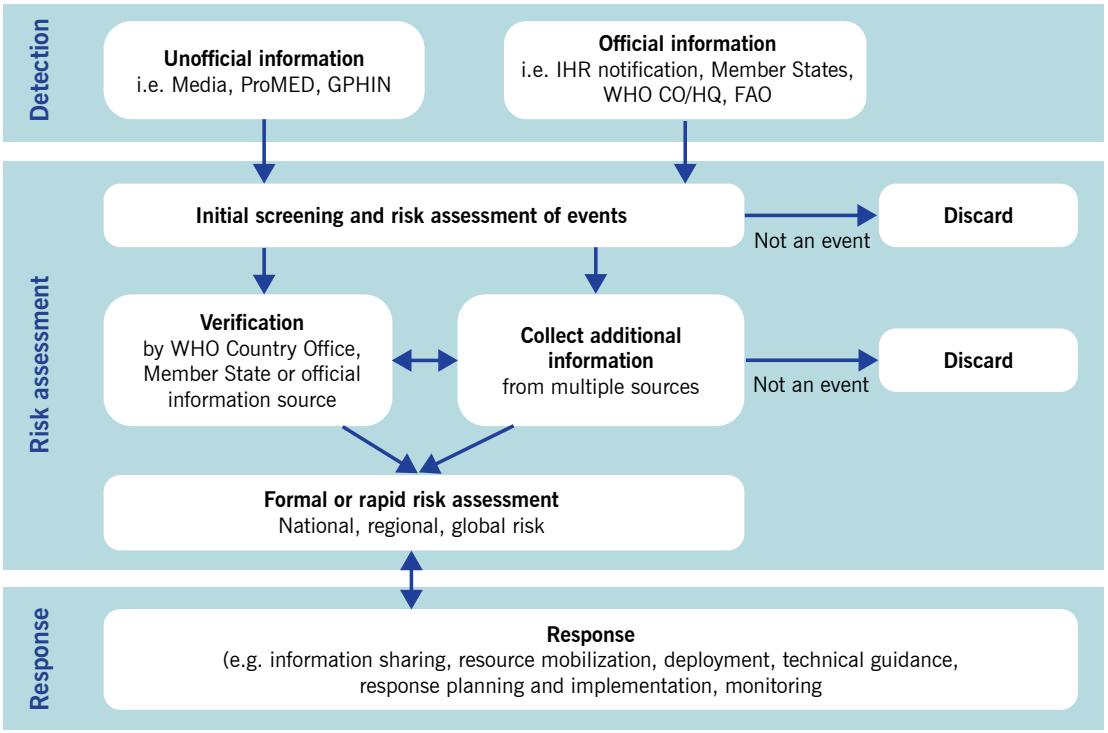
Lessons learnt from the 2014–2016 Ebola outbreak in West Africa led to the establishment of the WHO Health Emergencies (WHE) programme. The WHE programme provides a standard structure and mission across the Organization globally. The WHE programme includes a dedicated Health Emergency Information and Risk Assessment (HIM) unit for detecting events, assessing risks and managing information about emerging health threats. The WHE programme integrated the Regional Office for the Western Pacific's EBS team into HIM and broadened the scope of event detection to include information management, using an all-hazards approach that includes outbreaks, emerging diseases, natural disasters, conflicts and other potential risks to human health.

The Western Pacific Region's event-based surveillance system

Since 2008, the Western Pacific's regional EBS system has employed a standardized approach for surveillance, risk assessments and responses to public health events (**Fig. 1**). The system is operated by a team of epidemic intelligence officers, medical officers and epidemiologists. The epidemic intelligence officers include WHO staff and fellows from the regional FETP as well as professionals who have been seconded to the system, and volunteers and interns who have experience in communicable disease surveillance.

Event screening is undertaken twice daily, seven days a week. Information from both unofficial and official sources is screened using an event assessment tool (**Table 1**) that provides criteria for determining whether the information requires further assessment. Unofficial sources that are screened include internet-based early warning systems (e.g. the Global Public Health Intelligence Network, the Program for Monitoring Emerging Diseases [ProMED], and FluTrackers.com) and other web-based media sources. Official sources of information screened include communications from national IHR focal points to regional IHR contact points; WHO email communications with country and regional offices, headquarters and collaborating centres; reports from partner agencies, such as international public health agencies and humanitarian and nongovernmental organizations; and surveillance reports, press releases and other official documents

Fig 1. **WHO's Western Pacific Region event-based surveillance, risk assessment and response system**



CO, Country Office; FAO, Food and Agriculture Organization of the United Nations; GPHIN, Global Public Health Intelligence Network; HQ, headquarters; IHR, International Health Regulations; ProMED, Program for Monitoring Emerging Diseases; WHO, World Health Organization.

Table 1. **Regional event-based surveillance information screening tool used in WHO's Western Pacific Region**

1. Screening
• Screen all information sources for potential events daily
2. Assessment
Assess each piece of information against the following criteria. • Can the suspected disease cause outbreaks that have a high potential to spread (e.g., cholera, measles)? • Does the event involve a notifiable disease or defined notifiable syndrome with higher than expected morbidity or mortality? • Is the disease unusual or unexpected, or is there a new or unknown causal agent in the community? • Is there a cluster of cases or deaths with similar symptoms? • Could the event be caused by a product that is contaminated and commercially or widely available (e.g., a commercial food item)? • Does the event have possible consequences for trade or travel to or from the affected area? • Is there suspected spread of the infection in a healthcare or mass gathering setting? • If no human cases have been reported, does the event have a known or suspected consequence for human health (e.g., a chemical spill, unexplained deaths in animals)?
3. Outcome
• If the answers to all of the above criteria are no, then discard the information. • If the answer to one or more of the above criteria is yes or unknown, conduct additional assessments.

and reports from ministries of health that are shared with WHO or published online. To detect and monitor disasters and humanitarian emergency events, the Global Disaster Alerting Coordination System, Member States' national disaster management offices, and websites, such as ReliefWeb.int, are screened. Signals and events related to avian influenza are closely monitored within the Region. The websites and media reports of the OIE and FAO are used to identify avian influenza events in animals within the Region and their potential public health risk.

Information that meets any two criteria within the event screening tool (**Table 1**) is assessed daily. This assessment includes using an algorithm-based risk assessment (**Fig. 2**) that determines whether an event may have implications for regional health security or there is a potential need for WHO support. Further assessment of the level of risk may be undertaken in relation to specific questions, as determined to be relevant to the event. Additional information may be obtained to inform the risk assessment, such as data on baseline disease incidence and contextual information about the setting in which the event is taking place. Events that are determined to pose a potential risk to public health are further reviewed by management and technical experts from within the WHE programme at the country, regional, subregional and global levels of WHO across the areas of epidemiology, laboratory expertise, risk communication, public health emergency preparedness, zoonoses, food safety, and emergency management, as well as by other technical divisions within WHO (**Fig. 3**).

In parallel with the initial internal WHO risk assessment process, verification of the information may be sought. Verification may involve confirming unofficial reports of an event with the national IHR focal point of a Member State or with the respective WHO country office. However, verification may also involve confirming an event through official information sources or through the triangulation of multiple unofficial or official information sources, or some combination of these.

The regional EBS system provides information and data with which to conduct the risk assessment, which is then used to make decisions about WHO's response to public health events, in line with WHO's emergency response framework.[7] Key response actions at the regional level may include conducting ongoing monitoring of the event; providing technical support; or deploying human, material or financial resources, or some combination of these, to affected countries and areas.

Events are entered into an internal EBS database daily. The EBS database serves as a repository of events with public health implications for the Western Pacific Region. Fields within the EBS database include event name, the class of hazard, disease, country affected, date of detection, and source of information. Daily, weekly and ad hoc summary and event-specific reports are produced by the HIM team and disseminated to all levels of WHO. The dissemination of these surveillance reports enhances situational awareness across WHO to improve readiness to respond to events when needed.

METHODS

A retrospective descriptive analysis of events in the EBS database in the Western Pacific Region was carried out for the period July 2008 through June 2017. This period was determined by the availability of data, and begins 1 year after the IHR (2005) came into force. In keeping with the Regional Office's guidelines, events included clustered cases of a disease or syndromes, unusual patterns of disease or unexpected deaths, or situations that might lead to a potential exposure of humans to disease.[5] For the purposes of this report, events were classified into three categories: communicable diseases, avian influenza A(H5N1) outbreaks, and disasters and other events.

The number of new events by category was calculated for the study period by fiscal year (1 July to 31 June). A further analysis of events reported during the 2015 calendar year was conducted to determine the proportion that resulted in a response by Member States alone or with support from the WHO country office or Regional Office, or both. Between January and March 2016, data on the number of reports received by the surveillance system per day was collected to determine the average number of reports screened per day.

Ethics statement

As this work is a report on routine EBS undertaken in line with IHR (2005) and does not involve human research, ethical clearance was not sought.

RESULTS

Between July 2008 and June 2017, a total of 2396 events were recorded in the EBS database (**Table 2**). Of these, 1176 (49%) were classified as infectious disease events, 653 (27%) were classified as disaster (all types) or other, and 567 (24%) were classified as avian influenza A(H5N1) events. An average of 266 events were recorded per year (range, 206 to 357 events). Between 2012 and 2017, the regional EBS system detected an average of 124 events related to influenza infection in either humans or animals. A selection of significant public health events detected by the surveillance system is listed in **Box 1**.

Fig 2. **WHO's Western Pacific Region algorithm for initial public health risk assessments**

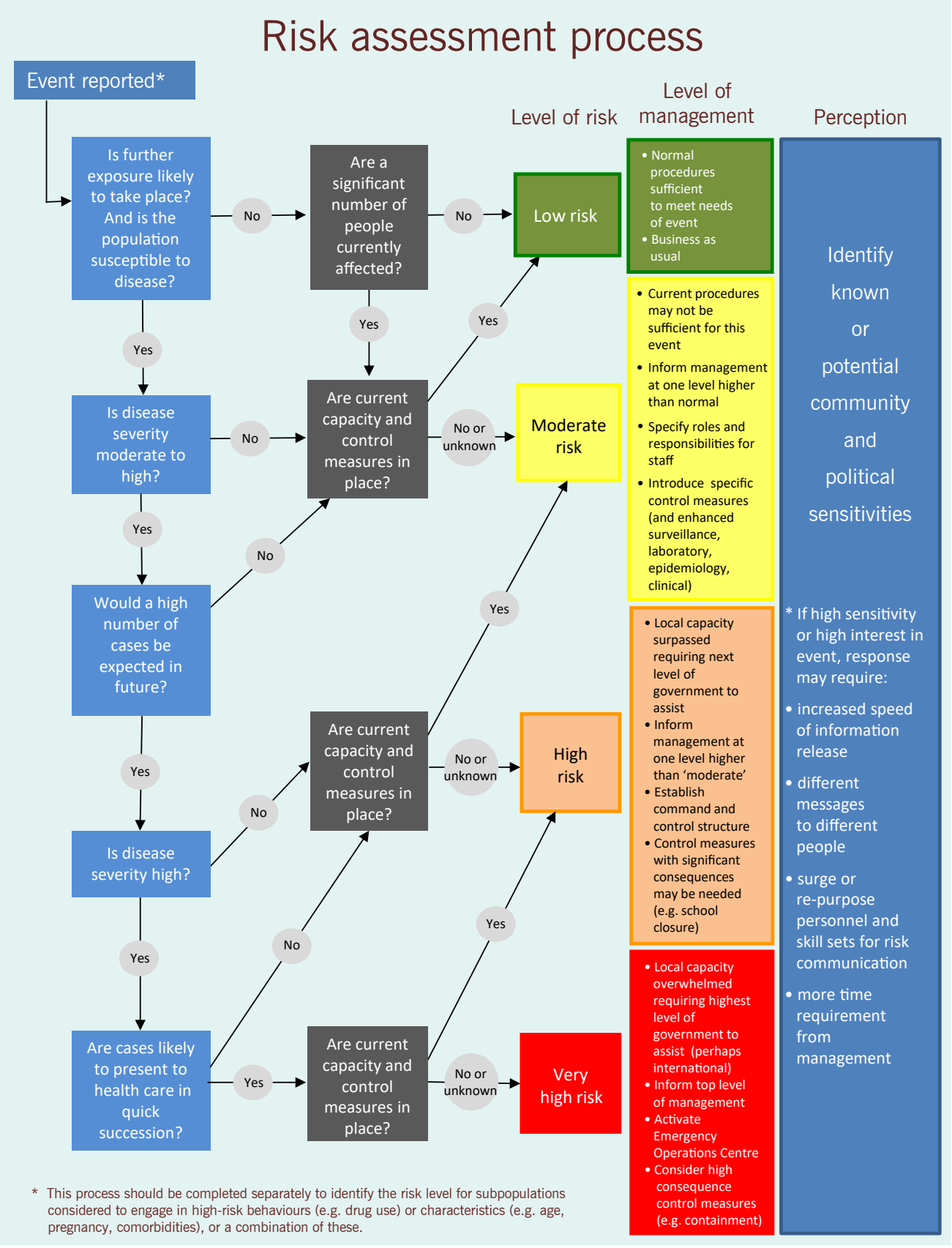
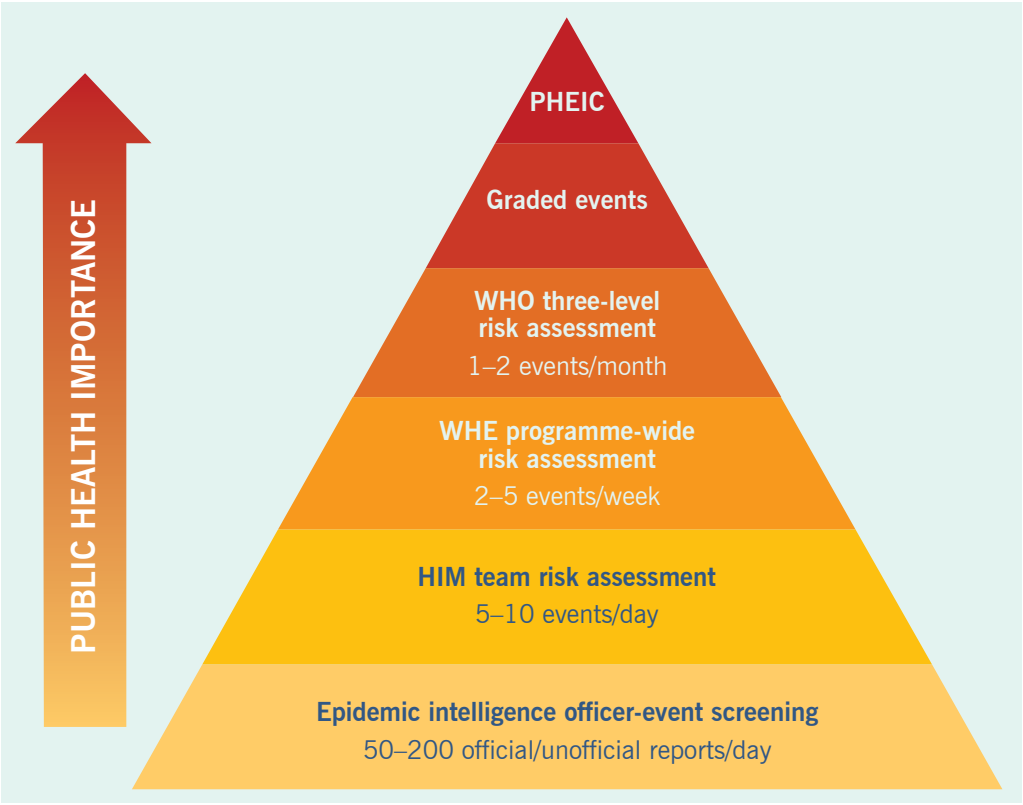


Fig 3. **The regional surveillance and risk assessment triangle used in WHO's Western Pacific Region**



HIM: Health Emergency Information and Risk Assessment
PHEIC: public health emergency of international concern
WHE: World Health Organization Health Emergencies programme

Table 2. **Number (%) of events recorded in WHO's Western Pacific Region event-based surveillance database, by year, 2008 to 2017**[a]

Event type	Year																		Total	
	2008–2009		2009–2010		2010–2011		2011–2012		2012–2013		2013–2014		2014–2015		2015–2016		2016–2017			
Infectious diseases[b]	142	(69)	174	80%	206	(58)	114	(39)	47	(22)	67	(27)	70	(33)	208	(63)	148	(46)	1176	(49)
Avian influenza A(H5N1)	35	(17)	26	(12)	136	(38)	86	(29)	65	(31)	107	(43)	41	(19)	21	(6)	50	(16)	567	(24)
Disaster (all types) and other events[c]	29	(14)	18	(8)	15	(4)	94	(32)	99	(47)	72	(29)	101	(48)	102	(31)	123	(38)	653	(27)
Total by year	**206**		**218**		**357**		**294**		**211**		**246**		**212**		**331**		**321**		**2396**	

[a] A year is from 1 July to 30 June. The monitoring and reporting of disaster events became formalized in mid-2011. In 2013, they were further modified based on the official criteria of the Centre for Research on the Epidemiology of Disasters (CRED) criteria.

[b] Numbers exclude animal avian influenza events.

[c] Category includes natural and other types of disasters. Other events included in this category include pharmaceutical related, food related, chemical and unknown or unspecified.

Between 2008 and 2017, 1398 (58%) events were detected from an official information source. There was an increasing trend in the proportion of events that were identified from official information sources up until 2014–2015, with a subsequent decline during 2015–2017 (**Fig. 4**).

In 2015, there were 218 public health events recorded in the database. Based on the records of these events, 131 (60%) were responded to by Member States without the support of WHO (although WHO monitored and assessed the events). Sixty-five (30%) were supported by WHO country offices, and 22 (10%) were supported either by WHO country, regional and headquarter offices or by the regional office if there was no country office.

Box 1. **Significant public health events detected by event-based surveillance in WHO's Western Pacific Region, 2008–2017**

Implementation of the event-based surveillance system led to the early detection of, assessment of and response to several major health events, including:

- a large outbreak of enterovirus 71 in Cambodia in 2012
- an outbreak of Middle East respiratory syndrome coronavirus in the Republic of Korea in 2015
- the spread of Zika virus disease within the Western Pacific Region in 2016
- a large outbreak of dengue in Solomon Islands in 2016
- an outbreak of measles in Papua New Guinea in 2017
- human infections with novel avian influenza viruses, including A(H7N9), in China.

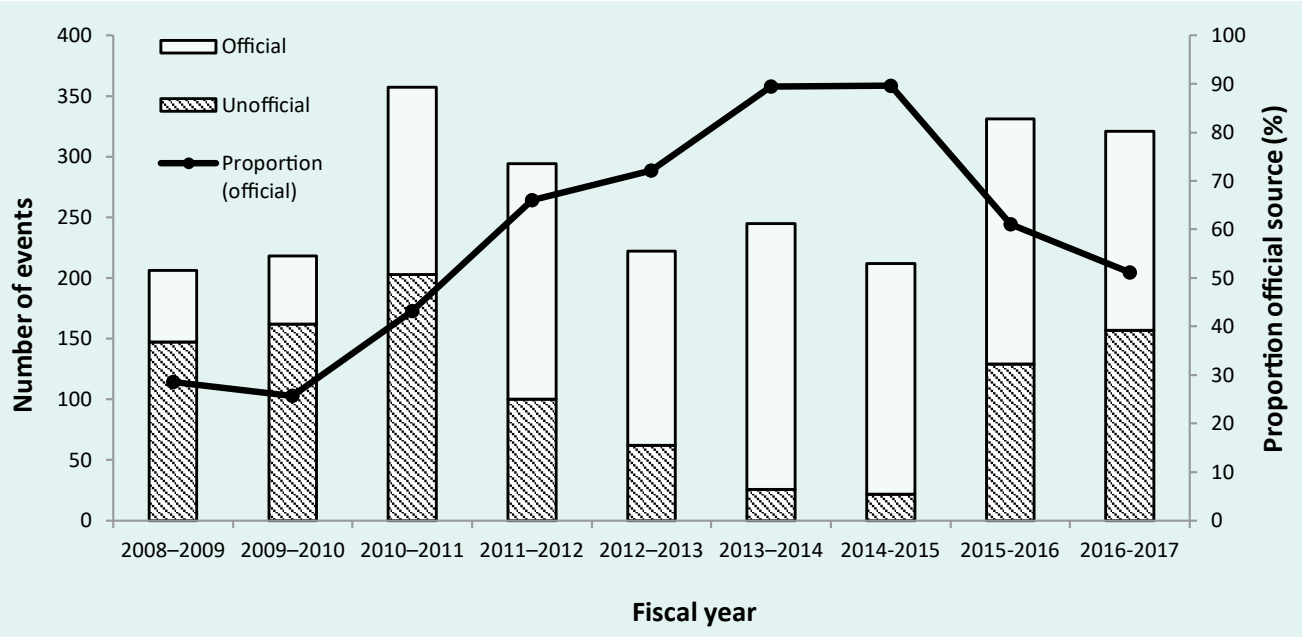
DISCUSSION

Regional EBS and risk assessment are well established in WHO's Regional Office for the Western Pacific, based on the substantial number of events that have been detected and responded to by WHO. It is a core function of the Regional Office to support event responses, including by providing technical support and deploying staff, material or financial resources. As such, EBS and risk assessment have been embedded within APSED.[6] Since the system's beginnings as a basic rumour surveillance system, the Regional Office's surveillance and risk assessment system has continuously evolved to detect signals earlier, assess risk more systematically, and manage information better. An analysis of the events reported to WHO under the IHR (2005) and published in WHO's Disease Outbreak News reports, found a statistically significant improvement in the timeliness of outbreak discovery in the Western Pacific Region between 1996 and 2009.

The value of the regional EBS system's ability to detect and assess information from multiple sources is highlighted by its applicability to influenza. For influenza, the regional EBS system captures events and signals from both the human and animal health sectors. Traditional and social media sources are monitored for early reports of severe acute respiratory infection or poultry die-off. Official reports from the OIE and the FAO are reviewed to detect and verify influenza events among animals. Reporting by Member States through the IHR (2005) mechanism is used to verify reports of human infection with avian influenza. The regional EBS system synthesizes information from these sources and others to provide timely and robust assessments and information to inform public health responses. In July and August 2017, the first poultry outbreaks of avian influenza A(H5N6) were detected in the Philippines. The regional EBS system synthesized information from the media, internal communications, OIE reports and official communications from the Philippines Department of Health to perform the risk assessment for this event.

Considerable effort has been made by WHO to strengthen the IHR (2005) core capacities of Member States within the Western Pacific Region through the implementation of APSED. An example that demonstrates the value of EBS and IHR (2005) reporting by Member States occurred in 2012 when a cluster of deaths among children of unknown etiology was notified through IHR (2005) by the Cambodian Ministry of Health. The etiology was later confirmed to be enterovirus 71. This event highlighted the benefit of the expanded scope of the IHR (2005) by using the IHR channel to report a public health event despite an unknown etiology.[8]

Fig 4. **Acute public health events in WHO's Western Pacific Region detected by official and unofficial information sources, by fiscal year, 2008–2017**



FETP and FET fellows and alumni in the Western Pacific Region have been crucial contributors to the regional surveillance system. Involving FETP and FET fellows and alumni from Member States in the Region as epidemic intelligence officers enables them to develop their skills and knowledge of EBS and risk assessment and also facilitates broader capacity-building in Member States through the dissemination of this knowledge within their respective countries.

Several limitations need to be considered when interpreting the results of our study. There is high turnover of staff within the surveillance system because FETP and FET fellows and alumni, volunteers and interns rotate every 2 months as part of the Regional Office's on-the-job learning programme, and this may contribute to inconsistencies in data entry. Although there are standard operating procedures for epidemic intelligence officers, language, experience, technical knowledge and other factors may lead to differences in detection, accuracy and comprehensiveness. Furthermore, standard definitions and criteria for what constitute an event are lacking and vary depending on the hazard type. For disasters, the Centre for Research on the Epidemiology of Disasters (CRED) criteria[9] were used, and these criteria differed from those used for public health events related to infectious diseases. The CRED criteria may have made officers more sensitive to including disasters in the database. With the adoption of an all-hazards approach within the WHE programme, there have been increasing efforts to monitor small-scale disasters in the Region, which may account for the increasing trend seen in such events within the database. The number of animal outbreaks is an underestimate because during the earlier years of data collection, only avian influenza A(H5N1) events were recorded.

APSED III, a revision of APSED (2015), was published in 2017 and aims to further strengthen surveillance to support Member States in the Western Pacific Region.[6] The availability of new and innovative technologies for data management offers opportunities to improve surveillance systems, both through streamlining current processes for data management and providing enhanced functionality for analysis and reporting. To ensure that the regional surveillance system meets the needs of Member States, partners and internal stakeholders within WHO, particularly, those in country offices, we recommend ongoing evaluation and monitoring of the system.

CONCLUSIONS

This 10-year analysis of the Western Pacific Region's EBS system illustrates its functions in early detection

and risk assessment of all-hazard public health events by using information from diverse official and unofficial sources. Maintaining this well-established surveillance system is critical to support rapid detection, assessment and responses to public health events, thus maintaining and advancing health security in WHO's Western Pacific Region and globally. As such, the Regional Office for the Western Pacific continues to strengthen its function as the hub for regional surveillance and risk assessment to better serve the needs of Member States.

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Factors affecting vaccine hesitancy among families with children 2 years old and younger in two urban communities in Manila, Philippines

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Objective: The study aimed to determine the factors that influence vaccine hesitancy among parents and caregivers of children 2 years old and younger in selected urban communities in Manila, Philippines.

Methodology: The study used a cross-sectional study design with a modified questionnaire adapted from the SAGE Working Group on Vaccine Hesitancy. Self-administered surveys were conducted in two highly urbanized barangays (smallest administrative divisions) in Manila, Philippines.

Results: The survey was completed by 110 respondents, comprised mostly of 20–39-year-old mothers. Most respondents (95.5%) believed that vaccines are protective however vaccine hesitancy rates among the respondents reached 36.4%. Respondents who believed in the protective nature of vaccines were less likely to report vaccine hesitancy and were nine times less likely to refuse vaccination for their children because of negative media exposure. The main reasons identified for vaccine hesitancy were exposure to negative media information and concerns about vaccine safety. The main negative media information identified by the respondents was related to the dengue vaccine, Dengvaxia®. Health-care workers and political leaders were the main supporters of vaccination in the community.

Discussion: The recent events surrounding the Dengvaxia® controversy contributed to a decrease in vaccine confidence. The role of mass media in vaccine hesitancy was highlighted in this study, supporting previous evidence that vaccine-hesitant parents tend to be more susceptible to media reports. The lack of association between sociodemographic factors and vaccine hesitancy implies that the determinants of vaccine hesitancy can be highly varied depending on context and setting.

Immunization has been one of the most important strategies in public health, and it is one of the most cost-effective interventions that lead to improvement of global health outcomes. Childhood mortality from measles and tetanus has drastically decreased through effective national immunization programmes,[1] and it is estimated that 2–3 million deaths per year are prevented through vaccination.[2] However, for immunization strategies to make significant strides in curbing morbidity and mortality, uptake rates for vaccines need to reach critical levels. Measles vaccination, for example, needs to reach a population rate of around 83–94% to elicit herd protection and prevent outbreaks.[3,4] While global trends show an increase in the vaccination rates for specific antigens, there have been resurgences or increases in the rates of some vaccine-preventable diseases (e.g. measles, circulating vaccine-derived poliovirus) in the past few years.[5] Beginning in early 2019 in the Philippines, the Department of Health (DOH) declared measles outbreaks in at least six regions – Davao Region, Metro Manila, Central Luzon, Calabarzon, Western Visayas and Central Visayas.[6] There was a staggering eight-fold increase in the incidence rate from late 2017 to 2018, and the trend continued with more cases of measles reported in the first quarter of 2019 compared to all of 2018.[7]

In November 2017, a media frenzy erupted. One year after the Philippines initiated a mass vaccination campaign with the first licensed dengue vaccine (Dengvaxia®) that reached around 800 000 schoolchildren, Sanofi Pasteur, the manufacturer of Dengvaxia®, re-

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vealed that the vaccine potentially increased the risk of severe dengue in children who had never been infected with dengue prior to vaccination.[8] The DOH and several studies identified the controversy that arose as one of the probable reasons for the loss of vaccine confidence in the Philippines,[8–11] which could have contributed to the rise in measles cases in 2018.[8–10]

Vaccine hesitancy is defined as a "delay in acceptance or refusal of vaccines despite availability of vaccination services."[12] While the reasons for delays or refusals to accept vaccines are complex, the Strategic Advisory Group of Experts (SAGE) technical working group has accepted two working models regarding the determinants of vaccine hesitancy.[12] The 3Cs model, composed of complacency, convenience and confidence, is a simpler intuitive model. The Working Group Matrix ("Matrix") is more comprehensive and aims to categorize the determinants of vaccine hesitancy into three major groups: contextual influences (influences arising due to historic, sociocultural, environmental, health system/institutional, economic or political factors); individual and group influences (influences arising from personal perception of the vaccine or influences of the social/peer environment); and vaccine/vaccination-specific issues (issues directly related to vaccines or vaccination).[12,13] It is clear that vaccine hesitancy is a problem, and addressing its determinants using either model is key at the policy level to prevent vaccine hesitancy and the emergence of outbreaks of vaccine-preventable diseases in groups with low vaccination rates.[14]

Evidence about factors associated with vaccine hesitancy in the Philippines is lacking. The subject is timely due to the recent Dengvaxia® controversy, a subsequent decrease in vaccine confidence and the more recent outbreak of measles in the country. The objective of this study was to determine the factors associated with vaccine hesitancy in urban communities in Manila, Philippines. Identifying and understanding these factors are crucial to inform interventions that can address the issues and lead to increased vaccination rates.

METHODS

We developed a survey that was adapted from a previous vaccine hesitancy survey.[15] The revised questionnaire consisted of 10 core closed questions to assess vaccine hesitancy of parents and caregivers at a community level (**Fig. 1**). Probe questions were also included for questions 4, 7, 8 and 10 to determine specific reasons respondents answered "yes" to these questions (**Table 1**). The questionnaire was translated into Filipino and was back-translated into English for the purposes of content validation and pretesting before administration. Data were collected using self-administered questionnaires.

The study sites were two small and highly urbanized barangays (smallest administrative divisions) situated in the district of San Miguel in Manila, Philippines. These sites were purposively selected based on ongoing health services collaboration between San Beda University College of Medicine and the barangays. A sample size of 109 was calculated using OpenEpi[16] based on the estimated number of families with children 2 years old or younger from the study sites (n = 154, sample proportion = 0.32, confidence level = 95%, α = 0.05).[17] Purposive recruitment of eligible respondents was done with the help of barangay health workers, as well as snowball sampling from previous respondents, until the minimum sample size was accomplished. Sampling was started at the house nearest the health centre and then at the nearest house with an identified eligible respondent. Parents and caregivers aged 18 years or older of at least one child 2 years old or younger who had lived in the study sites for at least one year were eligible to be included in the study. Written informed consent containing the study's brief introduction, nature of risks and benefits, provision for confidentiality and voluntary nature was collected from each participant before the survey. Parents and caregivers of children who had contraindications to routine vaccinations (e.g. severe allergic reactions to previous exposure, immunocompromised status) were excluded from the study. Ethical approval of the study was provided by San Beda University Office for Research and Innovation.

All data were entered in Microsoft Excel and then coded and analysed using StataCorp. 2013. (Stata Statistical Software: Release 13. College Station, TX) Categorical variables were summarized using frequencies and percentages; χ^2 analyses with Phi coefficient post-hoc tests were used to determine correlations with and among the factors associated with vaccine hesitancy and refusal. Binary logistic regression was used to determine the odds ratio (OR) and 95% confidence intervals (CI).

Fig. 1. **Summary of survey responses of parents or caregivers of children 2 years old or younger in two barangays in Manila, Philippines (n = 100)**

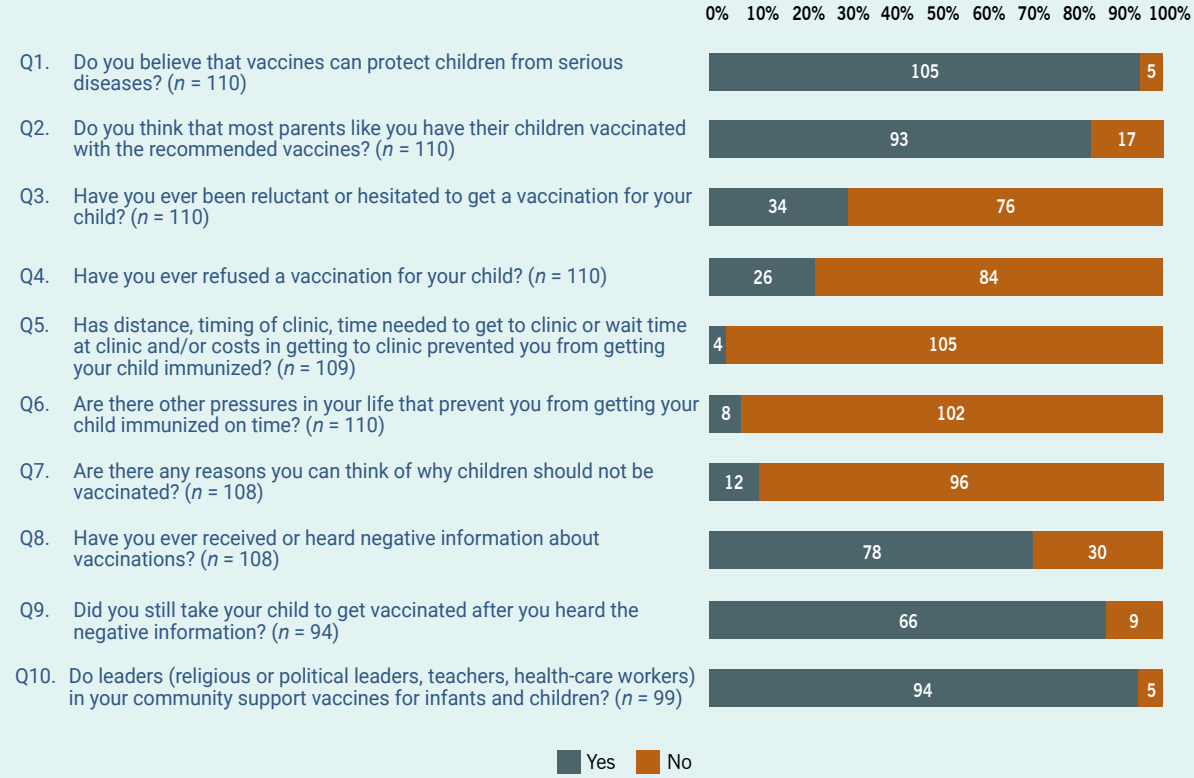

Table 1. **Answers to probe questions from respondents who answered "Yes" to core questions Q4, Q7, Q8 and Q10**

	Frequency	Percentage
Q4. Have you ever refused a vaccination for your child? (n = 26)		
Heard or read negative media	18	69.2%
Did not think the vaccine was safe or concerned about the side-effects	12	46.2%
Did not think vaccine was effective	5	19.2%
Someone else told me that vaccine was not safe	5	19.2%
Did not think it was needed	4	15.4%
Someone else told me they/their child had a bad reaction	3	11.5%
Did not know where to get good/reliable information	1	3.8%
Had a bad experience or reaction with previous vaccination	1	3.8%
Others	1	3.8%
Q7. Are there any reasons you can think of why children should not be vaccinated? (n = 12)		
They choose not to vaccinate	5	41.7%
They do not feel welcome at the health service	1	8.3%
Health services do not reach them	1	8.3%
Q8. Have you ever received or heard negative information about vaccinations? (n = 78)		
"Dengvaxia®"	59	75.6%
"Vaccines are deadly"	1	1.3%
Q10. Do leaders (religious or political leaders, teachers, health-care workers) in your community support vaccines for infants and children? (n = 94)		
Health-care worker	76	76.8%
Political	68	68.7%
Teacher	23	23.2%
Religious	18	18.2%

*Note: respondents may give more than one answer

ETHICS STATEMENT

The study was reviewed and approved on 18 January 2019 by the San Beda University Office for Research and Innovation. Permission and approval were obtained from the Division of Planning and Coordination, Manila Health Department, City of Manila, approval number 8159759.

RESULTS

A total of 150 houses were identified with eligible respondents; 31 of them were excluded from the sampling frame (either nobody was home or the children were older than 2 years). A total of 119 respondents completed the survey (100% response rate); however, only 110 responses were included in the final data due to incomplete survey or informed consent information. **Table 2** summarizes the demographic characteristics of the respondents. Most of the respondents were women (81.8%), and most were the mothers (73.6%). Fathers accounted for 17.3% of the total respondents. The median age of the respondents was 29 years old (interquartile range = 25–33). Almost 65% of the respondents finished at least some high school education, and 34.6% had some college-level education. The predominant religion was Roman Catholic (76.4%). The reported monthly household incomes varied, but 87.3% reported that their monthly household income was less than 20 000 Philippine pesos.

Fig. 1 summarizes the answers of the respondents to the survey questionnaire. Almost all (95.5%) respondents believed that vaccines are protective to children, and many (84.6%) believed that most parents have their children vaccinated with recommended vaccines. Ninety-six per cent of respondents reported that financial and logistical concerns have not prevented them from getting their children vaccinated; 92.7% mentioned that other pressures in life have not prevented them from getting their children vaccinated on time. Almost 11% of respondents believed that there could be reasons why children should not be vaccinated; 41.7% of them believed that they can choose not to vaccinate. The majority (72.2%) of respondents had heard negative information about vaccinations, and of these, 75.6% reported hearing negative information about Dengvaxia®. Despite this, 88.0% of respondents who reported receiving negative information about vaccinations said that they would still take their children to get vaccinated. A large majority (95.0%) agreed that community leaders support child vaccination. Health-care workers and political leaders were identified as top vaccination advocates (76.8% and 68.7%, respectively) followed by teachers and religious leaders (23.2% and 18.2%, respectively).

Table 2. **Answers to probe questions from respondents who answered "Yes" to core questions Q4, Q7, Q8, Q10**

	Frequency	Percentage
Gender		
Female	90	81.8%
Male	20	18.2%
Relationship to child		
Mother	81	73.6%
Father	19	17.3%
Grandmother	8	7.3%
Grandfather	1	0.9%
Aunt	1	0.9%
Age range (years)		
less than 20	10	9.1%
20–29	50	45.5%
30–39	36	32.7%
40–49	6	5.5%
50–59	3	2.7%
60 and above	5	4.6%
Educational attainment		
Elementary school	11	10.0%
High school	60	54.6%
College	38	34.6%
Vocational school	1	0.9%
Religion		
Roman Catholic	84	76.4%
Iglesia ni Cristo	3	2.7%
Christian, other denomination or nondenominational	11	10.0%
Muslim	11	10.0%
Others	1	0.9%
Household monthly income (Philippine pesos)		
less than 5000	24	21.8%
5000 to < 10 000	33	30.0%
10 000 to < 15 000	24	21.8%
15 000 to < 20 000	15	13.6%
20 000 and above	14	12.7%

1 USD = 50.4 PHP, at the time of publication

Thirty-one per cent reported hesitating to give at least one vaccination to their children, and 23.7% outright refused at least one vaccination for their children. Cumulatively, 36.4% of the respondents either hesitated or refused to give at least one vaccination (or both) to their children. Respondents who hesitated to have their children receive at least one vaccination were also 16.7 times more likely to have refused least one vaccination for their children (OR = 16.7, 95% CI = 5.7-49.0, $P < 0.001$). A χ^2 analysis with Phi coefficient post-hoc test revealed that respondents who have hesi-

tated to have their child vaccinated were (1) less likely to believe that vaccines protect children from serious diseases ($\chi^2(1) = 9.2$, $P < 0.01$, $\Phi = -0.3$), and (2) more likely to have experienced significant life events that prevented them from having their children vaccinated on time ($\chi^2(1) = 9.7$, $P < 0.01$, $\Phi = 0.3$). There were no significant associations between vaccine hesitancy and demographic data (respondent's age, gender, educational attainment, religion, income category and relationship of the respondent to the child).

The main reasons for refusing to have their child vaccinated are shown in **Table 1**. The primary reason for vaccine refusal was negative information from the media (69.2%), followed by concerns about the safety of vaccines (46.2%). There was a strong association between these reasons ($\chi^2(1) = 68.8$, $P < 0.001$, $\Phi = 0.8$). Further analysis revealed that respondents who believed in the protective nature of vaccines were 9.0 times less likely to refuse vaccination for their children because of negative media exposure (OR = 0.11, 95% CI = 0.017–0.72, $P < 0.05$, pseudo $R^2 = 0.12$) and 6.3 times less likely to refuse vaccination for their children because of vaccine safety concerns (OR = 0.16, 95% CI = 0.024–1.1, $P < 0.1$, pseudo $R^2 = 0.07$).

Other reasons for refusing to have their children vaccinated at least once included the beliefs that vaccines were not effective (19.2%) and that vaccines were not safe (19.2%), doubts about the need for vaccination (15.4%), someone telling them about adverse reactions following vaccinations (11.5%), having a bad experience during previous vaccinations (3.8%) and not knowing where to get reliable information (3.8%). There were no significant associations between reasons for vaccine refusal and respondent's age, gender, educational attainment, religion, income bracket and relationship to child.

DISCUSSION

This study identified the presence of vaccine hesitancy in about one third of the respondents from two highly urbanized communities in Manila, Philippines. The main reasons for refusing at least one vaccination for their children were negative media information and concerns about the safety of vaccines and their side-effects; the main negative media information identified by the respondents was related to the Dengavaxia® vaccine.

Vaccine hesitation is a threat to individuals and also to public health. In the Philippines, it has been suggested that the recent events surrounding the dengue vaccine Dengvaxia® has contributed to a decrease in vaccine confidence;[9,18] however, data supporting this contention are lacking particularly in many low- and middle-income countries. Many reasons have been identified as potential sources of vaccine hesitancy, and beliefs and attitudes towards vaccine efficacy and safety are among them.[14,15] One study reported that vaccine hesitancy was found to be low in parents who perceive vaccination as important.[19] This is consistent with the results of our study that showed respondents who believe in the protective nature of vaccines were less likely to have hesitated or refused vaccination for their child. Circumstantial life events surrounding vaccination have also been identified in literature as potential factors of vaccine hesitancy, where parents attach significance to events such as their child's birth timing, sleep patterns or behaviour, rather than rely on a science-based approach to health care, including immunization.[14] This was consistent with our study findings: respondents with some form of significant event during vaccination periods were more likely to be vaccine-hesitant.

Mass media, such as newspapers, television, radio, the Internet and social media, has contributed to the growing problem of vaccine distrust primarily by over-reporting adverse events of immunization.[20–22] A compounding factor is that vaccine-hesitant parents tend to be more susceptible to media reports, whether verified or not,[21,23] and they frequently rely on the Internet as their source for vaccination information.[14] This phenomenon has been characterized in this study: there was a significant positive association between exposure to negative media information about vaccines and vaccine hesitancy among the study population. Negative media information was positively correlated with safety concerns that correlated with refusal to have children vaccinated at least once in the past. The Dengvaxia® issue in the Philippines was propagated in all types of media beginning in late 2017, and three quarters of study respondents who reported having heard negative information about vaccines said they had heard negative information about Dengvaxia®. Most of the media information was reported on Internet news sites, newspapers and social media that contained reports of adverse events during or after the vaccination campaign, including official statements on fatalities and

growing distrust of the vaccine.[10,24–26] These events are not unique to the Philippines. In 2013, Viet Nam experienced a similar story surrounding Quinvaxem® (diphtheria, tetanus, whooping cough, hepatitis B, *Haemophilus influenzae* type B pentavalent vaccine), where some young infants allegedly had allergies, seizures or reduced muscle tone shortly after receiving the vaccine. Vaccine hesitancy and refusal, and the resulting decrease in vaccine coverage, were linked to extensive print and online media campaigns of the adverse effects of immunization.[20] The controversy led to loss of public trust, and parents had to wait for another pentavalent vaccine to become available.[20]

The results of our study suggest vaccine hesitancy is an issue for parents and caregivers of children 2 years old and younger regardless of age, gender, educational attainment, religion, income bracket or relationship to the children. Some international effects of gender inequality[27] on vaccination attitudes and practices (including vaccine hesitancy), such as men's purported distrust towards vaccinations and women's greater motivation to access health services for their children, did not seem to be present in the study population. One study suggested that educational levels and religious affiliations of caregivers may influence vaccine hesitancy; however, we did not find this in our study. The SAGE Working Group study[12] noted that the level of education may both promote and impede vaccine acceptance depending on the setting. Because the determinants of vaccine hesitancy can be highly varied, contextualization of determinants in each setting (and not general assumptions) is advised by the experts before interventions can be devised.[12]

The purposive nature of the study site and convenience sampling method in respondent selection limits the generalizability of the study to similar study sites (i.e. small, highly urbanized communities); however, literature suggests that different communities have different determinants of vaccine hesitancy. There is always the need to identify these determinants that collectively influence vaccination beliefs and practices and not solely rely on generalizations.[12] Another limitation of the study is the exclusion of parents and caregivers of children who have any contraindications to routine vaccination; contraindication to one vaccine does not necessarily mean contraindication to all vaccines, and this important population subgroup might have been missed in the study. Potential biases that may have affected the results include recall bias and social desirability bias.

The results of this study suggest that vaccine hesitancy might be addressed by a multi-stakeholder approach in the community. The role of political and religious community leaders in supporting vaccination strategies appears to be evident. The role of health workers needs to be re-emphasized and strengthened; they were the most commonly cited advocates for vaccination in this study. In a previous study, they were found to be the most influential persons addressing vaccine hesitancy. Empowering and mobilizing health workers to take an active role in promoting accurate and timely information on the benefits of immunization and allaying the community's fears and distrust of vaccines is still the most important strategy.[21]

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Impact of seasonal influenza on polyclinic attendances for upper respiratory tract infections in Singapore

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Purpose: The burden of influenza on primary health-care services is not well established in tropical countries, where there are no clearly defined influenza seasons. We aimed to estimate the association between influenza infection activity and polyclinic attendance rates for upper respiratory tract infections (URTIs) in the Singapore population.

Methods: We used generalized additive time series models to estimate the association between the proportion of respiratory tests positive for influenza infection in Singapore reported to the World Health Organization every week, and the population rate of polyclinic attendances in Singapore for physician-diagnosed URTI, which includes influenza-like illness (ILI), for six years from 2012 through 2017. Where data were available, we controlled for other infections that can cause fever or respiratory symptoms.

Results: Influenza, dengue fever and chickenpox (varicella) were positively associated with acute URTI polyclinic attendances. The estimated URTI polyclinic attendance rates attributable to influenza, dengue fever and chickenpox were 618.9 (95% confidence interval [CI]: 501.6–736.3), 153.3 (95% CI: 16.5–290.2) and 1751.5 (95% CI: 1246.3–2256.8) per 100 000 population per year, respectively.

Conclusions: Influenza poses a considerable burden on primary health-care services in Singapore. However, a substantial number of polyclinic attendances due to febrile infections such as dengue fever and chickenpox appear to be recorded as URTI in the polyclinic database. These associations require further investigation.

Recent global estimates of influenza-associated mortality are in the range of 290 000–650 000 deaths every year.[1] Availability of hospital admission and vital statistics databases on mean hospitalizations or deaths attributable to influenza are most often studied.[2] However, influenza infections leading to health care for relatively mild symptoms often go unobserved at the population level. The milder outcomes of influenza have not been fully studied despite their greater prevalence.[3]

Singapore is a highly developed country with strong health information systems. This, combined with its equatorial location, makes Singapore an ideal candidate for estimating influenza burden in the tropics. Singapore's health information systems include a database of attendances at polyclinics. Polyclinics are the first point of contact that patients have with the health-care system when they present with a medical condition. There are around 20 government polyclinics that provide 20% of Singapore's primary health care.[4] Patients can present to these polyclinics for the treatment of acute conditions or for the follow-up of chronic conditions.[5]

A widely used method to estimate the burden of influenza is the Serfling regression model.[6] The model was originally used to estimate influenza-attributable excess mortality from a time series of deaths classified due to pneumonia or influenza. However, one of the limitations is that the model assumes a cyclical baseline activity of influenza due to the distinct seasonality of background (non-influenza) deaths in temperate countries.[7,8] Yet this may be less applicable in tropical countries such as Singapore, where seasonality is less clearly defined.[9,10]

The generalized additive model (GAM) can be used for time series analysis that more flexibly addresses the issue of less distinct seasonality from which excess

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outcomes attributable to influenza can be discerned. The GAM approach models the baseline activity using a more flexible approach than the Serfling model.[11] Unlike Serfling's traditional approach, which excluded influenza periods to ensure the model was not influenced by the effect of epidemics on the time series, the GAM approach requires independent variables that are a complete time series. One of these time series, a parametric component of the model, needs to reflect the changing incidence of influenza in the population over time. The GAM approach also includes a non-parametric smoothing function of time that reflects the background incidence of unmeasured causes of disease that contribute to the time series, typically a spline curve.[7]

The objective of this study was to estimate the burden of milder influenza infections on polyclinic attendance rates in Singapore. We used time series analysis to estimate the association between influenza and polyclinic attendances for upper respiratory tract infections (URTIs), which include influenza-like illness (ILI), from 2012 through 2017. Where data were available, we controlled for other infections that can cause fever or upper respiratory symptoms.

MATERIALS AND METHODS

Study setting and study period

We performed a retrospective observational time series analysis of influenza infections and polyclinic attendances in Singapore for 2012 through 2017, for 313 weeks over the six-year period. The first week of 2012 was recorded as Week 1.

Data sources

Available data relevant to URTI or ILI and other fever-causing infections were downloaded from the Singapore Government's data portal.[12] These were average daily polyclinic attendances in each week with a physician diagnosis of URTI. The definition of URTI in the database includes ILI. Patients are diagnosed with URTI at the polyclinic when they present with acute upper respiratory symptoms including cough or sore throat, with or without fever (> 38 °C). Patients are diagnosed with ILI when they present only with cough and fever (> 38 °C) (Ministry of Health Singapore, personal communication, 10 July 2018). We also obtained average daily polyclinic attendances for chickenpox (varicella) as chickenpox is a possible cause of fever or upper respiratory symptoms in the early stages of infection.

Influenza surveillance data for Singapore were retrieved from the World Health Organization's FluNet database.[13] The weekly number of respiratory specimens reported to FluNet that were positive for influenza was obtained.[14]

Weekly counts of all available infectious diseases from the Weekly Infectious Diseases Bulletin published by the Ministry of Health, Singapore,[15] that could produce fever or upper respiratory symptoms were obtained. The illnesses available were dengue fever, *Haemophilus influenzae* type b, legionellosis and malaria.

Polyclinics are open only for half a day on Saturdays and closed on Sundays and public holidays. Public holidays affect the hours that polyclinics are open each week and thus the number of weekly attendances. Thus, holidays were included in the model to account for their effects. The number of public holidays in each week was tabulated from press releases from the Ministry of Manpower, Singapore.[16] School holidays may also affect patient demand and were compiled based on publicly available information provided by the Ministry of Education, Singapore.[17]

Analysis

We used a GAM to investigate the association of influenza and other infectious diseases with acute URTI polyclinic attendances. Since the daily average counts of weekly polyclinic attendances for acute URTIs were large (~3000 in 2017), a model with normally distributed residuals was assumed. GAMs can include linear parametric terms and a non-parametric, nonlinear smoothing functions of the independent variables.[18] A natural cubic spline of week number was used as the non-parametric smoother to account for unobserved background variation in acute URTI polyclinic attendances not associated with the included parametric, independent variables, as described previously.[7]

The model equation for the daily average number of acute URTI polyclinic attendances included the fol-

lowing variables: a model intercept; parameter estimates for all six diseases each multiplied by their respective independent variable; public holidays; school holidays; week number; and an error term. Consistent with similar studies,[7,18,19] the smoothing spline of week number included 36 degrees of freedom (six per year), to control for medium- and longer-term variation and seasonality of background polyclinic attendances. This effectively controlled for variation in the time series on time scales longer than two months, leaving shorter time scale variation to be explained by the independent variables in the model.

To estimate the weekly values of average daily polyclinic attendances attributable to each independent variable, the parameter estimates were multiplied by the observed value of the variable in that week. The parameter estimate of chickenpox was multiplied by the weekly number of chickenpox polyclinic attendances. The parameter estimate of influenza was multiplied by the number of positive specimens in a week. For dengue fever, its parameter estimate was multiplied by the number of infections in one week.

To obtain annual total polyclinic attendances attributable to each variable, the estimates of average daily acute URTI polyclinic attendances were multiplied by the number of days that polyclinics were open each year. Since polyclinics only operate for half a day on Saturdays and are also closed on public holidays, the number of days that polyclinics are open can vary each week. The total number of attendances each year was converted to population rates using annual population estimates.[20]

SAS Version 7.1 was used for data analysis. Quantile-quantile (QQ) plots were used to check the modelling assumption that the error term was normally distributed. Autocorrelation plots were used to identify autocorrelation in the error term time series, which is another modelling assumption (independence of residuals).

Ethical approval

This project was approved by the UNSW Sydney Human Research Ethics Committee as a negligible risk project (HC number: 180169).

RESULTS

Data characteristics

A total of 313 weeks from January 2012 to December 2017 was included in the study. During that period, the mean number of average daily acute URTI polyclinic attendances each week was 2694.0 (**Table 1**, **Fig. 1**). The mean number of average daily chickenpox polyclinic attendances was 15.0, and attendances occurred throughout the year without apparent seasonality (**Table 1**, **Fig. 2**). The mean number of weekly positive influenza specimens was 18.2, and infections increased during epidemic periods that varied in amplitude between years and occurred at different times of the year (**Table 1**, **Fig. 3**). The mean number of dengue infections each week was 230.7. There were dengue epidemics in some, but not all, years and background rates varied between years (**Table 1**, **Fig. 4**).

The mean number of reported *Haemophilus influenzae* type b, malaria and legionellosis cases each week were markedly lower at 0.1, 1.0 and 0.5, respectively, over the six-year period.

Model fit

The QQ plots showed that the model assumption of a normally distributed error term was reasonable, although there were some departures from normality at the extremes. The modelling assumption of a non-autocorrelated error term was incompletely met, with some low but statistically significant autocorrelation evident in the model residuals.

We attempted to reduce this residual autocorrelation by introducing first-order autoregressive terms into the model. This may be plausible due to delayed health-care seeking following infection. The resulting model therefore included a lag term of one week for each of the three diseases. Autocorrelation in the error term was not affected by this change to the model so the autoregressive terms were discarded.

As a sensitivity analysis, we changed the functional form of the GAM to a Poisson model, with a log link

Table 1. **Descriptive statistics of variables considered**

Variable	Measured as	Mean	Median	Minimum	Maximum	Interquartile Range
URTI	Average daily polyclinic attendances each week	2694	2648	1839	4001	448
Chickenpox	Average daily polyclinic attendances each week	15	14	7	26	4
Positive influenza specimens	Weekly count	18	14	0	86	17
Dengue fever	Weekly count	231	204	24	888	233
Haemophilus influenzae type b	Weekly count	0	0	0	3	0
Malaria	Weekly count	1	1	0	9	2
Legionellosis	Weekly count	1	0	0	5	1

URTI = upper respiratory tract infection

Fig 1. **Average daily acute URTI polyclinic attendances, by week, Singapore, 2012–2017**

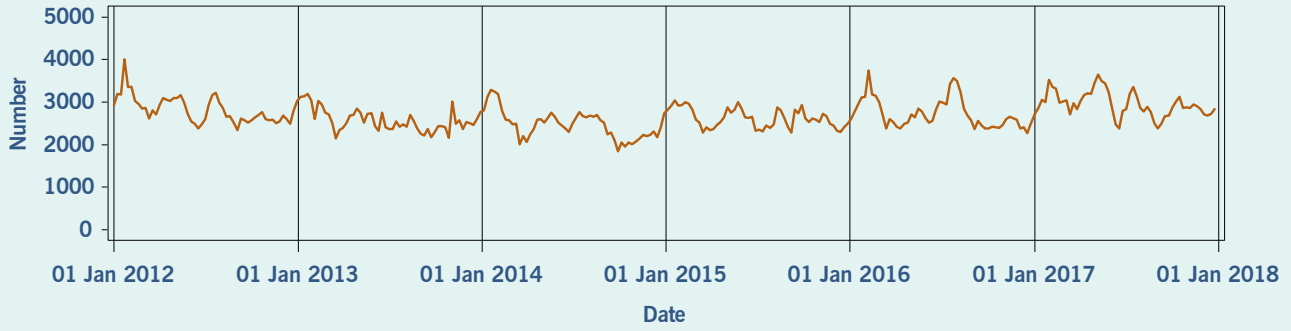


Fig 2. **Average daily chickenpox polyclinic attendances, by week, Singapore, 2012–2017**

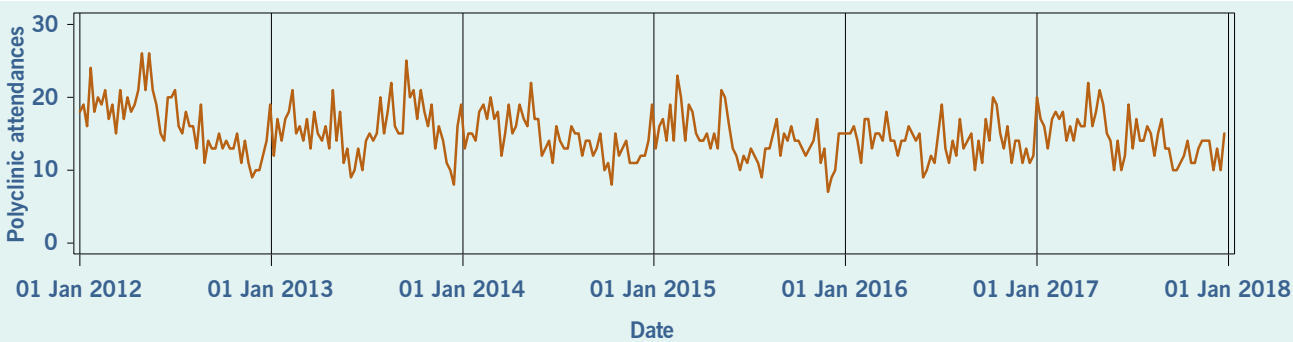


Fig 3. **Number of positive influenza specimens, by week, Singapore, 2012–2017**

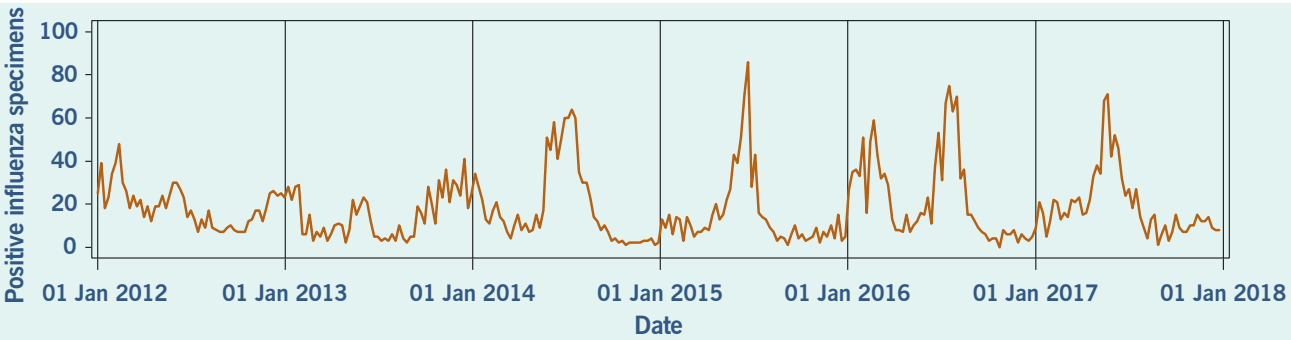
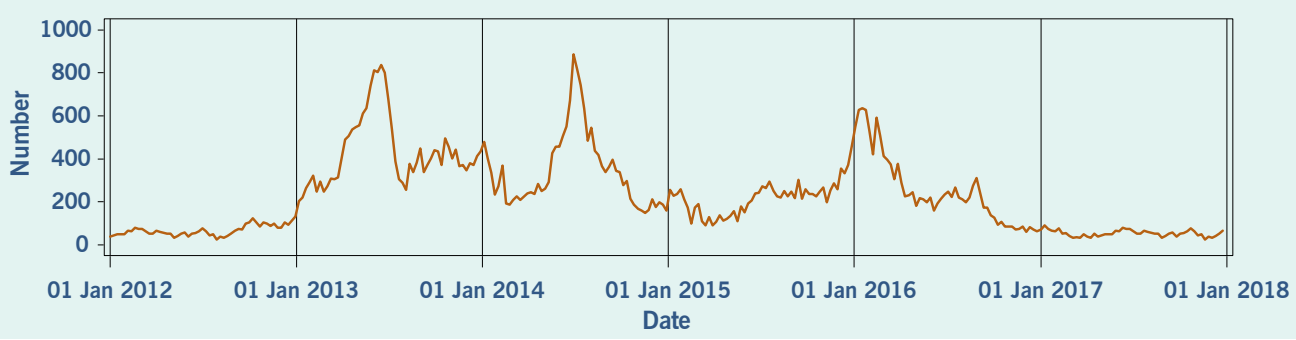


Fig 4. **Number of reported dengue fever infections, by week, Singapore, 2012–2017**



function and Poisson error term. This did not alter the error term autocorrelations. Therefore, this model was discarded in favour of the simpler linear GAM model form with a normally distributed error term.

Main results

In the initial model with all available independent variables, weekly occurrences of laboratory-confirmed influenza infections and dengue fever, and of physician-diagnosed chickenpox, were statistically significantly associated with weekly rates of acute URTI polyclinic attendances. The parameter estimates for each of these variables were 6.9 (95% CI: 5.6–8.2), 0.1 (95% CI: 0.02–0.3), and 24.0 (95% CI: 17.2–30.8), respectively (**Table 2**).

Haemophilus influenzae type b, legionellosis and malaria did not show a significant association with acute URTI polyclinic attendances. Due to their lack of association and extremely low frequencies, they were excluded from the final model.

In the revised model, chickenpox, influenza and dengue fever remained statistically significantly associated with the number of acute URTI polyclinic attendances. The parameter estimate for chickenpox was 23.3 (95% CI: 16.5–30.0), while the parameter estimate for influenza was 6.8 (95% CI: 5.5–8.0). The parameter estimate for dengue fever was 0.1 (95% CI: 0.01–0.2) (**Table 3**).

The average annual estimated polyclinic attendance rate per 100 000 population was estimated to be the highest for chickenpox at 1751.5 (95% CI: 1246.3–2256.8), as compared to influenza and dengue fever at 618.9 (95% CI: 501.6–736.3) and 153.3 (95% CI: 16.5–290.2) respectively (**Table 4**, **Fig. 5**). When aggregated by year, chickenpox was estimated to constitute the greatest proportion of acute URTI polyclinic attendances across all six years. The percentage of acute URTI polyclinic attendances attributable to chickenpox, influenza and dengue fever was 13.0%, 4.6% and 1.2%, respectively, over the study period.

DISCUSSION

This study quantifies the influenza activity associated with polyclinic attendances for acute URTIs. An estimated average of 618.9 URTI polyclinic attendances per 100 000 population per year were attributable to influenza. Assuming these polyclinic attendances represent 20% of total primary health-care episodes in Singapore with the remainder of primary care services delivered privately,[21] the national rate of total influenza-attributable primary care attendances may be around 3100 per 100 000. This is higher than the estimated rate of 2156 per 100 000 in England.[22] The percentage of URTI polyclinic attendances in Singapore that were estimated to be attributable to influenza was 4.6%, and this is also higher than the estimated 2.2% for primary care in Beijing, China, but lower than the estimated 8.7% in the United States of America.[23,24]

The total influenza burden also comprises hospitalizations and deaths in addition to primary care encounters. A study on influenza-associated deaths in Singapore found that the average estimated rate was 14.8 per 100 000 person-years from 1996 to 2003.[25] The rate of influenza-associated hospitalizations diagnosed with influenza or pneumonia was 29.6 per 100 000 person-years from 2010 to 2012.[10] This is likely to underestimate total hospitalizations attributable to influenza, which are

Table 2. **Parameter estimates for each variable in the initial model**

Parameter	Parameter estimate	95% confidence interval	*p*-value
Intercept	2086.7	1944.0, 2229.4	< 0.0001
Influenza	6.9	5.6, 8.2	< 0.0001
Dengue fever	0.1	0.02, 0.3	0.03
Chickenpox	24.0	17.2, 30.8	< 0.0001
Haemophilus influenzae type b	34.0	-11.4, 79.5	0.1
Malaria	-1.4	-15.6, 12.8	0.8
Public holidays	92.1	47.8, 136.4	< 0.0001
School holidays	-208.2	-256.0, -160.4	< 0.0001
Week number	0.7	0.5, 1.0	< 0.0001

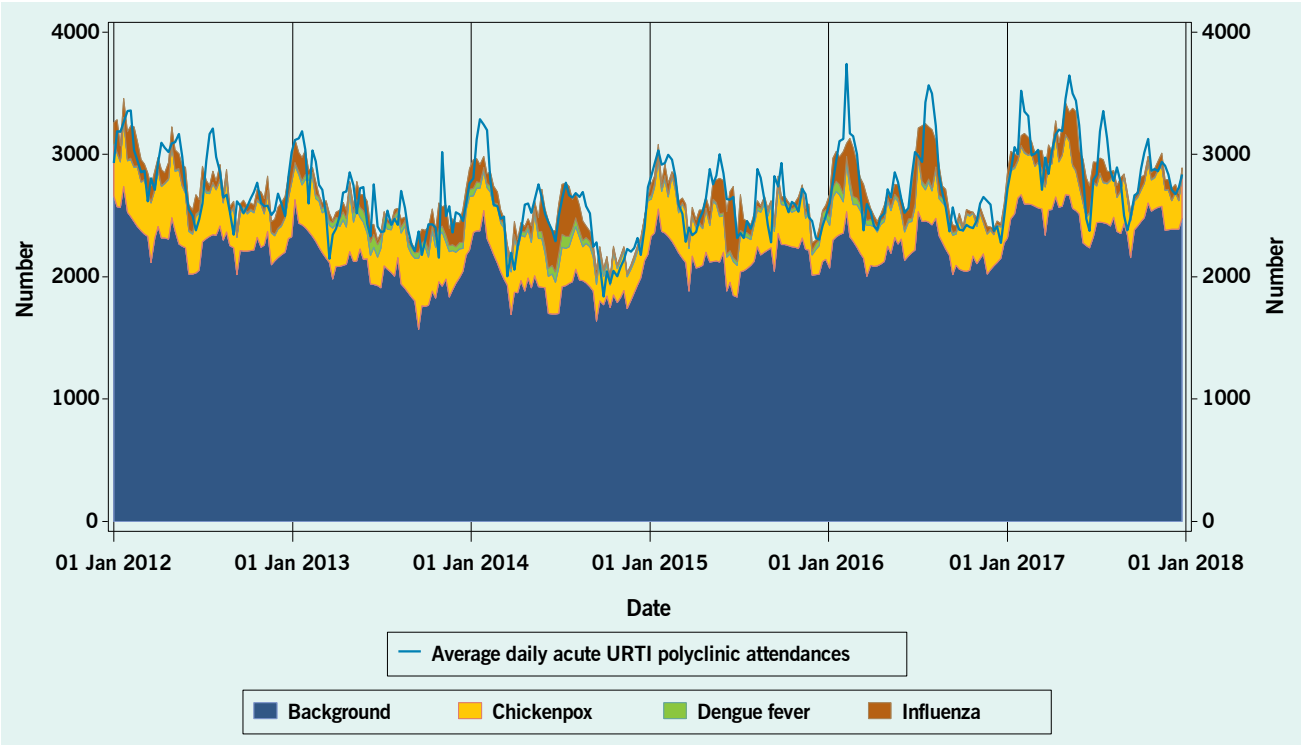
Table 3. **Parameter estimates for each variable in the revised model**

Parameter	Parameter estimate	95% confidence interval	*p*-value
Intercept	2105.2	1975.7, 2234.7	< 0.0001
Influenza	6.8	5.5, 8.0	< 0.0001
Dengue fever	0.1	0.01, 0.2	0.02
Chickenpox	23.3	16.5, 30.0	< 0.0001
Public holidays	92.3	48.2, 136.4	< 0.0001
School holidays	-206.2	-253.6, -158.9	< 0.0001
Week number	0.8	0.5, 1.0	< 0.0001

often estimated based on broader diagnosis categories such as all respiratory diagnoses.[26] The rate of influenza-attributable URTI polyclinic attendances is far higher than these more severe outcomes. This is in line with the understanding that mild influenza infections constitute a large proportion of the influenza burden.[3,27]

The number of influenza-attributable polyclinic attendances dipped slightly in 2015 before rising in 2016. This may be due to the introduction of a novel influenza A(H3N2) strain to Singapore in 2016, against which the population did not have prior immunity.[28] Furthermore, although vaccines including one active against A(H3N2) strain were available in Singapore, there are low levels of vaccination uptake in the Singaporean population.[29] In addition, the reduced effectiveness of the vaccine protec-

Fig 5. **Observed totals and estimated averages of daily URTI polyclinic attendances attributable to each disease and to background causes, by week, Singapore, 2012–2017**



URTI = upper respiratory tract infection

Table 4. **Estimated polyclinic attendance rate per 100 000 population by disease and year, Singapore, 2012–2017**

Disease	Year	Estimated attendances	95% CI	% of total URTI attendances	Rate/100 000	95% CI
Influenza	2012	35 181	28 510, 41 853	4.5	662.2	536.7, 787.8
	2013	27 071	21 938, 32 205	3.8	501.4	406.3, 596.5
	2014	35 214	28 536, 41 892	5.2	643.8	521.7, 765.9
	2015	27 751	22 488, 33 013	3.8	501.4	406.3, 596.4
	2016	43 049	34 885, 51 213	5.7	767.7	622.1, 913.3
	2017	35 755	28 974, 42 535	4.4	637.1	516.3, 757.9
	Average	34 004	27 555, 40 452	4.6	618.9	501.6, 736.3
Dengue fever	2012	3216	347, 6085	0.4	60.5	6.5, 114.5
	2013	15 415	1661, 29 170	2.2	285.5	30.8, 540.3
	2014	12 573	1355, 23 791	1.8	229.9	24.8, 435.0
	2015	7875	849, 14 902	1.1	142.3	15.3, 269.2
	2016	9391	1012, 17 770	1.3	167.5	18.0, 316.9
	2017	1928	208, 3648	0.2	34.4	3.7, 65.0
	Average	8400	905, 15 894	1.2	153.3	16.5, 290.2
Chickenpox	2012	106 324	75 655, 136,993	13.7	2001.4	1424.1, 2578.7
	2013	99 859	71 055, 128 663	14.1	1849.5	1316.0, 2383.0
	2014	93 851	66 780, 120 922	13.8	1715.8	1220.9, 2210.7
	2015	90 759	64 580, 116 938	12.6	1639.7	1166.7, 2112.7
	2016	91 645	65 210, 118 080	12.2	1634.4	1163.0, 2105.8
	2017	93 634	66 626, 120 643	11.5	1668.4	1187.1, 2149.6
	Average	96 012	68 318, 123 706	13.0	1751.5	1246.3, 2256.8

URTI = upper respiratory tract infection
CI = confidence interval

tive against A(H3N2) vaccine virus strains could have also contributed to the increase in influenza-attributable polyclinic attendances in 2016.[30,31]

A surprising result was that both dengue fever and chickenpox were associated with acute URTI polyclinic attendances. This could be because the clinical symptoms of dengue fever and chickenpox both include fever and these diseases could therefore be mistaken for acute URTI in the early days following infection.[32,33] This highlights the discriminatory limitations of syndromic data for estimating the burden of influenza infection in primary care.[34,35] In Taiwan, China, it was found that predictors such as the absence of rashes, platelet count, rhinorrhoea, malaise and sore throat were useful in distinguishing influenza from dengue fever or other febrile illnesses.[36]

The estimated average annual rate of influenza-attributable URTI polyclinic attendances was approximately one third that of chickenpox-attributable URTI polyclinic attendances. This suggests that chickenpox may have a very high incidence compared with influenza in Singapore. Varicella is highly infectious, and a high incidence of infection has been reported in Singapore and Hong Kong SAR (China).[37–30] Varicella is not currently included in the Singapore childhood immunization schedule, but it is recommended for adults.[40,41] It is no longer a notifiable disease, but a seroprevalence study from 2008 to 2010 showed that seroprevalence of infection was around 30% in Singapore infants and around 80% by age 17 years and varicella vaccination uptake was estimated at 52%.[42] Thus, a high rate of infection is not surprising. The time series of chickenpox polyclinic attendances shows that chickenpox circulates throughout the year, which could

also explain the relatively high estimates. Influenza and dengue fever, on the other hand, showed varying incidence over time associated with epidemic activity. The relationship of chickenpox with URTI polyclinic attendances, however, does require further investigation; it may be able to be further elaborated through age-specific analysis.[43]

Our results also showed that public holidays had a positive association with URTI polyclinic attendances, whereas school holidays a negative association. This is consistent with the trend shown by other infectious diseases in Singapore, where hand, foot and mouth disease demonstrated a seasonal trough during school holidays.[44] A European study investigating the spread of infectious diseases showed that the highest incidence of cases in an epidemic occurred in schoolchildren.[45] This is because contact made within this age group was more likely to be physical, and also because children tended to have a larger social circle than other age groups, leading to a greater dissemination of diseases. These reasons could therefore explain the lower rates of influenza-attributable polyclinic attendances for URTIs during school holidays in Singapore. On the other hand, mass gatherings during public holidays are likely to contribute to greater spread of diseases like influenza.[46]

An advantage of our study is that we were able to use a time series of laboratory-confirmed influenza infections to provide a proxy for week-to-week changes in the incidence of influenza infections in Singapore. By using only laboratory-confirmed infections, this potentially allows for a more accurate estimation of influenza-attributable URTI polyclinic attendance incidence.

The study had some limitations. Our results did not account for the mild-to-moderate influenza infections where medical care is not sought. In addition, the main limitation is that government-run polyclinics represent only around one fifth of primary care services in Singapore, with the remainder delivered privately. Thus, our results do not represent the total primary care burden of influenza in Singapore. Nevertheless, polyclinics remain an important component of the primary health-care sector in Singapore, and the database of information on polyclinic attendances can allow for a relatively continuous estimation of influenza's burden on primary health care in the country. Also, we were unable to obtain age-specific information for this study. The data available also did not include information on lower respiratory tract infections or other common respiratory pathogens such as rhinovirus and respiratory syncytial virus. Lack of information on other sources of variation in the time series may have explained some of the low residual first-order autocorrelation ($r = 0.29$), despite the use of the smoothing spline. The degree of smoothing we chose was predetermined to avoid over-fitting the model. In Singapore, school holidays can vary by institution, and we used the holiday dates associated with the main educational institutions. Sick leave entitlements may influence health-care-seeking behaviour. Singaporeans are entitled to a maximum of 14 days of paid outpatient sick leave every year.[16] This limited entitlement may lead patients to avoid seeking treatment of relatively mild infections. Alternately, it may increase presentations because of the need to obtain a medical certificate. There is limited information on influenza vaccination levels in Singapore, although a recent estimate is 14% coverage in 65–74 year olds.[47] The vaccine is recommended for all residents, but it is only subsidized for employed citizens and permanent residents with a high risk for severe infection outcomes through the national medical savings scheme (MediSave).[48] Depending on citizenship or residency status, a polyclinic visit can cost up to 68 Singapore dollars in 2019.[49] This cost, with the additional cost of a vaccine, may lead to a lower vaccine uptake.

In summary, influenza may pose a considerable health-care burden on primary health-care services in Singapore. The data from our study may be helpful in supporting cost-effectiveness studies to evaluate if an influenza immunization policy would be beneficial to the Singaporean population. This could, in turn, lower the rates of polyclinic attendances for influenza. The surprising finding that a substantial proportion of URTI presentations appears to be associated with chickenpox and dengue fever activity requires further study.

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Declaration of interests

The authors have no relevant financial information or potential conflicts of interest to disclose.

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Delay in health-care-seeking treatment among tuberculosis patients in Japan: what are the implications for control in the era of universal health coverage?

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Objectives: To study the trends in and risk factors for patient delay (the time from the onset of symptoms to the initial doctor visit) in pulmonary tuberculosis (PTB) using three temporal categories – short (2 weeks to <2 months), medium (2 months to <6 months) and long (≥6 months) – and discuss implications for social protection measures.

Methods: A descriptive cross-sectional study was conducted by analysing Japanese TB surveillance data from patients with symptomatic PTB registered between 2007 and 2017 (n = 88 351).

Results: While the proportion of patients with short delay has decreased significantly ($P < 0.001$), the proportions of those with medium or long delays have decreased slightly ($P = 0.0015$ and $P < 0.001$, respectively). Not having health insurance, receiving public assistance, being a temporary worker, and having a history of homelessness were some of the risks identified for patient delay. Being male and working full-time were two risks specifically associated with long delay (for males, the adjusted odds ratio = 1.17, $P < 0.05$; for being a full-time worker, the adjusted odds ratio = 1.72, $P < 0.05$).

Discussion: Despite the implementation of universal health coverage decades ago, patient delay remains a challenge in Japan. Our study identified various risk factors, many of which could have been resolved if appropriate social protection measures were in place, indicating shortcomings in universal health coverage in Japan and the need for continued effort to ensure that no one is left behind.

Tuberculosis (TB) continues to be a major global health issue, with 10 million people having newly diagnosed disease and 1.2 million dying from it in 2018.[1] The World Health Organization (WHO) developed the End TB Strategy in 2014, with three major targets to be achieved by 2035: a 90% reduction in TB incidence compared with 2015, a 95% reduction in TB deaths compared with 2015, and no affected families facing catastrophic financial losses from TB.[2] Early case detection is one of the key components of this strategy, not only to allow for early diagnosis and treatment, and thus better treatment outcomes for patients, but also to terminate the chain of transmission.[3] Yet previous studies have shown that delays on the part of the patient and the health system have continued to be unacceptably high, with factors such as unemployment and poverty playing major roles in affecting a delay in diagnosis.[4,5] Increasingly, it is recognized that policy efforts are needed to address these socioeconomic factors in line with the overarching framework for achieving universal health coverage (UHC).[6]

Japan introduced the first national policy for social health insurance in 1922. Later, in response to the call for welfare policies to mitigate social instability after Second World War, UHC was achieved in 1961 through the co-existence of different public health insurance schemes.[7] Additionally, Japan has maintained cost equality across schemes by regulating fee schedules and co-payment rates, with charges for elderly people and children being one third of those for other adults.[7] UHC ensures free access to any medical institution, and community-based health services are available at municipal public health centres, including TB screening for high-risk groups in the

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community. Today, Japanese people have access to one of the most affordable, high-quality and egalitarian health systems in the world.[8]

Yet, the rate of decrease in Japan's TB notification rate has stagnated since the 1990s, reaching 13.3 cases/100 000 population in 2017, and the prospect of achieving the national target of less than 10 cases/100 000 by 2020 seems unlikely.[9] One of the possible issues lies with the time from the onset of symptoms of TB to the initial doctor visit, which is known as patient delay; while the proportion of patients with TB experiencing doctor delay, the time from the initial doctor visit to diagnosis, has remained relatively constant, the proportion with patient delay has been increasing during the past 20 years.[9] In 2017, the proportion of patients with symptomatic pulmonary TB (PTB) who took more than 2 months to access medical services after the onset of symptoms was as high as 20.0%.[9]

The objectives of this study were to conduct a detailed analysis of patient delay in Japan, investigate the risk factors for patient delay and discuss implications for social protection measures for TB patients, especially in a country where UHC was achieved decades ago.

METHODS

We conducted a cross-sectional study of symptomatic PTB patients, newly notified to the nationwide TB surveillance system, Japan Tuberculosis Surveillance (JTBS), between 1 January 2007 and 31 December 2017. In the current JTBS system, providing information regarding symptoms for all patients notified as having PTB is mandatory. A symptomatic PTB patient is defined as someone who has complained not only of respiratory but also of any other general symptoms.

Japan Tuberculosis Surveillance system

Japan introduced its first nationwide computerized TB surveillance system in 1987. TB is a notifiable disease, and public health centres are responsible for collecting and entering data about notified patients into the system. Data items included in the JTBS system are sex, age, nationality, occupation, whether the patient has health insurance and what type, history of homelessness, history of treatment, symptoms, sputum smear result, presence of diabetes mellitus (DM), and delay information, including date of symptom onset and date of initial doctor visit. The data are summarized monthly and annually and are available online. Mechanisms to ensure data quality include the system's automatic verification programme, as well as regular meetings attended by staff from hospitals and public health centres. Periodic refresher trainings on data entry are also provided to staff at public health centres across the nation.

Definition of patient delay

Patient delay is defined in the JTBS system as the time between the date of symptoms onset and the initial doctor visit, and it is automatically calculated and categorized as <2 weeks, ≥2 weeks to <1 month, ≥1 month to <2 months, ≥2 months to <3 months, ≥3 months to <6 months, ≥6 months, unknown, and not applicable. Previous studies in Japan have generally used a binary definition, with patient delay being defined as a delay of >2 months between the onset of symptoms and the initial doctor visit and no delay defined as <2 months.[9–11]

We first extracted data from all PTB patients who were registered as having symptoms, then re-categorized them into four definitions of delay: no delay, short delay (≥2 weeks to <2 months), medium delay (≥2 months to <6 months) and long delay (≥6 months).

Data analysis and ethics

The numbers and proportions of symptomatic PTB patients in the three categories of delay were summarized, and trends were tested using the Cochran–Armitage test. The trends in the proportion of those in each delay category were also calculated by country of birth. More than 60% of Japan-born patients are elderly and they tend to present after a shorter delay, while the majority of younger patients are foreign born and they tend to present after a longer delay.[9] Due to this heterogeneity in age variance by country of birth, comparisons were made for all age groups combined and then repeated for those who were younger than 65 years.

Characteristics of patients with and without patient delay were summarized and proportions were compared; multinomial logistic regression analysis was conducted to identify possible risk factors for the three categories of patient delay. Risk factor variables were selected based on the associated factors identified in previous studies.[8–11]

R version 3.1.3 (R Development Core Team, Vienna, Austria) was used for all statistical analyses.

Ethics statement

The study protocol was approved by the Institutional Review Board of the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association (reference no. RIT/IRB 30–9). Informed consent was deemed not necessary by the review board, as the surveillance data do not contain personal identifiers.

RESULTS

Between 2007 and 2017, a cumulative total of 134 869 symptomatic PTB patients were newly notified, of whom 88 351 (65.5%) had information regarding patient delay.

Annual trends by duration of patient delay

The annual number of symptomatic PTB patients with any delay decreased from 5242 in 2007 to 3093 in 2017 (**Fig. 1**). The proportion of TB patients with a short delay decreased from 32.5% (3371/10 368) in 2007 to 28.3% (1781/6295) in 2017 ($P < 0.001$). In contrast, the proportions of those with a medium or long delay have been constant or have increased during the study period, from 14.3% (1485/10 368) to 17.0% (1071/6295) ($P = 0.0015$) for those with a medium delay and from 3.7% (386/10 368) to 3.8% (241/6295) for those with a long delay ($P < 0.001$). The annual trends in proportions of those in the three different categories of patient delay for all age groups and for those aged <65 years, stratified by birthplace (Japan or outside of Japan), are shown in **Fig. 2**.

Characteristics of patients with delay

The characteristics of PTB patients with and without delay are summarized in **Table 1**. Compared with patients who did not delay seeking treatment, the proportions of men, patients aged 25–54 years, and foreign-born patients were higher in those who delayed seeking treatment. Similarly, the proportions of those receiving public assistance and those without insurance were higher among those with patient delay, and they were higher among those with long delay compared with those with short or medium delay. The proportions of those receiving public assistance among the different types of health insurance status were 11.1% for those with long delay, 8.9% for those with medium delay, and 8.1% for those with short delay. For those who had no insurance among the different types of health insurance status the proportions were 3.1% for those with long delay, 2.4% for those with medium delay, and 1.1% for those with short delay. The proportions of full-time workers (those employed full-time on a mid- to long-term contract), temporary workers (those employed part-time or on a short-term contract) and those with a history of homelessness (those who had been homeless within 1 year of diagnosis) were also higher in those with delay than in those without delay.

Risk factors for patient delay

The results of the multinomial regression analysis are summarized in **Table 2**. Male sex was a significant risk factor for long delay (adjusted odds ratio [aOR] = 1.17, $P < 0.05$). Compared with students, being a full-time worker was a risk factor for long delay (aOR = 1.72, $P < 0.05$), while being a temporary worker was a risk factor for any delay (aOR = 1.22, $P < 0.05$ for short delay; aOR = 1.34, $P < 0.05$ for medium delay; and aOR = 1.99, $P < 0.05$ for long delay).

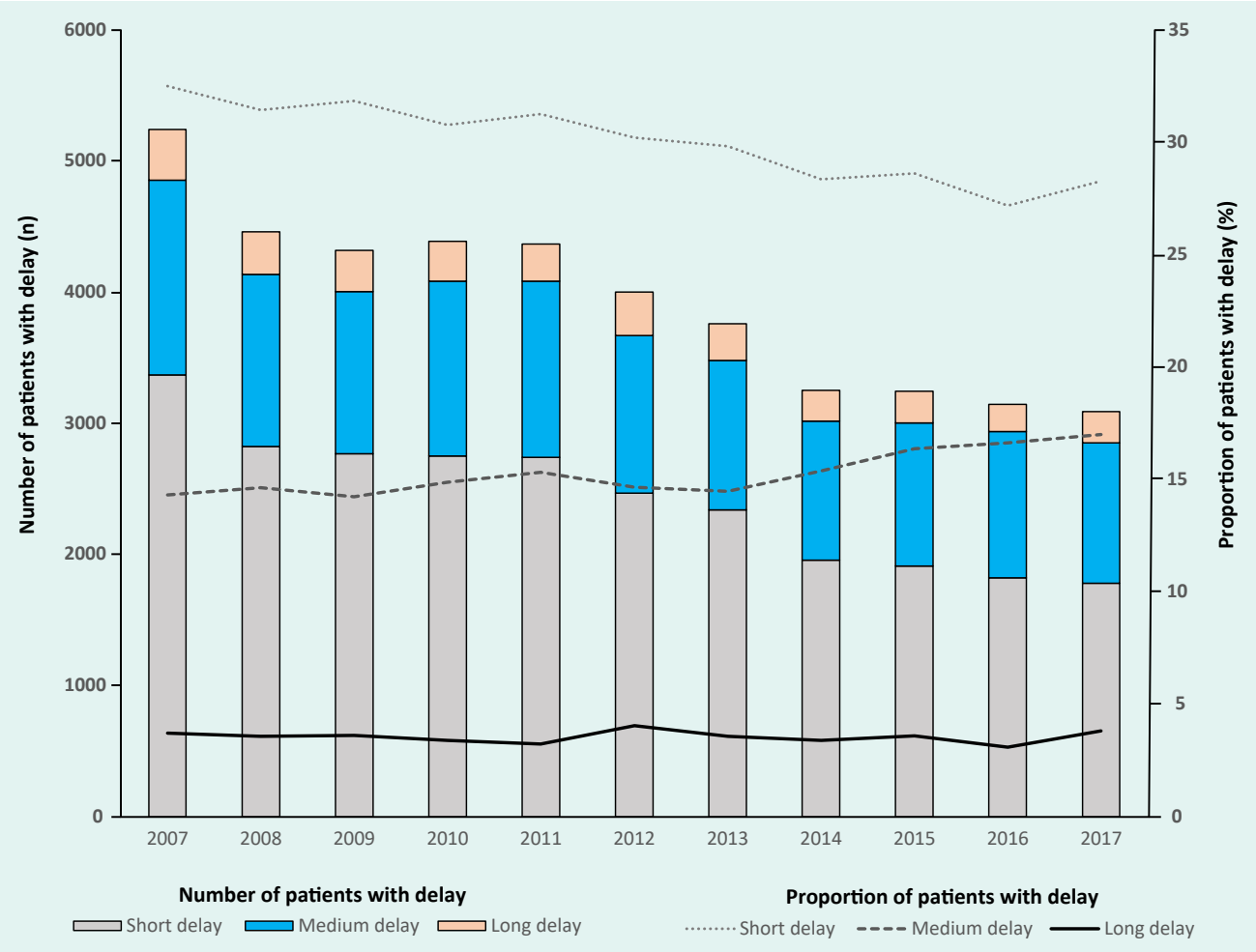
Not having health insurance was a risk factor for all types of delay (aOR = 1.63, $P < 0.05$ for short delay; aOR = 2.81, $P < 0.05$ for medium delay; aOR = 2.75, $P < 0.05$ for long delay) and having a history of homelessness was also a risk factor for all types of delay (aOR = 1.46, $P < 0.05$ for short delay; aOR = 1.73, $P < 0.05$ for medium delay; aOR = 2.09, $P < 0.05$ for long delay). Receiving public assistance was specifically a risk factor for medium and long delays (aOR = 1.19, $P < 0.05$ for medium delay; aOR = 1.36, $P < 0.05$ for long delay) (**Table 2**).

Reporting respiratory symptoms and DM were identified as risk factors for delay. In contrast, being aged ≥65 years was a protective factor against all categories of patient delay (aOR = 0.75, $P < 0.05$ for short delay; aOR = 0.60, $P < 0.05$ for medium delay; aOR = 0.38, $P < 0.05$ for long delay).

Patient delay by health insurance status

The proportions of patients in each delay category by health insurance status are shown in **Fig. 3**. For all types of health insurance status, the proportions of patients with a short delay were all approximately 30%. However,

Fig. 1. **Number and proportion of patients with symptomatic pulmonary tuberculosis categorized by length of delay in seeking care, Japan, 2007–2017***



* Delays were defined as short (≥2 weeks to <2 months), medium (≥2 months to <6 months) or long (≥6 months). Solid and dashed lines indicate trends.

the proportions of patients who had medium delay or long delay were greater among those without health insurance (32.9% and 9.9%, respectively).

DISCUSSION

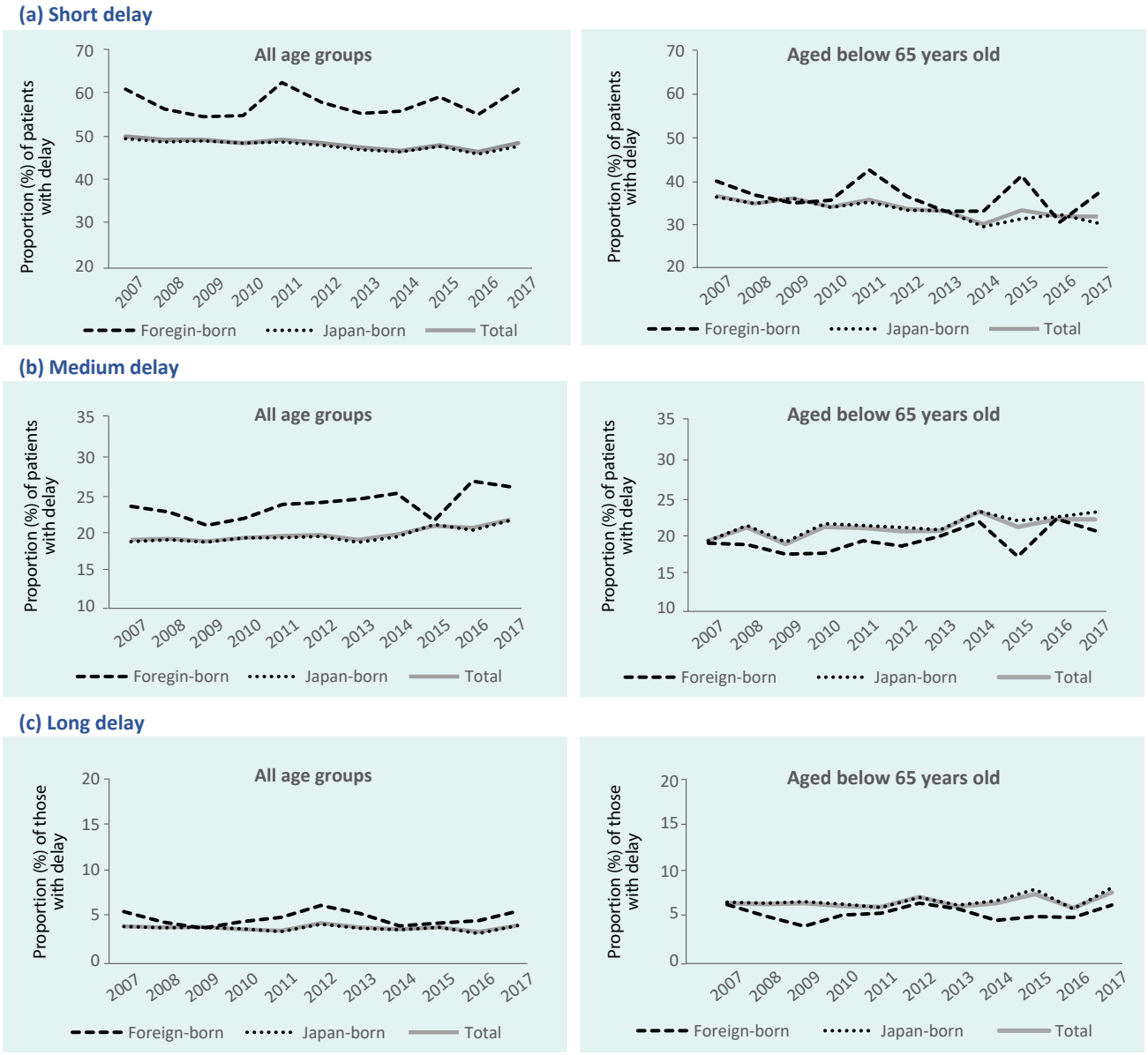
In the absence of a universal definition of patient delay, some international guidelines have stated that all patients with unexplained cough lasting 2 to 3 weeks or longer should be evaluated for TB.[10] In fact, definitions of patient delay have varied from 7 to 60 days in previous studies.[5,11,12] Our study is unique in that it is the first detailed study of the trends in and risk factors for patient delay in Japan to use three categories, namely short, medium and long.

We found that the proportions of those with short delay steadily declined during the study period ($P < 0.001$), while the proportions of those with medium or long delay have been constant or even increased ($P = 0.0015$ and $P < 0.001$, respectively), indicating that patient delay remains a major challenge, even in a country where UHC was achieved decades ago.

Although the proportions of those with any delay tended to be higher among foreign-born patients for all age groups and higher for medium or long delay among Japan-born patients younger than 65 years, country of birth was not a significant factor in the multinomial regression analysis.

However, our study identified not having health insurance as one of the key risk factors for patient delay. Previous studies have not agreed on the influence of health insurance, with some suggesting that a lack of health insurance affects patient delay,[13] while others

Fig. 2. **Annual trends in the proportion of patients with pulmonary tuberculosis and (a) short delay (≥2 weeks to <2 months), (b) medium delay (≥2 months to <6 months) or (c) long delay (≥6 months) in seeking care, by birthplace (born in Japan or outside of Japan) and age group, Japan, 2007–2017**



have not found this.[14] To a certain extent, the inconsistency may reflect country-level differences in health insurance systems and patient eligibility. In Japan, under UHC all residents, including foreign-born persons, are expected to be covered by national health insurance schemes. However, the number of those who are unable or unwilling to pay their premiums has been increasing recently, leading to widening health disparities among people in Japan.[15] Those who fail to pay the premium for more than 18 months are disqualified from receiving health insurance benefits; in the event of disqualification, they must pay the full cost of medical services after each visit to a medical facility.[16] According to a report from the Japan Medical Practitioner's Association, the frequency of outpatient clinic utilization was significantly lower among those without health insurance – that is, it was one seventieth of those with health insurance.[17] Such a study strongly indicates that not having health insurance is a serious barrier to accessing health care; our study found that TB patients are not an exception.

Receiving public assistance was another risk factor for patient delay. In Japan, public assistance is available to low-income households that are not capable of paying

Table 1. **Characteristics of patients with symptomatic pulmonary tuberculosis with and without delay in seeking care, by length of delay, Japan, 2007–2017 (n = 88 351)**

Category[a]	Patient delay[b]						No delay	
	Short		Medium		Long			
	n	%	n	%	n	%	n	%
TOTAL	26 746	100	13 394	100	3 151	100	45 060	100
Sex								
Male	17 351	64.9	8 890	66.4	2 195	69.7	28 778	63.9
Female	9 395	35.1	4 504	33.6	956	30.3	16 282	36.1
Age group (years)								
0–24	969	3.6	498	3.7	115	3.6	1 209	2.7
25–44	4 102	15.3	2 348	17.5	660	20.9	4 894	10.9
45–64	5 410	20.2	3 475	25.9	1 065	33.8	6 591	14.6
≥65	16 265	60.8	7 073	52.8	1 311	41.6	32 366	71.8
Country of birth								
Japan-born	24 556	91.8	12 284	91.7	2 864	90.9	41 993	93.2
Foreign-born	1 299	4.9	681	5.1	172	5.5	1 544	3.4
Unknown	891	3.3	429	3.2	115	3.6	1 523	3.4
Health insurance								
Covered	23 690	88.6	11 501	85.9	2 587	82.1	40 425	89.7
Public assistance	2 155	8.1	1 195	8.9	349	11.1	3 449	7.7
No insurance	307	1.1	328	2.4	99	3.1	264	0.6
Others	594	2.2	370	2.8	116	3.7	922	2
Job category								
Full-time workers	7 036	26.3	3 909	29.2	1 071	34	8 561	19
Temporary workers	1 252	4.7	822	6.1	222	7	1 370	3
Students	442	1.7	238	1.8	41	1.3	574	12.7
Unemployed	16 822	62.9	7 775	58	1 634	51.9	32 770	72.7
Others	767	2.9	390	2.9	107	3.4	1 099	2.4
Unknown	427	9.3	260	1.9	76	2.4	686	1.5
History of homelessness								
Yes	440	2.6	343	4	117	6	421	1.5
No	13 886	82.6	6 834	79.8	1 499	76.2	22 798	83.4
Unknown	2 485	14.8	1 383	16.2	350	17.8	4 113	15
Respiratory symptoms								
Yes	21 729	81.2	11 417	85.3	2 748	87.2	33 502	74.3
No	5 017	18.8	1 977	14.8	403	12.8	11 558	25.7
Sputum smear								
Positive	17 495	65.4	9 909	74	1 205	73.1	25 802	57.3
Negative	9 070	33.9	3 413	25.5	829	26.3	18 950	42.1
Not tested	136	0.5	47	0.4	13	0.4	232	0.5
Unknown	45	0.2	25	0.2	5	0.2	76	0.2

[a] Public assistance denotes those who were receiving social welfare benefit at the time of diagnosis. Covered indicates those who had health insurance. Full-time workers are those who were employed full-time on a mid- to long-term contract. Temporary workers are those who were employed part-time or on a short-term contract. History of homelessness refers to those who had been homeless within 1 year of diagnosis. Respiratory symptoms included cough, sputum, bloody sputum, and haemoptysis.

[b] Delays were defined as short (≥2 weeks to <2 months), medium (≥2 months to <6 months) or long (≥6 months).

health insurance premiums – such as households in which people have a long-term illness or disability or are headed by a single parent – and those receiving social welfare are totally exempt from health insurance premiums as well as out-of-pocket payments. Indeed, a recent report by a governmental working group on social welfare described a higher frequency of hospital visits among those receiving public assistance compared with those covered under other health insurance schemes.[18] In contrast, several studies have suggested that those receiving

Table 2. **Results of the multinomial regression analysis for odds ratio (95% confidence interval [CI]) for delays in seeking care among patients with pulmonary tuberculosis, Japan, 2007–2017**

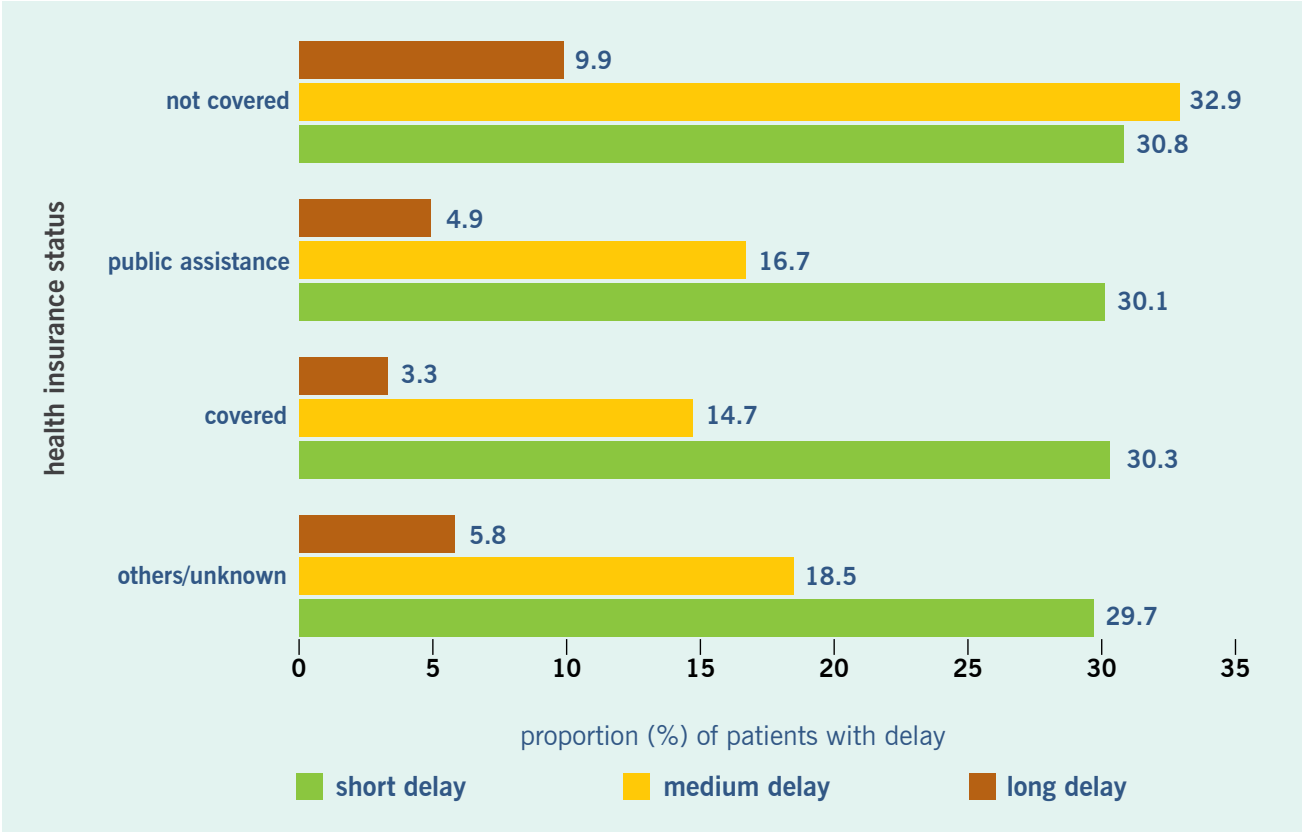
Category (reference group)	Patient delay[a]					
	Short		Medium		Long	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex (female)						
Male	1 (0.65 to 1.04)	0.84	1.01 (0.96 to 1.07)	0.68	1.17 (1.06 to 1.31)	<0.05
Age (25−44 years)						
0–24	0.93 (0.81 to 1.06)	0.27	0.91 (0.78 to 1.07)	0.27	0.95 (0.72 to 1.25)	0.72
45–64	0.99 (0.92 to 1.06)	0.68	1.05 (0.96 to 1.14)	0.28	1.08 (0.94 to 1.24)	0.29
>65	0.75 (0.69 to 0.80)	<0.05	0.6 (0.55 to 0.65)	<0.05	0.38 (0.32 to 0.44)	<0.05
Job (students)						
Full-time workers	1.14 (0.95 to 1.37)	0.17	1.13 (0.91 to 1.42)	0.27	1.72 (1.01 to 2.67)	<0.05
Temporary workers	1.22 (1.00 to 1.49)	<0.05	1.34 (1.05 to 1.70)	<0.05	1.99 (1.25 to 3.16)	<0.05
Unemployed	0.86 (0.71 to 1.04)	0.12	0.83 (0.66 to 1.04)	0.11	1.3 (0.83 to 2.03)	0.25
Others	1.05 (0.87 to 1.27)	0.65	1.06 (0.84 to 1.34)	0.61	1.83 (1.17 to 2.87)	<0.05
Insurance (covered)						
No insurance	1.63 (1.33 to 2.00)	<0.05	2.81 (2.29 to 3.46)	<0.05	2.75 (2.03 to 3.71)	<0.05
Public assistance	1.06 (0.98 to 1.14)	0.15	1.19 (1.09 to 1.31)	<0.05	1.36 (1.16 to 1.60)	<0.05
Others	1.06 (0.89 to 1.26)	0.54	1.27 (1.04 to 1.54)	<0.05	1.53 (1.12 to 2.08)	<0.05
History of homelessness (no history)						
Yes	1.46 (1.26 to 1.69)	<0.05	1.73 (1.47 to 2.04)	<0.05	2.09 (1.63 to 2.67)	<0.05
History of treatment (yes)						
No	1.1 (1.02 to 1.18)	<0.05	1.29 (1.17 to 1.42)	<0.05	1.27 (1.05 to 1.52)	<0.05
Symptoms (no respiratory symptom)						
Respiratory symptoms	1.5 (1.42 to 1.58)	<0.05	1.8 (1.67 to 1.93)	<0.05	1.89 (1.63 to 2.19)	<0.05
Diagnosed with diabetes (No)						
Yes	1.13 (1.07 to 1.20)	<0.05	1.23 (1.15 to 1.32)	<0.05	1.14 (1.00 to 1.30)	<0.05

[a] Delays were defined as short (≥2 weeks to <2 months), medium (≥2 months to <6 months) or long (≥6 months).

public assistance had a low participation rate in community health screenings[19] and a higher smoking rate.[20,21] As smoking is often perceived as being associated with non-specific "smoker's cough," it has been identified by several studies as a risk factor for patient delay among TB patients.[22,23] In other words, there may be confounding effects between smoking and receiving public assistance. Another study has suggested that even among those receiving public assistance, participation rates in community health checks were lower among those who had been receiving public assistance for longer than 5 years and among those who had not had any health insurance before receiving public assistance.[24] Further studies are necessary to explore the health-seeking behaviour of TB patients who are receiving public assistance.

Our results also indicated that being a temporary worker and having a history of homelessness are risk factors for patient delay, consistent with previous studies from Japan.[25–27] In fact, the populations of temporary

Fig. 3. **Proportions of patients with pulmonary tuberculosis with delays in seeking care, by health insurance status, Japan, 2007–2017[a]**



[a] Delays were defined as short (≥2 weeks to <2 months), medium (≥2 months to <6 months) or long (≥6 months).

laborers and homeless people overlap, as temporary laborers may lack permanent addresses and, thus, may be classified as homeless, and people who are truly homeless often earn income from ad hoc jobs, such as construction and cleaning. The fear of losing income or a job as a result of taking time off from work to seek health care or being diagnosed with an illness are major barriers to seeking health care among people with precarious job situations.[26]

TB control activities specifically targeting homeless people have been in place in several urban areas in Japan, including mobile screening by chest X-ray, free screening at accommodation for people seeking asylum and screening upon moving into affordable housing.[28,29] Yet various studies continue to indicate that homeless people have limited access to health care for a variety of sociopsychological and economic reasons.[30,31] One of the major issues in TB control among homeless people is the increasing diversification of the profile of so-called homeless people, a label that can include elderly people without night-time shelter, middle-aged men living on day-to-day jobs and sleeping in internet cafes, and teenagers who cannot live with their parents and so move from one friend's house to another.[32] Traditional outreach services, such as mobile screening on streets and in shelters, may not reach a significant proportion of people who are classified as homeless.

Two distinct factors were associated with long delays, namely being male and being a full-time worker. A study from Osaka city, Japan, similarly reported that TB patients with a job were more likely to delay seeking care compared with those without a job.[26] In the same study, the authors compared the reasons for not seeking care promptly among those who delayed seeking care and those who did not and revealed that the proportion of those who had been too busy with work and were unable to take time off was significantly higher among those who delayed seeking care. In another study that examined participation rates for general medical check-ups, the authors similarly reported that compared with those without jobs, a higher proportion of those with jobs did not participate in medical check-ups.[33]

In our study, being male was an independent risk factor for long delay. However, contrary to our findings, a systematic review of delay among TB patients in Asia reported that being male was significantly associated with shorter patient delay.[34] TB prevalence is generally higher among men, possibly leading to a greater awareness of TB and subsequent health-care-seeking behaviour among men compared with women; women also may face greater financial and cultural barriers to seeking care. However, a different study concluded that the higher prevalence of TB among men was precisely due to a longer delay before diagnosis.[35] Further analyses should explore the inconsistencies in these findings; however, several studies on health-seeking behaviour in Japan have shown that men are generally less motivated to participate in medical check-ups[36] and community screening opportunities.[37]

Being diagnosed with TB for the first time (i.e. being a new case), having respiratory symptoms and having DM as a co-morbid condition were also identified as risk factors for patient delay. A new case may be considered to be a proxy for a lack of or limited knowledge of TB, which has been reported to hinder patients from accessing care; several studies have shown that individuals with a previous history of TB were more likely to seek care earlier because of their previous exposure to the disease and TB-related services and also, potentially, their increased knowledge.[38,39] Conclusions from previous studies on the association between patient delay and symptoms have been contradictory: while some have shown that patients with symptoms tended to seek care early,[40,41] others have found the opposite, which was attributed to the possibility that patients did not consider their symptoms serious enough to need health care.[42] In our study, a similar explanation may be possible. Because our definition of respiratory symptoms included non-severe and general symptoms, such as cough, it is possible that patients misjudged their illness. As for DM, a previous study in Japan on DM among patients with PTB also similarly reported a longer delay among those with DM.[43] It has been previously reported that, in general, patients with DM are less willing to seek medical care,[44] and the authors suggested that this may have also affected delays in seeking TB care.

Finally, being aged 65 years or older was identified as a protective factor against patient delay. Similar results have been reported from other countries, including Norway[45] and Italy.[46] It has been suggested that elderly patients often have coexisting illnesses and thus routinely visit hospitals, thereby increasing the likelihood of seeking care when they have TB-related symptoms.

Our study has several limitations. First, patients for whom there was no information regarding their delay in seeking care were excluded from our analyses. Some of these patients eventually died as a result of an extremely long delay, but because the patients were already too sick at the time of diagnosis, public health nurses were unable to interview them and collect the data that allow us to calculate the length of delay. In the surveillance data, approximately one third of patients had no information on delay, and, as such, it is possible that our results may underestimate the real magnitude of patient delay. Second, because we analysed data from the JTBS system, other potential risk factors, such as smoking, could not be considered. The results of our study should be interpreted along with results from local studies that have used local data held by public health centres. Last, as the onset date of symptoms was self-reported by patients, it could have been affected by recall bias.

Interventions to prevent patient delay should be designed to address specific risk factors. Providing waivers for out-of-pocket expenses under certain conditions, especially for those without health insurance, and providing a sickness allowance for those with precarious work situations would potentially improve access. Furthermore, it is equally important to implement more general interventions to improve the working environment to allow workers to take leave to seek medical services without feeling ashamed or guilty. Actions taken within the health sector alone cannot achieve and maintain UHC, and increasing effort is required to build the capacity for multisectoral approaches. Community health screening tailored to those who do not have health insurance or are receiving social welfare could help early case detection, especially if undertaken in collaboration with municipal health authorities. Activities to increase the awareness of TB symptoms should also be strengthened, especially among groups likely to have longer delays seeking care, particularly men and full-time workers.

CONCLUSIONS

In spite of the implementation of UHC decades ago in Japan, a detailed analysis of surveillance data has revealed that patient-led delays in TB diagnosis are still a major

challenge. This study's results identified various risk factors, many of which could be mitigated by implementing appropriate social protection measures, indicating the shortcomings of UHC in Japan and the need for continued effort to ensure that no one is left behind.

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Ongoing rubella epidemic in Osaka, Japan, in 2018–2019

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Rubella is a typically mild contagious disease caused by the rubella virus.[1] However, when a pregnant woman is infected with rubella virus, fetal death or congenital rubella syndrome (CRS) can occur.[1] The number of rubella and CRS cases has been reduced in many countries as a result of rubella vaccinations.[2] To prevent the occurrence of CRS, the World Health Organization (WHO) Global Vaccine Action Plan 2011–2020 set the goal of achieving rubella elimination in at least five WHO regions by 2020.[3]

In Japan, an estimated 100 000 cases of rubella occurred every year and outbreaks occurred approximately every 5 years until about 1990. With routine immunizations, the scale of the epidemics has been shrinking and the length of time between epidemics has been growing longer. The last outbreak occurred in 2012–2013, with more than 17 000 cases of rubella and 45 cases of CRS.[4] From 2013 to mid-2018, only sporadic or imported cases of rubella were reported in Japan.[4,5] However, an upsurge of rubella cases was observed between July and August 2018 in the south Kanto region (Chiba, Kanagawa and Tokyo prefectures), and epidemics were subsequently reported in regions of Japan.[6] In 2018, 2917 cases of rubella were reported, marking the second largest epidemic since 2008, when rubella was classified as a notifiable disease in Japan.[6] During the first half 2019, 1935 cases of rubella and three cases of CRS were reported.[7] The characteristics of rubella epidemics in Osaka prefecture are described in this text. We also speculate about the cause of the nationwide epidemics.

In total, 123 cases of rubella were reported in 2018 and 118 cases were reported in 2019 (weeks 1–27) (**Fig. 1a**). The first rubella case in Osaka prefecture was reported in week 17 of 2018 (**Fig. 1a**). After the third case was reported in week 34 of 2018, cases of rubella were regularly reported until week 20 of 2019. Among 241 cases reported in 2018–2019, 176 (73.0%) occurred in males. The median patient ages were 40 (range: 1–71) years for males and 32 (range: 0–65) years for females. Vaccination history was unknown in most cases (163 cases, 67.6%), followed by no history of vaccination (57 cases, 23.7%), one dose (18 cases, 7.5%), and two-doses (three cases, 1.2%).

Among the 241 cases reported in 2018-2019, genotypes could be determined in 119 cases. Genotypes were classified as genotype 1E (118/119; 99.2%) and 2B (1/119; 0.8%) (**Fig. 1b**). All genotype 1E strains belonged to genotype 1E lineage 2, and the genotype 2B strain belonged to genotype 2B lineage 1 (**Fig. 1b**).[8] All genotype 1E strains detected after week 34 of 2018 in Osaka prefecture were closely related to each other with 99.2–100% nucleotide identity and the representative strains detected before and after week 34 in the Kanto region (accession numbers: LC466969, LC422203, LC422829, LC422204 and LC422205) with 100% nucleotide identity.

The rubella epidemic in Osaka prefecture was part of a large ongoing epidemic of rubella across Japan. Most patients were adult males born on or before 1 April 1979, who had not been targeted for routine rubella immunization during childhood, and males and females born on or after 2 April 1979 with low vaccination coverage. After the 2012–2013 epidemic, the seropositive proportion (haemagglutination-inhibition antibody titre ≥1:8) of the total population remained steady at 91.0% (5148/5656). However, among males in their 30s to 50s the seropositive proportion was 84.2% (974/1157) in 2017, in line

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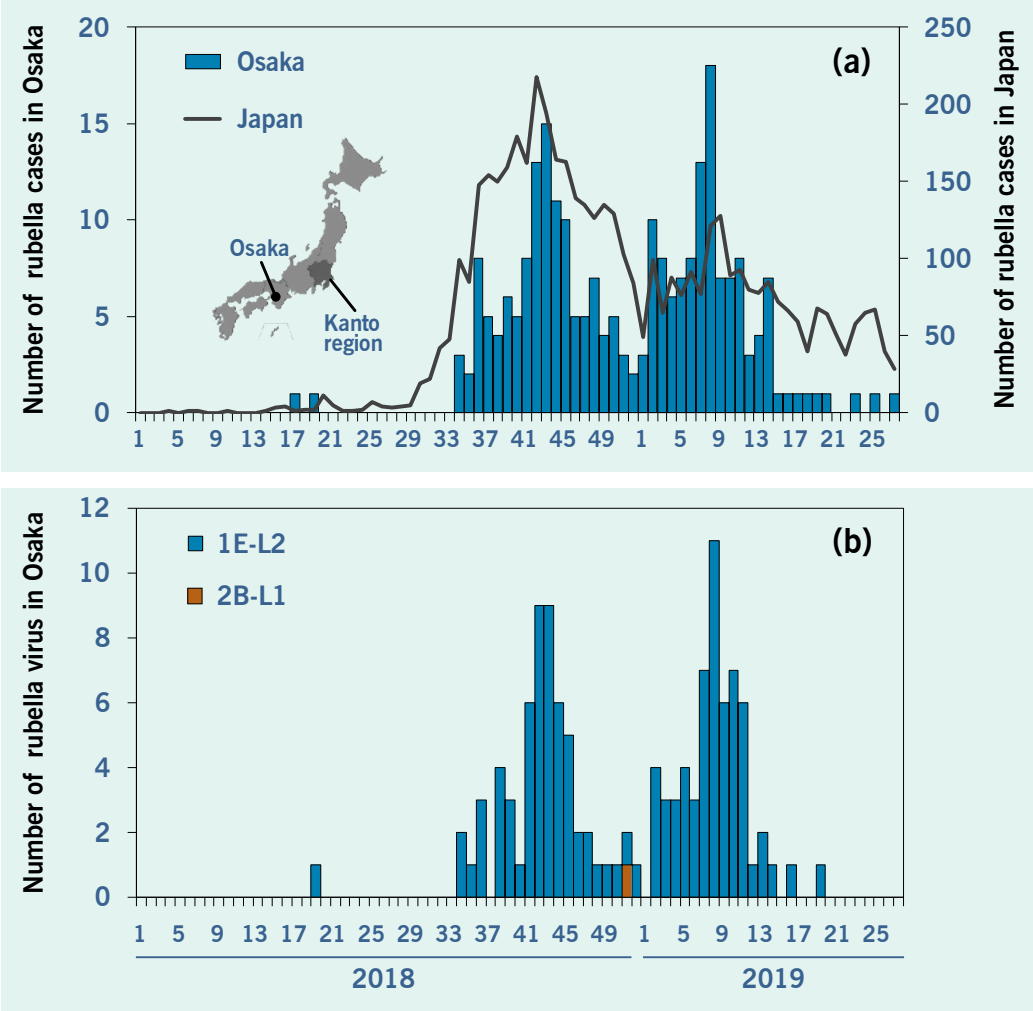
Fig. 1 **Weekly distribution of (a) the number of reported rubella cases and (b) the number of detected rubella viruses in 2018–2019**



Suspected cases of rubella were identified according to the diagnostic criteria of the Ministry of Health, Labour and Welfare of Japan. These criteria include a fever, systemic rashes and lymphadenopathy. All of the patients with clinically diagnosed rubella were immediately reported to the local government from all hospitals and clinics in Osaka under the law of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. In principle, specimens (including blood, throat swabs and urine) were collected from almost all patients with rubella and used for nucleic acid amplification testing (NAT) because it has been obligatory for all cases to be confirmed via NAT since January 2018. For NAT-positive specimens, the molecular window region (739 nucleotides; 8731–9469) within the E1 protein-coding region was amplified and sequenced.[8] All sequences were submitted to GenBank (deposited in GenBank under accession numbers LC406753, LC428034 LC428032, LC428033, LC428035, and LC485342–LC485455). The genotype and lineage were determined via maximum-likelihood phylogram of the molecular window region (739 nucleotides) within the E1 protein-coding region using MEGA version 7.0 (https://www.megasoftware.net/) and the Tamura-Nei model (data not shown). The data for the weekly distribution of rubella in Japan were retrieved from the website of the National Institute of Infectious Diseases of Japan.[6,7]

with that observed before the 2012–2013 epidemic in Japan.[9] Therefore, insufficient vaccine coverage may have created a situation in which a new epidemic of rubella emerged in Japan when rubella virus was imported.

The 2012–2013 epidemic was caused by rubella virus strains with a variety of genetic backgrounds, suggesting that these strains were introduced from multiple sources.[8] In contrast, the 2018–2019 epidemic was mainly caused by rubella virus strains with the same or very close genetic background. It is unclear whether the 2018–2019 rubella epidemic was caused by the expansion from a single source or several sources in Kanto region. This is because the epidemiological link of most cases is unclear, which is a limitation of the current study. The number of rubella cases related to importation from South-eastern and East Asia doubled in Japan in 2018, compared with the number over the past four years.[10]

We believe that the epidemic may be in part attributable to immunization strategies that left a susceptible population in Japan as well as potential introduction of

rubella virus from other countries. Although the WHO position paper on rubella vaccines, published in July 2011, stated that the effect of a selective immunization policy is limited,[11] the current outbreak highlights that high vaccination coverage with two doses of a rubella-containing vaccine targeting children as well as adults who are hard-to-reach and vulnerable is needed to eliminate rubella. The Ministry of Health, Labour and Welfare of Japan began subsidizing antibody testing and vaccination costs for 16.1 million adult males to raise the vaccine coverage, as indicated by rubella antibody seropositivity of the target generation to at least 90% by the end of 2021. The lessons learnt from this outbreak can be of value to achieve rubella elimination for other countries that have introduced or have planned selective immunization policies.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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