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Staphylococcal poisoning during a village festival, Medina, Misamis Oriental, Philippines in 2014

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Introduction: On 18 August 2014, cases of food poisoning in San Vicente Village were reported to the Event-Based Surveillance & Response Unit of the Philippine Department of Health. An investigation was conducted to identify the implicated source, describe the outbreak and evaluate the risk factors.

Methods: A case-control study was conducted. A suspected case was a previously well individual of Medina who attended the village festival and developed abdominal pain and vomiting with or without nausea, diarrhoea and fever from 18 to 19 August. A confirmed case was a suspected case with a rectal swab positive for bacterial culture. Rectal swabs, water and food samples were sent to the national reference laboratories. Food source and consumption interviews and environmental inspections were conducted.

Results: Sixty-four cases and 123 unmatched controls were identified. The median incubation period was 1 hour 15 minutes. Five cases (8%) were positive for *Staphylococcus aureus,* one (2%) for *Aeromonas hydrophilia* and one (2%) for *Shigella boydii.* One (14%) water sample was positive for *Aeromonas spp.* Of the collected food samples, beef steak was positive for *Staphylococcus aureus*. Risk factors were consumption of Filipino-style beef stew (odds ratio [OR]: 6.62; 95% confidence interval [CI]: 2.90–15.12) and stir-fried noodles (OR: 3.15; 95% CI: 1.52–6.50). Prolonged serving time and improper food storage were noted.

Discussion: In this foodborne outbreak, *Staphylococcus aureus* was the likely causative agent. Meals were contaminated due to improper food handling practices. We recommend that a policy be created to mandate that village-appointed food handlers undergo food safety training.

Staphylococcus aureus is a Gram-positive bacterium that is predominantly associated with food poisoning[1] and causes one of the most common foodborne illnesses worldwide.[2] About 25% of healthy people are carriers of *Staphylococcus aureus*. The bacterium is associated with skin, eye, nose or throat infections.[3] The most common way for food to be contaminated by the bacteria is through contact with infected food handlers. Other food contamination sources are the equipment or surfaces on which food is prepared[3] and infected house flies.[4] When food is contaminated, bacteria quickly multiply at room temperature and produce a fast acting enterotoxin[5] that can cause nausea, abdominal pain, vomiting and diarrhoea.[1]

On 18 August 2014, the Event-Based Surveillance & Response Unit of the Philippine Department of Health received a report of food poisoning among villagers of San Vicente Village, a rural village in Medina, Misamis Oriental on the island of Mindanao. The village is subdivided into seven areas and has a total population of 978.[6] Every 18 August, the village celebrates its founding with a festival with free meals for all community members.

A team from the Philippines Field Epidemiology Training Program was deployed to conduct an epidemiologic investigation to identify the implicated source, describe the outbreak and evaluate the risk factors.

METHODOLOGY

Epidemiologic investigation

A descriptive study was conducted by reviewing medical records of outpatients and inpatients at the local hospitals. A suspected case was defined as a previously well indi-

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vidual of Medina, Misamis Occidental who attended the village festival and developed abdominal pain and vomiting with or without nausea, diarrhoea and fever from 18 to 19 August 2014. A confirmed case was a suspected case with a positive rectal swab in bacterial culture.

An unmatched case-control study was conducted. Controls were individuals of Medina who attended the village festival and did not develop any symptoms and were negative on bacterial stool cultures. Subjective sampling from suspected and confirmed patient lists was used to identify cases for the study. Controls were identified from the same household and/or nearby households of the cases. Cases and controls were interviewed using a standard questionnaire that included demographics, symptoms (except for controls), history of food consumption within the past 24 hours, source of drinking-water, hygiene practices and other environmental factors.

Statistical analysis, including calculation of odds ratios (OR) and 95% confidence intervals (CI), was done using EpiInfo version 3.5.4 software. Significant bivariate analysis results were then tested by multivariable analysis.

Laboratory examinations

Rectal swabs were collected for culture and sensitivity testing from cases and controls including food handlers. Water samples from the water reservoir and communal faucets were collected for bacteriologic analysis. Both were sent to the national reference laboratories. Food samples were sent to the Food and Drug Administration Satellite Laboratory for Mindanao for bacteriologic analysis.

Environmental investigation

We visited the food handling and preparation area and water sources. We interviewed food handlers on the food production chain, food consumption history and presence of signs and symptoms.

Ethical approval

Ethics clearance was not required according to local regulations as this investigation was part of an emergency response to an outbreak. However, a signed consent was obtained before interviews and specimen collection.

RESULTS

Case-control study

All 64 cases (57 suspected and seven confirmed) and 123 controls were included in the study. All cases and 121 controls ate food served at the festival. Six out nine food handlers were included in the case-control study. One food handler did not meet the definition of case or control, and two others could not be located for the study. All of the interviewed food handlers fit the control definition. All of the individuals approached agreed to be involved in the study.

The first case manifested signs and symptoms in less than 15 minutes after ingestion of food. The number of subsequent cases peaked by 14:00. The median incubation period was 1 hour 15 minutes (range: 10 minutes to 16.98 hours). No deaths were reported (**Fig. 1**). All cases had abdominal pain and vomiting. Other symptoms reported were nausea (88%), diarrhoea (52%) and fever (16%). There were 40 (63%) female cases; ages ranged from 1 to 75 years (median: 22 years, interquartile range: 7 to 38 years). The most affected age group was 21–35 years (25%).

Bivariate analysis revealed that consumption of Filipino-style beef stew (OR: 8.16, 95% CI: 3.77–17.66) and stir-fried noodles (OR: 2.38; 95% CI: 1.28–4.40) were risk factors for food poisoning (**Table 1**). After adjusting for demographics and exposure variables, consumption of Filipino-style beef stew (OR: 6.62; 95% CI: 2.90–15.12) and stir-fried noodles (OR: 3.15; 95% CI: 1.52–6.50) remained statistically significant risk factors for food poisoning. On the contrary, consumption of pork humba (OR: 0.42; 95% CI: 0.20–0.89) and Filipino-style pork stew (OR: 0.22; 95% CI: 0.06–0.83) were inversely associated with being a case.

Laboratory examinations

A rectal swab was collected from each of the 64 cases and 123 controls. Of the samples from cases, five (8%) were positive for *Staphylococcus aureus,* one for (2%) for *Aeromonas hydrophilia* and one (2%) for *Shigella boydii.* However, 45 (70%) of the cases were given antibiotics before specimen collection. All controls showed no growth in the bacterial culture test. One out of the seven (14%) rectal swab cultures from food handlers was positive for *Aeromonas sobria.*

Fig. 1. **Distribution of foodborne illness cases by onset of illness (n = 64), San Vicente Village, Medina, Misamis Oriental, Philippines, 18–19 August 2014**

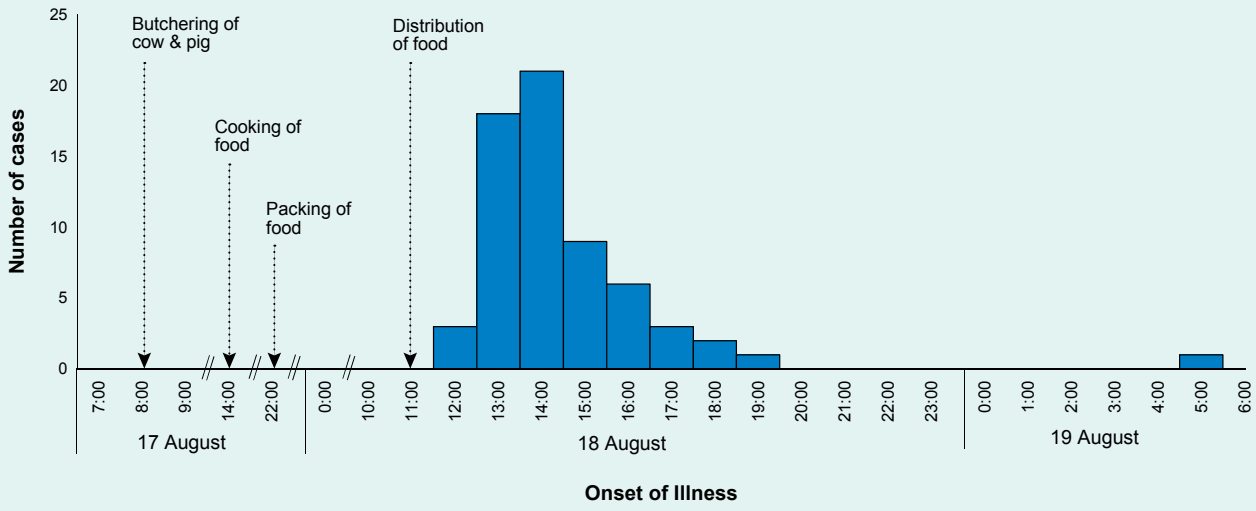

Table 1. **Factors associated with staphylococcal foodborne illness cases, San Vicente Village, Medina, Misamis Oriental, Philippines, 18-19 August 2014**

Factors	Case *n* (%)	Control *n* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	24 (37)	63 (51)	0.57 (0.31–1.06)	-
Female	40 (63)	60 (49)		
Type of food consumed*				
Filipino-style beef stew	30 (47)	12 (10)	8.16 (3.77–17.66)	6.62 (2.90–15.12)
Stir-fried noodles	37 (58)	45 (37)	2.38 (1.28–4.40)	3.15 (1.52–6.50)
Beef innards stew	2 (3)	3 (2)	1.29 (0.11–11.60)	-
Beef curry	7 (11)	11 (9)	1.25 (0.46–3.40)	-
Pork curry	0 (0)	0 (0)	-	-
Rice	47 (73)	91 (74)	0.97 (0.49–1.93)	-
Beef steak	33 (51)	80 (65)	0.57 (0.31–1.06)	-
Pork humba	19 (30)	62 (50)	0.42 (0.22–0.79)	0.42 (0.20–0.89)
Filipino-style pork stew	3 (5)	27 (22)	0.17 (0.03–0.61)	0.22 (0.06–0.83)
Other factors				
Washed hands before eating	63 (98)	118 (96)	1.06 (0.09–11.90)	-
Used both spoon and fork to eat	60 (94)	116 (94)	0.52 (0.09–2.89)	-
Boiled drinking-water	25 (39)	70 (57)	0.49 (0.26–0.90)	-
Washed hands after toilet use	62 (97)	119 (97)	0.26 (0.02–2.91)	-
Consumed packed lunch	64 (100)	121 (98)	-	-
Drank from communal faucet	64 (100)	123 (100)	-	-

OR, odds ratio; CI, confidence interval.

* May have had more than one response.

One out of the eight (13%) water samples collected was found to be positive for *Aeromonas species.*

Beef steak and rice were the only leftover food samples collected. Bacterial culture revealed that the beef steak was positive for *Staphylococcus aureus;* the culture from the rice yielded no bacterial growth.

Environmental investigation

Seven out of the nine village-appointed food handlers were interviewed. All were asymptomatic. Food source investigation revealed that a cow and a pig were bought from a local farm, while the vegetables and commercially prepared seasonings came from a nearby market. Animals were slaughtered in an open space at the town hall by 08:00 on 17 August 2014 (the day before consumption). Meat and entrails were butchered to desired cuts. Cooking of dishes started by 14:00 with beef dishes prepared first followed by the pork dishes. The cooking process ended by 22:30. Water from communal faucets was used to wash raw ingredients and for cooking. Cooked dishes were cooled in a separate room and covered with banana leaves.

Meals were packed between 22:45 on 17 August 2014 and 06:00 the following day. Two varieties of dishes were packed in a "chorizo-like" manner where one plastic bag was used (**Fig. 2**). Packed meals were stored in either a plastic tray, carton box or empty rice sack at room temperature.

By 11:30, packed meals were distributed among villagers.

No food handlers wore aprons or hair nets during food preparation. They did not have formal food safety training, and proper hand hygiene was not observed. Flies were also claimed to be present during food preparation.

No chlorine residue was noted inside the water reservoir, and breakage in water distribution pipelines was seen.

DISCUSSION

The epidemiological evidence suggests that the most likely source of this foodborne outbreak was the consumption of contaminated packed meals served during the village festival. The short incubation period (median 1 hour 15 minutes) and the symptoms manifested by cases suggest a *Staphylococcus aureus* enterotoxin poisoning. *Staphylococcus aureus* was seen in the human specimens and food samples (beef steak); both consumption of Filipino-style beef stew and stir-fried noodles were statistically most likely to be associated with the illness.

Fig. 2. **Packed meal**

The issue of food safety practices by the food handlers played a part in this outbreak. The observed improper food handling practices such as poor hand washing technique, prolonged serving time[2,7] and improper temperature for food storage[1,2,5,7] have been linked to staphylococcal foodborne outbreaks.

The isolation of *Aeromonas hydrophilia* and *Shigella boydii* in one of the cases could have been incidental to this outbreak. The typical incubation period of 12 to 72 hours[1] after ingestion of food contaminated by both bacteria does not coincide with the incubation period of the cases.

The Sanitation Code of the Philippines requires all food caterers, regardless of type and enterprise size, to secure sanitary permits and health certificates for all their employees before operation.[8,9] This policy only covers licensed food establishments. However, most foodborne outbreaks in the Philippines occur in home settings and at events where the food handlers are not trained on food safety.[10]

This study has some limitations. First, we were not able to locate and test all the food handlers. Second, a majority of the cases were already treated with antibiotics before stool collection. This may have contributed to low positivity rates in clinical specimens. Third, dose–response was not investigated. Fourth, there is the possibility of recall bias on the specific food exposure due to the retrospective nature of data finding. In spite of these limitations, we were able to identify the source of this outbreak from both the clinical and epidemiological results.

As a response to the outbreak, we recommended the reinforcement of the Sanitation Code of the Philippines by municipal governments through the release of an ordinance mandating that village-appointed food handlers secure updated health certificates and attend formal food safety training before engaging in mass feeding activities to prevent further outbreaks.

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Conflicts of interest

None declared.

References

1. Bad bug book (second edition). Silver Spring, MD: United States Food and Drug Administration; 2017 (https://www.fda.gov/food/foodborneillnesscontaminants/causesofillnessbadbugbook/).
2. Kadariya J, Smith TC, Thapaliya D. Staphylococcus aureus and staphylococcal food-borne disease: an ongoing challenge in public health. BioMed Res Int. 2014;2014:827965. doi:10.1155/2014/827965 pmid:24804250
3. Food poisoning: Staphylococcus. In: FoodSafety.gov [website]. Washington, DC: United States Department of Health & Human Resources; 2014 (https://www.foodsafety.gov/poisoning/causes/bacteriaviruses/staphylococcus/, accessed 14 October 2014).
4. Robertson J. The epidemiology of Staphylococcus aureus on dairy farms. Wisconsin: National Mastitis Council Proceedings Library (http://www.nmconline.org/articles/staphepid.htm, accessed 14 October 2014).
5. Javier R, Sy L, de los Reyes V, Sucaldito M, Tayag E. Staphylococcal food-borne illness among participants of Sui Generis Leadership Summit in Ateneo De Davao University on July 29, 2012. Scientific paper. 2013;23(3):2013. National Epidemiology Center.
6. 2010 Census of Population and Housing. Quezon City: National Statistics Office; 2012 (http://www.census.gov.ph/sites/default/files/attachments/hsd/pressrelease/Northern%20Mindanao.pdf, accessed 19 August 2014).
7. Michino H, Otsuki K. Risk factors in causing outbreaks of foodborne illness originating in schoollunch facilities in Japan. J Vet Med Sci. 2000 May;62(5):557–60. doi:10.1292/jvms.62.557 pmid:10852411
8. Implementing rules and regulations of Chapter III: food establishments of the Code on Sanitation of the Philippines (P.D. 856). Manila: Department of Health; 1995 (https://www.doh.gov.ph/sites/default/files/publications/Chapter_3_Food_Establishments.pdf).
9. Sanitation Code of the Philippines (2013). Republic Act No. 10611, August 23, 2013, Official Gazette of the Philippines (https://www.gov.ph/2013/08/23/republic-act-no-10611/, accessed 22 February 2017).
10. Rebato N, Ballera J, Hizon H, de los Reyes V, Sucaldito M, Magpantay R. No.4. A 10-year meta analysis of foodborne disease outbreaks, 2005–2015. Scientific paper. Volume 26. Epidemiology Bureau; 2016.

Assessment of the risk posed to Singapore by the emergence of artemisinin-resistant malaria in the Greater Mekong Subregion

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Objective: To assess the public health risk to Singapore posed by the emergence of artemisinin-resistant (ART-R) malaria in the Greater Mekong Subregion (GMS).

Methods: We assessed the likelihood of importation of drug-resistant malaria into Singapore and the impact on public health of its subsequent secondary spread in Singapore. Literature on the epidemiology and contextual factors associated with ART-R malaria was reviewed. The epidemiology of malaria cases in Singapore was analysed. The vulnerability and receptivity of Singapore were examined, including the connectivity with countries reporting ART-R malaria, as well as the preparedness of Singaporean health authorities. Sources of information include international journals, World Health Organization guidelines, data from the Singapore Ministry of Health and National Public Health Laboratory of the National Centre for Infectious Diseases, and the International Air Transport Association.

Results: The importation of ART-R malaria into Singapore is possible given the close proximity and significant travel volume between Singapore and the GMS countries reporting artemisinin resistance. Singapore's vulnerability is further enhanced by the presence of foreign workers from neighbouring endemic countries. Nonetheless, the overall likelihood of such an event is low based on the rarity and decreasing trend of imported malaria incidence.

With the presence of *Anopheles* vectors in Singapore, imported cases of drug-resistant malaria could cause secondary transmission. Nevertheless, the risk of sustained spread is likely to be mitigated by the comprehensive surveillance and control system in place for both infected vectors and human cases.

Discussion: This risk assessment highlights the need for a continued high degree of vigilance of ART-R malaria locally and globally to minimize the risk and public health impact of drug-resistant malaria in Singapore.

Despite remarkable global progress in the fight against malaria since 2010, growing resistance to antimalarial drugs remains the biggest challenge on the path towards malaria elimination.[1] To date, drug resistance has been recorded in *Plasmodium falciparum, P. vivax* and *P. malariae.*[2,3] The development of resistance by *P. falciparum* to nearly all antimalarial drugs, including current first-line treatments artemisinin and its derivatives, has become an issue of utmost concern. The Greater Mekong Subregion (GMS), which comprises Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand, Viet Nam and Yunnan Province of China, has long been the epicentre of antimalarial drug resistance.[4] The first cases of artemisinin resistance were reported in Cambodia in 2008.[5] Since then, artemisinin resistance has been observed in other countries in the GMS and in neighbouring India.[5,6] Concomitantly, variable levels of resistance to the partner drugs used in artemisinin-based combination therapies (ACTs) have been reported.[4]

Singapore is a globally connected city-state in South-East Asia with high travel connectivity with many countries in the world, including those in the GMS, due to its position as a travel and trade hub. Although Singapore has been declared malaria-free by the World Health Organization (WHO) since 1982, Singapore is at risk of importation of emerging diseases including artemisinin-

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resistant (ART-R) malaria. In view of the emergence of resistance across the GMS and the spread beyond its borders, we carried out an analysis to assess the risk of importation and secondary spread of ART-R malaria infection in Singapore.

METHODS

The risk of importation of drug-resistant malaria into Singapore and the public health impact of its subsequent secondary spread in Singapore were assessed following WHO guidance on the risk assessment of acute public health events.[7] The process of risk assessment included relevant literature review, epidemiological analysis of malaria cases in Singapore, analysis of the air travel volume between Singapore and countries reporting artemisinin resistance, an assessment of the vulnerability and receptivity of Singapore, and the preparedness of Singaporean health authorities to a potential (case/introduction/outbreak) of ART-R malaria. The risk assessment was conducted by four public health officers specializing in public health surveillance, epidemiology and risk analysis of infectious diseases. Their findings were reviewed by a broader group of experts from the Singapore Ministry of Health (MOH) in the areas of public health, laboratory medicine, epidemiology, infectious diseases, risk communication and emergency preparedness and response.

The epidemiology of malaria cases in Singapore was analysed based on information released by the MOH.[8] A qualitative review of the public health measures taken by Singapore in response to the emerging threat was conducted based on information released by the MOH and the Singapore National Environment Agency (NEA). The volume of travellers on commercial flights originating from countries with ART-R malaria and with final destinations in Singapore in 2017 was analysed using data from the International Air Transport Association (IATA) in Singapore. The IATA data are reported monthly and contain anonymized, itinerary-level passenger volumes. The data capture an estimated 90% of the world's air traffic, with the remainder being imputed using market intelligence. Full itineraries of the travellers have been used, including the initial airport of embarkation, final destination and any connecting flights. IATA data have been used previously to inform risk assessments of the spread of pathogens of epidemic potential.[9] Among the imported *P. falciparum* cases, the monitoring of artemisinin resistance based on the Kelch 13 (K13) gene was performed by the Malaria Reference Centre from the National Public Health Laboratory (MRC-NPHL) by polymerase chain reaction (PCR) amplification and sequencing according to the protocol of Ariey et al.[10]

RISK ASSESSMENT

Hazard assessment

Malaria is caused by *Plasmodium* parasites that are transmitted to people through the bites of female *Anopheles* mosquitoes with infectious sporozoites of malaria parasites.[11] Five *Plasmodium* species cause malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. *P. falciparum* is responsible for most malaria-related deaths globally and is the most prevalent malaria parasite in Africa, while *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa including those in South-East Asia.[1] The first symptoms of malaria—fever, headache, chills and vomiting—usually appear between 10 to 15 days after a bite from a vector mosquito with infectious sporozoites of malaria parasites. Without prompt diagnosis and treatment, *P. falciparum* malaria can rapidly progress to severe illness and death.[11] Currently, the most effective treatments are ACTs.[12,13]

Drug resistance has been one of the greatest challenges in fighting malaria. Resistance usually develops progressively, from the initial delay of parasite clearance in a few locations to the gradual expansion of geographic range and increase in prevalence, eventually leading to treatment failure. Of the various antimalarial drugs available, chloroquine was the agent of choice for many years because of its safety, efficacy and affordability. However, since its first detection along the border of Cambodia and Thailand in 1957, resistance of *P. falciparum* to chloroquine has spread to almost everywhere that *P. falciparum* exists.[14] *P. falciparum* has also developed resistance to nearly all other available antimalarial drugs, including sulfadoxine, pyrimethamine, amodiaquine, mefloquine, piperaquine, atovaquone and an increasing frequency of reported quinine resistance in several regions.[15]

The first clinical evidence of artemisinin resistance originated in western Cambodia in 2008; however, further retrospective studies of molecular markers have indicated that artemisinin resistance likely emerged before 2001 and the widespread usage of ACTs.[5,16,17] The extensive and often suboptimal usage of monotherapies

as well as the genetic background of parasites in the GMS were thought to have contributed to the development of resistance.[18] Since then, emergence of resistance to artemisinin and ACT partner drugs such as piperaquine have been reported in other areas in the GMS.[19,20] Nevertheless, most patients with delayed parasite clearance can still be cured using ACTs as long as the partner drug remains effective; there is no evidence that higher levels of artemisinin resistance (full resistance) have emerged.[4]

Exposure assessment

Reports of imported malaria infections in Singapore

In Singapore, malaria was the most common vector-borne disease in the early 20th century, resulting in substantial morbidity and mortality.[21] With strengthened epidemiological and vector control measures, Singapore was certified malaria-free by WHO in November 1982. Since 2010, the annual incidence of malaria has continued to decrease from 3.7 cases per 100 000 population in 2010 to 0.7 cases per 100 000 population in 2017. Incidence has been maintained below 1 per 100 000 population in recent years. The number of imported malaria cases steadily decreased from 187 cases in 2010 to 39 cases in 2017.

Among the 290 cases of malaria reported in Singapore between 2013 and 2017, 289 (99.7%) were imported cases, of whom 141 (49%) were work-permit or employment pass holders. The majority of imported cases were from South-East Asia (16%), Africa (16%) and India (62%). Among the cases imported from South-East Asia, most were from Indonesia and Malaysia, which accounted for 8% and 4% of cases, respectively. Most of the cases of malaria reported in Singapore between 2013 and 2017 were caused by *P. vivax* (70%) followed by *P. falciparum* (22%).

In a retrospective survey from 2008 to 2017, 12 out of 209 (5.7%) *P. falciparum* cases tested had mutations possibly associated with artemisinin resistance (**Table 1**). Of the 12 cases, three cases had validated K13 resistance mutations while two cases had candidate K13 resistance mutations classified by WHO.[4] However, none experienced treatment failure and all recovered without complications.

Travel volume from the GMS to Singapore

Among cities outside the GMS, Singapore receives the highest number of travellers from the GMS (**Table 2A**). From 2013 to 2017, there was an average of more than 303 000 travellers each month from the GMS to Singapore (**Table 2B**). Thailand accounted for the highest number of travellers followed by Viet Nam and Myanmar. More than 15 000 monthly travellers to Singapore came from Cambodia where artemisinin resistance was first detected. Despite being a major international transportation hub with high connectivity to the GMS, importation of malaria into Singapore appears to be rare (**Table 2B**).

Context assessment

Vector distribution

Singapore remains vulnerable and receptive to the reintroduction of malaria and the introduction of drug-resistant malaria due to the presence of *Anopheles* vectors. Among the over 400 species of *Anopheles* mosquitoes discovered globally to date, about 70 species are potential vectors of malaria.[22] In Singapore, the two most common *Anopheles* species are *Anopheles epiroticus* and *Anopheles sinensis*.[23] *Anopheles epiroticus*, *Anopheles maculatus* and *Anopheles letifer*, were reported to be involved in malaria outbreaks in Singapore in the 1960s and 1970s, while *Anopheles sinensis* was implicated in the 2009 outbreak.[24,25]

Preparedness and response in Singapore

Malaria surveillance and control in Singapore is under the purview of two public health agencies: the NEA, which undertakes the surveillance and control of *Anopheles* mosquitoes, and the Singapore MOH, which is responsible for case surveillance and epidemiological investigation. Vector control remains the cornerstone for controlling mosquito-borne diseases, including malaria. NEA has put in place an integrated vector surveillance and control programme comprising environmental management and source reduction.[26] NEA has also identified specific malaria receptive areas for regular *Anopheles* surveillance and control.[27] Malaria is a legally notifiable disease under the Infectious Disease Act and all medical practitioners and laboratories are required to notify the MOH within 24 hours of diagnosis.[28] The MOH then investigates all cases of malaria to determine if transmission is likely to

Table 1. **Number of *P. falciparum* malaria cases in Singapore with mutations possibly associated with artemisinin resistance detected by K13 molecular marker analysis**

Years	No. of notified cases	No. of tested cases*	Wild types‡	Mutants			
				SNPs^	Numbers	Origins	GenBank accession numbers
2008	37	20	18	**F446I**	**1**	Myanmar	MH341694
				N412T, D452E, V454A, K503K#	**1**	India	MH341695 MH341696#
2009	33	24	22	**C580Y**	**1**	Myanmar	MH341697
				Y630Y	1	Indonesia	MH341698
2010	55	52	46	**F446I**	**1**	Myanmar	MH341703
				G453C	**2**	Myanmar	MH341701/MH341704
				N458D	**1**	Ghana	MH341700
				R575K	**2**	Myanmar	MH341699/MH341702
2011	25	25	22	**G453C**	**2**	Myanmar	MH341705/MH341706
				S623N	**1**	Malaysia	MH341707
2012	28	28	28				
2013	21	21	21				
2014	9	8	8				
2015	13	12	12				
2016	3	2	2				
2017	18	17	15	C469C	2	Ghana United Republic of Tanzania	MH341708 MH341709
Total	242 (100%)	209 (86.4%)	194 (92.8%)‡	15 mutants (7.2%) 3 synonymous (1.4%) **12 non-synonymous (5.7%)**			

SNP: single nucleotide polymorphism.

* Not all notified cases were tested due to unavailability of samples.

‡ All wild-type sequences were identical to *P. falciparum* 3D7 control strain sequence: MH341710.

Case with a mixed *P. falciparum* strain infection harbouring an alternative synonymous mutation: V454V.

^ Non-synonymous mutations are bolded. Double and single underlined variants represent validated and associated (without statistical significance) K13 resistance mutations, respectively, according to WHO.[4] Non-underlined variants represent other mutations detected but non-evaluated by WHO.[4]

be locally acquired or imported and assess whether any clusters are present. The MRC-NPHL has the capability to detect a large panel of molecular markers associated with antimalarial drug resistance, including the WHO-recommended K13 gene (as a marker of artemisinin resistance) and several genes associated with partner drug resistance.

To address the issue of imported malaria cases among foreign workers, Singapore implemented compulsory screening for malaria for foreign workers in 1997 as part of the pre-employment medical examinations. Among Singapore residents diagnosed with imported malaria infections from 2012 to 2016, more than 90% did not observe adequate preventive measures such as taking chemoprophylaxis before overseas travel.[29] Such behaviours could be due to the lack of risk perception associated with travel, especially within Asia, and the lack of awareness of travel medicine among travellers.[29]

Past outbreaks of malaria in the event of an imported case

Although imported cases continue to pose challenges for malaria control, the chances of resumption of endemic transmission are small as elimination tends to be a stable state.[30] Singapore has maintained its malaria-free status[31] since 1982. Between 1983 and 2009, 32 outbreaks involving 225 cases were reported, and the majority of the cases were imported through foreign workers with relapsing *P. vivax* malaria.[26] Further transmissions from these occasional outbreaks were promptly curbed by aggressive preventive and remedial actions, including extensive vector surveillance and control measures; early

Table 2. **Connectivity between Singapore and the GMS countries**

A. Top 10 final destination cities outside the GMS for travellers originating from countries/areas with artemisinin-resistant malaria in the GMS, 2017

Rank	Final destination city	Final destination country	Total travel volume received	% of travellers
1	Singapore	Singapore	4 012 918	6.2
2	Seoul	Republic of Korea	3 652 737	5.6
3	Shanghai	China	3 006 325	4.6
4	Hong Kong Special Administrative Region	China	2 865 969	4.4
5	Guangzhou	China	2 608 468	4.0
6	Beijing	China	2 467 999	3.8
7	Kuala Lumpur	Malaysia	2 413 439	3.7
8	Chengdu	China	2 144 415	3.3
9	Tokyo	Japan	1 842 503	2.8
10	Chongqing	China	1 667 531	2.6

Source: data were obtained from the International Air Transport Association.

B. Number of malaria cases imported into Singapore from 2013 to 2017 from GMS countries/areas in relation to travel volume

Rank	Origin country/area	No. of imported cases from 2013 to 2017	Total travel volume received from 2013 to 2017	Average monthly travel volume received from 2013 to 2017	% of total traveller volume
1	Thailand	2	11 261 683	187 695	61.9%
2	Viet Nam	0	4 198 163	69 969	23.1%
3	Myanmar	8	1 484 219	24 737	8.1%
4	Cambodia	0	905 564	15 093	5.0%
5	Yunnan (China)	2*	227 237	3787	1.2%
6	Lao People's Democratic Republic	0	120 626	2010	0.7%
Total		**12**	**18 197 492**	**303 292**	**100%**

* The two cases were imported from China, but information on the provinces where the cases were from was not available.

case detection through blood and fever surveys in malaria receptive areas; and risk communication to medical practitioners as well as health education for the public.[26] No outbreaks have been reported since 2010.

Measures taken by GMS countries

To prevent global spread of artemisinin resistance, containment efforts have been initiated in the GMS. In 2015, WHO launched the *Strategy for malaria elimination in the Greater Mekong Subregion (2015–2030)*, which was endorsed by all GMS countries.[31] All GMS countries have begun to implement national malaria elimination strategies that have resulted in a significant reduction in malaria cases and death; the surveillance of the efficacy of antimalarial drugs has led to prompt updating of malaria treatment policies in most GMS countries.[1]

Risk characterization

The risk imposed to Singapore by the emergence of ART-R malaria was characterized using the information collected; key factors were considered to assess the likelihood of importation of cases into Singapore and the impact on public health (**Table 3**).

The risk characterization of likely based on the likelihood of importation and the according minimal consequence suggest that the overall risk of ART-R malaria to Singapore is low. The importation of a case of ART-R

Table 3. **Risk characterization matrix for the public health risk posed to Singapore**

	Hazard	Exposure	Context
Potential for importation of ART-R malaria into Singapore	Artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy or ACT. This represents partial resistance. Since its first detection in Cambodia in 2008, artemisinin resistance in *P. falciparum* has been found in the GMS and has spread to neighbouring India.	A long incubation period of malaria ranging from 7 to 30 days means that international travel of infected persons in incubation period is possible. Cases of recrudescence can also be imported. Imported cases were 99.7% of the malaria cases reported in Singapore between 2013 and 2017. Close connectivity between GMS countries and Singapore; an average of 303 292 travellers, come from the GMS every month. From 2008 to 2017, 12 out of 209 (5.7%) *P. falciparum* malaria cases imported to Singapore had mutations possibly associated with artemisinin resistance; none experienced treatment failure and all recovered without complications.	Singapore has foreign workers from neighbouring endemic countries who contribute to imported malaria cases in Singapore. All GMS countries have begun to implement national malaria elimination strategies that have resulted in significant reduction of malaria cases and deaths. The effectiveness of the strategies in stopping the spread of artemisinin resistance need to be closely monitored.
Potential public health impact to Singapore	Infection results in acute febrile illness. The first symptoms may be mild and difficult to recognize. Without treatment within 24 hours, *P. falciparum* malaria can progress to severe illness, often leading to death. To date, artemisinin resistance has not been associated with increased morbidity or mortality.	The majority of the population in Singapore are susceptible to malaria. Some population groups are at higher risk of infection and developing severe diseases, including infants, children under 5 years of age, pregnant women, patients with HIV/AIDS, and non-immune migrants, mobile populations and travellers.	The vector for malaria, *Anopheles* mosquitoes, is one of the most common mosquito genera present in Singapore. Comprehensive surveillance and control systems for both vectors and human cases are in place in Singapore. Policies are in place to prevent the importation of malaria by foreign workers; increased awareness for personal protective measures is needed among local residents travelling to malaria-endemic regions.

ACT: artemisinin-based combination therapy; ART-R: artemisinin-resistant; GMS: Greater Mekong Subregion.

malaria into Singapore is possible given the close proximity and significant travel volume between Singapore and the GMS countries reporting artemisinin resistance. Singapore's vulnerability is further enhanced by the presence of foreign workers from neighbouring endemic countries. Nonetheless, the overall likelihood of importation is considered low based on the rarity and the decreasing trend of imported malaria incidence over the past few years.

With the presence of *Anopheles* vectors in Singapore, imported cases of ART-R malaria can cause secondary transmission. The risk of sustained spread is likely to be mitigated by the comprehensive surveillance and control system in place for both infected vectors and human cases as observed in the past local outbreaks of malaria initiated by imported cases.

DISCUSSION

Singapore is the top destination for travellers from the GMS. Among the imported *P. falciparum* cases in Singapore, 5.8% had genetic mutations that may confer resistance to artemisinin. The presence of competent local vectors, the high volume of travel from regions with ART-R malaria, and the presence of foreign workers from neighbouring endemic countries make it possible that drug-resistant malaria could be imported and introduced to Singapore. To reduce the risk of Singapore residents acquiring malaria infections overseas, pre-travel health education, particularly by travel agents, the media and health-care providers, can increase awareness of the risk of contracting malaria overseas so that personal preventive measures can be taken.

Secondary spread following an imported case is also possible. However, any spread is not likely to be sustained. Malaria has not re-established itself as an endemic disease in Singapore despite local outbreaks since it was declared malaria-free in 1982. The Singapore MOH and NEA have implemented comprehensive malaria surveillance and control programmes to detect cases and curb the transmission of local outbreaks.

The risk assessment has some limitations. The assessment is based on limited data as the number of imported cases of malaria in Singapore is small. As the risk characterization was defined by the epidemiological and contextual knowledge available currently, conclusions could change as new information emerges. Ongoing studies on genetic mutations, particularly their underlying molecular and cellular mechanisms and their phenotypic manifestations in resistance, could provide a better understanding of an epidemic and facilitate the design of surveillance and control measures. Identification of new molecular markers and improvements in laboratory capability continues to impact disease surveillance as illustrated by the significant progress in global surveillance of artemisinin resistance expedited by the discovery of the molecular marker K13.[12] Risk assessment will also change as new treatment options become available. Even though an assessment of the risks posed by resistance to partner drugs in the ACTs is out of scope for this paper, we recognize the risk of such resistance and the importance of monitoring all molecular markers of antimalarial-drug resistance. Analysis is currently under way to test molecular markers for partner drugs and assess potential variations. In addition, artemisinin resistance has also been observed in non-GMS countries, including countries in Africa, although the occurrence is very rare.[4] The risk of importation of ART-R malaria from these non-GMS countries is not discussed in this paper because of low connectivity of Singapore with these countries. Nevertheless, it warrants our close monitoring of the development of global situations.

In conclusion, in view of the emergence of ART-R malaria in the GMS and its geographical expansion, this risk assessment highlights the need for a high degree of vigilance over the local and global situation to be maintained to minimize the risk and severity of the public health threat of ART-R malaria to Singapore.

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Conflict of interest

None.

References

1. World malaria report 2018. Geneva: World Health Organization; 2018 (https://www.who.int/malaria/publications/world-malaria-report-2018/en/, accessed 27 November 2018).
2. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014 Feb 22;383(9918):723–35. doi:10.1016/S0140-6736(13)60024-0 pmid:23953767
3. Worldwide Antimalarial Resistance Network [website]. Oxford: Worldwide Antimalarial Resistance Network; 2017 (https://www.wwarn.org/, accessed 29 December 2017).
4. Status report on artemisinin and artemisinin-based combination therapy resistance. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/274362/WHO-CDS-GMP-2018.18-eng.pdf?ua=1, accessed 28 November 2018).
5. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM; Artemisinin Resistance in Cambodia 1 (ARC1) Study Consortium. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med. 2008 Dec 11;359(24):2619–20. doi:10.1056/NEJMc0805011 pmid:19064625
6. Das S, Saha B, Hati AK, Roy S. Evidence of artemisinin-resistant Plasmodium falciparum malaria in eastern India. N Engl J Med. 2018 Nov 15;379(20):1962–4. doi:10.1056/NEJMc1713777 pmid:30428283
7. Rapid risk assessment of acute public health events. Geneva: World Health Organization; 2012 (https://www.who.int/csr/resources/publications/HSE_GAR_ARO_2012_1/en/, accessed 30 April 2018).
8. Resources & statistics. In: Singapore Ministry of Health [website]. Singapore: Singapore Ministry of Health; 2019 (https://www.moh.gov.sg/resources-statistics, accessed 11 April 2019).
9. Brent SE, Watts A, Cetron M, German M, Kraemer MU, Bogoch II, et al. International travel between global urban centres vulnerable to yellow fever transmission. Bull World Health Organ. 2018 May 1;96(5):343–354B. doi:10.2471/BLT.17.205658 pmid:29875519

10. Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois AC, Khim N, et al. A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature. 2014 Jan 2;505(7481):50–5. doi:10.1038/nature12876 pmid:24352242

11. Fact sheet on malaria. Geneva: World Health Organization; 2018 (https://www.who.int/en/news-room/fact-sheets/detail/malaria, accessed 30 April 2018).

12. Guidelines for the treatment of malaria, 3rd edition. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1, accessed 30 April 2018).

13. Artemisinin and artemisinin-based combination therapy resistance. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/10665/255213/1/WHO-HTM-GMP-2017.9-eng.pdf?ua=1, accessed 30 April 2018).

14. Payne D. Spread of chloroquine resistance in Plasmodium falciparum. Parasitol Today. 1987 Aug;3(8):241–6. doi:10.1016/0169-4758(87)90147-5 pmid:15462966

15. Thu AM, Phyo AP, Landier J, Parker DM, Nosten FH. Combating multidrug-resistant Plasmodium falciparum malaria. FEBS J. 2017 Aug;284(16):2569–78. doi:10.1111/febs.14127 pmid:28580606

16. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009 Jul 30;361(5):455–67. doi:10.1056/NEJMoa0808859 pmid:19641202

17. Amato R, Pearson RD, Almagro-Garcia J, Amaratunga C, Lim P, Suon S, et al. Origins of the current outbreak of multidrug-resistant malaria in southeast Asia: a retrospective genetic study. Lancet Infect Dis. 2018 03;18(3):337–45. doi:10.1016/S1473-3099(18)30068-9 pmid:29398391

18. Dondorp AM, Fairhurst RM, Slutsker L, Macarthur JR, Breman JG, Guerin PJ, et al. The threat of artemisinin-resistant malaria. N Engl J Med. 2011 Sep 22;365(12):1073–5. doi:10.1056/NEJMp1108322 pmid:21992120

19. Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, et al. The spread of artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. Lancet Infect Dis. 2017 05;17(5):491–7. doi:10.1016/S1473-3099(17)30048-8 pmid:28161569

20. Woodrow CJ, White NJ. The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. FEMS Microbiol Rev. 2017 Jan;41(1):34–48. doi:10.1093/femsre/fuw037 pmid:27613271

21. Goh KT. Eradication of malaria from Singapore. Singapore Med J. 1983 Oct;24(5):255–68. pmid:6669988

22. Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y, Chareonviriyaphap T, Coetzee M, et al. A global map of dominant malaria vectors. Parasit Vectors. 2012 Apr 4;5(1):69. doi:10.1186/1756-3305-5-69 pmid:22475528

23. Not all mosquitoes transmit dengue. Singapore: The National Environmental Agency; 2018 (https://www.nea.gov.sg/corporate-functions/resources/research/wolbachia-aedes-mosquito-suppression-strategy/not-all-mosquitoes-transmit-dengue, accessed 9 July 2018).

24. Ng LC, Lee KS, Tan CH, Ooi PL, Lam-Phua SG, Lin R, et al. Entomologic and molecular investigation into Plasmodium vivax transmission in Singapore, 2009. Malar J. 2010 Oct 29;9(1):305. doi:10.1186/1475-2875-9-305 pmid:21029478

25. Pang SC, Andolina C, Malleret B, Christensen PR, Lam-Phua SG, Razak MABA, et al. Singapore's Anopheles sinensis Form A is susceptible to Plasmodium vivax isolates from the western Thailand-Myanmar border. Malar J. 2017 Nov 16;16(1):465. doi:10.1186/s12936-017-2114-3 pmid:29145859

26. Lee YCA, Tang CS, Ang LW, Han HK, James L, Goh KT. Epidemiological characteristics of imported and locally-acquired malaria in Singapore. Ann Acad Med Singapore. 2009 Oct;38(10):840–9. pmid:19890574

27. Malaria receptive areas in Singapore. Singapore: The National Environmental Agency; 2018 (https://data.gov.sg/dataset/malaria-receptive-areas, accessed 9 July 2018).

28. List of infectious diseases legally notifiable under the Infectious Diseases Act. Singapore: Singapore Ministry of Health; 2019 (https://www.moh.gov.sg/docs/librariesprovider5/default-document-library/list-of-infectious-diseases-legally-notifiable-under-the-ida.pdf, accessed 11 April 2019).

29. Lin YJ, Badaruddin H, Ooi SPL. Epidemiology of malaria in Singapore, 2008–2015. Epidemiological News Bulletin. 2016;42(2):49–54.

30. Smith DL, Cohen JM, Chiyaka C, Johnston G, Gething PW, Gosling R, et al. A sticky situation: the unexpected stability of malaria elimination. Philos Trans R Soc Lond B Biol Sci. 2013 Jun 24;368(1623):20120145. doi:10.1098/rstb.2012.0145 pmid:23798693

31. Strategy for malaria elimination in the GMS (2015–2030). Geneva: World Health Organization; 2015 (https://iris.wpro.who.int/bitstream/handle/10665.1/10945/9789290617181_eng.pdf, accessed 11 April 2019).

An enterohaemorrhagic *Escherichia coli* outbreak spread through the environment at an institute for people with intellectual disabilities in Japan in 2005

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Objective: An enterohaemorrhagic *Escherichia coli* (EHEC) outbreak at an institute with multiple facilities for children and adults with intellectual disabilities was investigated to characterize the cases and identify risk factors for infection.

Methods: A case was defined as a resident, a staff member or a visitor at the institute from 16 May through 30 June 2005 testing positive for type 2 Vero toxin-producing EHEC O157:H7 (confirmed case) or exhibiting bloody diarrhoea for two or more days (probable case). We collected and analysed demographic, clinical, laboratory and individual behaviour data to identify possible risk factors for infection and infection routes.

Results: We recorded 58 confirmed cases, of which 13 were symptomatic. One probable case was also found. The median age of the patients was 37 years (range: 6–59 years). Thirty-six patients (61%) were male. Thirteen patients (93%) had diarrhoea and six (43%) had abdominal pain. Two developed haemolytic-uraemic syndrome but recovered. All the patients were treated with antibiotics and tested negative after treatment. Some residents had problems with personal hygiene. The residents of one of the facilities who cleaned a particular restroom had 18.0 times higher odds of being infected with EHEC (95% confidence interval: 4.0–102.4) than those who did not.

Discussion: The source of the outbreak could not be identified; however, the infection may have spread through environmental sources contaminated with EHEC. We recommend that institutional settings, particularly those that accommodate people with intellectual disabilities, clean restrooms as often as possible to reduce possible infection from contact with infected surfaces.

Enterohaemorrhagic *Escherichia coli* (EHEC) was first reported in 1983 in the United States of America.[1] Infection can cause diarrhoea, haemorrhagic colitis and haemolytic-uraemic syndrome (HUS).[2] Outbreaks involving EHEC can be spread through infected food,[2] water,[3] direct contact with infected humans[4] or animals[5,6] or exposure to infected environments.[7] In Japan, EHEC is a reportable communicable disease; the largest outbreak to date was associated with consumption of white radish sprouts affecting about 8400 schoolchildren in 1997.[8]

On 6 June 2005, a physician informed a local health office of Oita Prefecture in western Japan of two EHEC cases at an institute for adults and children with intellectual disabilities.

The objectives of the study were to characterize the epidemiology of the cases and identify possible risk factors for EHEC infection in this outbreak.

METHODS

A case was defined as a resident, a staff member or a participant in the activities at the institute for at least one day from 16 May through 30 June 2005 who had a stool specimen that tested positive for Vero toxin type 2 (VT2)-producing EHEC O157:H7 (confirmed case) or exhibited bloody diarrhoea for two days or more (probable case), considering the long incubation period (1 to 9 days) of EHEC.

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At the time of the outbreak, the institute had 162 long-term and 13 short-term residents, 20 participants of day care and vocational training and 81 staff members (total 276) in three facilities (Facilities A, B and C). Facilities A and B were for children and adults with intellectual disabilities, respectively, and Facility C was for vocational training and residence for adults with mild intellectual disabilities. Some residents of Facility A attended a school outside the facility run by another organization five days a week. Residents of Facility C worked outside the institute, and about 20 persons who lived outside the institute attended vocational training held at Facility C.

To obtain relevant epidemiological and clinical information, the local health office staff and the authors interviewed the staff members at the time of the outbreak and reviewed charts of the residents and participants at the institute using semi-standardized instruments, to determine demographics (e.g. age, sex), symptoms and signs, date of onset and potential exposure history. Affected patients were referred to a local hospital where we also reviewed patient charts. Environmental samples, including surface swabs of doorknobs, water taps and stair and hand rails, were also collected from the institute by the local health office staff and examined at the Oita Prefecture Hygiene and Environment Centre (OPHEC).[9] The local health office collected stool samples from residents, vocational training participants and staff of the school for the intellectually disabled. The samples were examined for EHEC at the local health office and OPHEC using the National Institute of Infectious Diseases' standard method.[10] Staff members of the institute collected stool samples from the kitchen staff that were examined at a private laboratory. We randomly selected half of the strains isolated from the confirmed cases which were further analysed with pulsed-field gel electrophoresis (PFGE).[11]

We conducted a nested, unmatched case-control study of the residents, vocational training participants and the staff at each facility. For the case-control study, we defined a case as a person with bacteriologically confirmed EHEC infection. All residents at the facilities who tested negative for EHEC and did not exhibit diarrhoea between 1 and 9 June were chosen as controls. Individuals who had diarrhoea but tested negative for EHEC were not included in the case-control study. We conducted interviews with the patients and controls with the assistance of the staff, if necessary, using a structured questionnaire. Potential risk factors were age; sex; daily living skills, including personal hygiene (whether one was able to wash hands, brush teeth or bathe independently); toilet hygiene (whether one was able to defecate independently or one had allotriophagic behaviours); and needing assistance in taking meals; participating in day care or vocational training; and specific restrooms used or cleaned. Stratified analysis by Mantel-Haenszel method was employed to explore and adjust odds ratios if the univariable analysis revealed statistically significant result (p-value < 0.05).

Statistical tests were conducted using R software (The R Foundation for Statistical Computing, Vienna, Austria), and a p-value of < 0.05 was considered statistically significant.

Ethics statement

The investigation was conducted in accordance with the Infectious Disease Control Act of 1999 and the Food Safety Act of 1947 of Japan, which grants the prefectural health director the authority to collect epidemiological information and biologic specimens from patients without obtaining formal consent, in the event of an outbreak of certain confirmed or suspected communicable diseases, including EHEC.

RESULTS

All 276 residents, staff members, and participants of day care and vocational training had stool specimens collected and examined for EHEC. Fifty-nine cases were reported, of which 58 (98%) were confirmed and one was probable (2%). The probable case was a resident of Facility C who had continuous bloody diarrhoea but had been treated with antibiotics before the stool examination and tested negative for EHEC. Overall, 14 (24%) cases were symptomatic. The median age of the cases was 37 years (range: 6–59 years), and 36 (61%) cases were male. Four staff members exhibited non-bloody diarrhoea during the outbreak period; all four tested negative for EHEC and were eventually determined not to be confirmed or probable cases.

Among the staff, there were five cases (6.2%). No staff members were out ill before the first case report on 1 June. No children in the school, except for those who were residents of Facility A, tested positive for EHEC.

Table 1. **EHEC O157:H7 positivity among staff, residents and day care participants of an institute for people with intellectual disabilities, Japan, 2005**

			Bacteriologically positive		
			n	%	Total
Facility A	Residents	Male	10	25.0	40
		Female	1	8.3	12
	Participants	Male	0	0	5
		Female	0	0	4
	Staff	Male	0	0	5
		Female	2	9.1	22
	Subtotal		**13**	**14.8**	**88**
Facility B	Residents	Male	18	37.5	48
		Female	8	36.4	22
	Participants	Male	0	0	2
		Female	0	0	0
	Staff	Male	2	16.7	12
		Female	0	0	22
	Subtotal		**28**	**26.4**	**106**
Facility C	Residents	Male	5	17.8	28
		Female	6	50.0	12
	Participants	Male	1	6.7	15
		Female	4	57.1	7
	Staff	Male	0	0	9
		Female	1	9.1	11
	Subtotal		**17**	**20.7**	**82**
Total			**58**	**21.0**	**276**

There were no reports of any diarrhoea among staff members and children at the school, except for those who were residents of Facility A.

The breakdown of bacteriological test results by facility is shown in **Table 1**. When stratified by sex and location, the infection rate was highest in women residents of Facility C (52.6%, 95% confidence interval [CI]: 28.8–75.5%).

Fig. 1 shows the epidemic curve of the 14 symptomatic (13 confirmed and one probable) cases. Four of the five residents who exhibited symptoms and signs from 1 to 2 June participated in a vocational training held on the 1st floor of Facility C; however, we were not able to identify a period of close contact or a possible event that may have transmitted EHEC among them during the training, since they participated in separate and different tasks. Three patients of Facility C are clustered on 7–8 June following the first case at the same facility on 1 June.

The predominant clinical symptoms and signs of the 14 symptomatic cases were diarrhoea (13/14 cases, 93%), including bloody diarrhoea (2, 14%); abdominal pain (6, 43%); nausea or vomiting (3, 22%); and fever ≥37.5 °C (1, 7%). Two patients (14%) developed HUS; however, both fully recovered. Of the 10 symptomatic patients (71%) who sought medical care, five (36%) were hospitalized. No residents or staff members died from this outbreak.

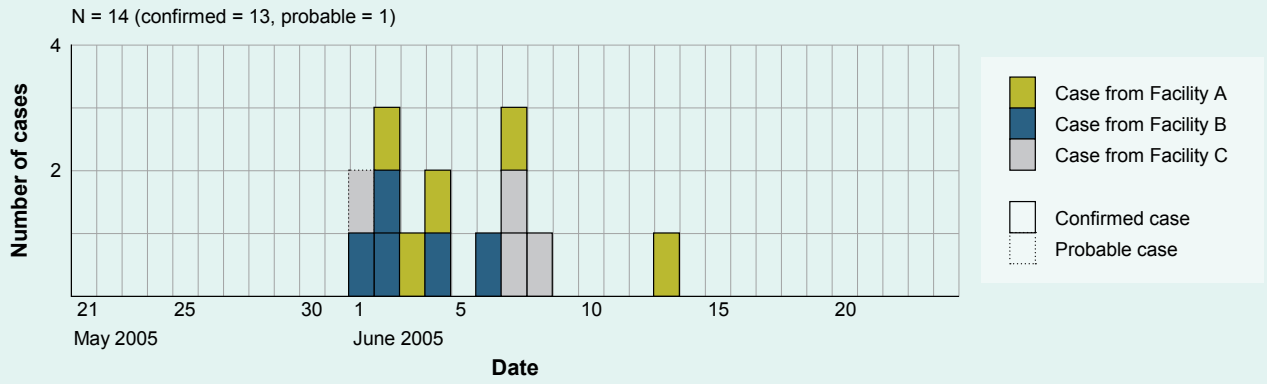
EHEC O157:H7 (VT2) was detected in the stool of 58 case patients. PFGE analysis found that all of the 28 randomly selected case patients had nearly identical strains with differences within two bands.[11] The strain was also later found in one patient in Nakatsu, about 100 km north-west of the institute in July 2005; however, an epidemiological investigation found no direct link between that case and cases detected in this outbreak.

All individuals with confirmed infection, including those who were asymptomatic, were treated with antibiotics and tested negative twice for EHEC O157:H7 48 hours after the end of treatment. One patient with HUS was treated with fosfomycin, and the other was treated with a fluoroquinolone before onset of HUS. Of 45 asymptomatic individuals, 37 took fosfomycin, six levofloxacin and one each tosufloxacin and cefpodoxime proxetil.

We studied potential risk factors for EHEC O157:H7 infection. Among the resident cases, 88% were independent with respect to feeding, and 54% were independent with respect to urinating. However, most residents required assistance with personal hygiene and grooming (assistance was required by 63% with hand washing, 67% with defecation, and 60% with brushing teeth). Some residents (16% of Facilities A and B) had problems with personal hygiene, in particular allotriophagic behaviour (i.e. eating one's own feces) and manipulating their own feces.

Eleven kitchen staff members, including three nutritionists, worked in a single kitchen preparing meals

Fig. 1. **Epidemic curve of symptomatic cases by date of symptom onset during an outbreak of EHEC O157:H7 at an institute for people with intellectual disabilities, Japan, 2005**



for the residents and staff who ate in dining halls in each facility. Food items served to the residents and staff were almost identical. Three nutritionists took turns eating each meal, and none of them exhibited diarrhoea during the outbreak period. All the kitchen staff tested negative for EHEC in three separate stool samples collected on 20 May (just before the outbreak as part of routine screening for food-handlers), on 3–4 June and 8–9 June. Samples of the meals provided from 23 to 30 May were stored in a freezer, and all samples tested negative for EHEC. Water samples from the tap water were all culture negative for EHEC. Chlorine levels of the tap water were checked and recorded every day and were consistently greater than 0.1 ppm.

We investigated the pre-outbreak routines for cleaning the toileting areas. The toilets of Facilities A and B were cleaned every day by the staff, two toilets on the 1st floor of Facility C were cleaned every day by external vocational training participants and residents of Facility C, and toilets on the 2nd and 3rd floors of Facility C were cleaned by the residents. The cleaning was normally done with detergent applied with reusable mops and cloths. Gloves were not always used during the cleaning before the outbreak. The time spent cleaning each restroom was normally 20 to 30 minutes.

No animals were brought into the facilities before or during the outbreak period.

Upon the recognition of the outbreak, the facilities introduced additional disease prevention and control measures, including encouraging intensive hand washing before meals and after toilet use, increasing monitoring of residents with allotriophagic behaviour, strengthening daily diarrhoea surveillance and cleaning surfaces three times per day. Prior to the outbreak, an infection control protocol was developed; anecdotally, the protocol was not followed consistently.

The results of the primary univariable analyses are shown in **Table 2,** and the stratified analyses for the residents of Facilities A and B are shown in **Table 3**. Additional univariable analyses are listed in **Table S1**. The univariable analysis found those residents who took meals at a certain table of Facility B were 9.7 (95% CI: 1.1–89.4) times the odds of being infected with EHEC (**Table S1B**). The inability to independently wash one's own hands was significantly associated with being a case (OR: 5.3, 95% CI: 1.5–29.4), specifically in men (OR: 12.9, 95% CI: 1.8–562.6) and not women (OR: 1.5, 95% CI: 0.2–18.7) (**Table 3**). Those who were unable to independently wash their own hands were more likely to be cases regardless of allotriophagic behavior (adjusted odds ratio [aOR]: 4.4, 95% CI: 1.2–16.0) or needing assistance in defecation (aOR: 4.3, 95% CI: 1.1–16.3). At Facility C, it was found that the residents who had cleaned the female restroom on the 1st floor had 18.0 (95% CI: 4.0–104.4) times the odds of being infected with EHEC than those who did not (**Table 2B**).

DISCUSSION

We investigated an EHEC outbreak that occurred during 1–13 June 2005, affecting 59 residents and staff members of an institute for children and adults with

Table 2. **Individual characteristics associated with EHEC O157:H7 infection in univariable analyses of an outbreak investigation at an institute for people with intellectual disabilities, Japan, 2005**

Individual risk factor	Cases (%)	Controls (%)	OR	95%CI
A. Residents of Facilities A and B (34 cases and 82 controls)				
Female sex	8 (23.5)	22 (26.8)	0.8	0.3–2.3
Manipulates own faeces	7 (20.6)	16 (19.5)	1.1	0.3–3.1
Has habit of touching own buttocks	6 (17.6)	8 (9.8)	2.0	0.5–7.2
Has used a toilet outside the facility	6 (17.6)	5 (6.1)	3.3	0.8–14.7
Lies on the floor daily	6 (17.6)	10 (12.2)	1.7	0.4–5.6
Licks walls and tiles daily	3 (8.8)	1 (1.2)	7.7	0.6–415.4
Sucks one's fingers daily	7 (20.6)	15 (18.3)	1.2	0.4–3.4
Engages in allotriophagic behaviour	**10 (29.4)**	**9 (11.0)**	**3.3**	**1.1–10.5**
Loiters in the facility daily	7 (20.6)	17 (20.7)	1.0	0.3–2.9
Takes medication	14 (41.2)	30 (36.6)	1.2	0.5–3.0
Being unable to wash own hands	**31 (91.2)**	**54 (65.9)**	**5.3**	**1.5–29.0**
Being unable to take meals independently	4 (11.8)	21 (25.6)	1.3	0.1–1.3
Being unable to defecate independently	25 (73.5)	48 (58.5)	2.0	0.8–5.4
Needs assistance or direction in defecating	**16 (47.1)**	**21 (25.6)**	**2.6**	**1.0–6.4**
Needs assistance in bathing	20 (58.8)	46 (56.1)	1.0	0.4–2.4
In day care group A1*	4 (11.8)	10 (12.2)	1.0	0.2–3.7
In day care group A2*	6 (17.6)	7 (8.5)	2.3	0.6–8.7
In day care group B1*	5 (14.7)	6 (7.3)	2.2	0.5–9.3
In day care group B2*	3 (17.6)	7 (8.5)	1.0	1.0–4.9
In day care group S*	3 (17.6)	7 (8.5)	1.0	1.0–4.9
In day care group V*	5 (14.7)	5 (6.1)	2.6	0.6–12.2
B. Residents, participants and staff members in activities of Facility C (18 cases and 65 controls)**				
Female sex	**11 (61.1)**	**19 (29.2)**	**3.7**	**1.1–13.3**
Being a staff member	1 (5.6)	19 (30.2)	0.1	0.0–1.0
Toilet use location				
1st floor male restroom	6 (35.3)	28 (47.5)	0.6	0.2–2.1
1st floor female restroom	**10 (58.8)**	**11 (18.6)**	**6.0**	**1.7–23.6**
2nd floor male restroom	**4 (23.5)**	**35 (59.3)**	**0.2**	**0.0–0.8**
2nd floor female restroom	**12 (70.6)**	**16 (27.1)**	**6.3**	**1.7–26.5**
3rd floor male restroom	5 (29.4)	25 (42.4)	0.6	0.1–2.0
Toilet cleaned at				
1st floor male restroom	1 (5.9)	11 (18.6)	0.3	0.0–2.2
1st floor female restroom	**10 (58.8)**	**4 (6.8)**	**18.0**	**4.0–104.4**
Bathing				
At Facility C	10 (58.8)	43 (72.9)	0.5	0.2–2.0
Bathed in a bathtub	10 (58.8)	30 (50.8)	2.6	0.5–27.6
Frequently drank the hot water when bathing	1 (5.9)	6 (10.2)	0.4	0.0–4.1

CI = confidence interval, OR = odds ratio

* The day care groups A1 and A2 consisted of mainly residents of Facility A; B1 and B2 consisted mainly of those of Facility B; S consisted of those who were on occupational therapy; and V consisted of those who need more attention of the staff.

** Not all individuals provided responses, so the number of responses may not be the total numbers of cases and controls.

The risk factors with statistically significant odds ratios are emphasized with bold font.

Table 3. **Individual characteristics associated with EHEC O157:H7 infection among individuals not able to independently wash their hands during an outbreak among residents of Facilities A and B at an institute for people with intellectual disabilities, Japan, 2005 (34 cases and 82 controls)**

Stratified risk factors	Unable to wash hands independently No. (n = 85)		OR	95% CI
	Cases (%)	Controls (%)		
Overall	**31 (91.2)**	**54 (65.9)**	**5.3**	**1.5–29.4**
Sex				
Male	**25 (96.2)**	**40 (65.6)**	**12.9**	**1.8–562.6**
Female	6 (75.0)	14 (66.7)	1.5	0.2–18.7
M-H adjusted	**–**	**–**	**5.3**	**1.5–18.7**
Allotriophagic behaviour				
Yes	10 (100.0)	9 (100.0)	–	–
No	**21 (87.5)**	**45 (61.6)**	**4.3**	**1.1–24.6**
M-H adjusted	**–**	**–**	**4.4**	**1.2–16.0**
Needs assistance in defecation				
Yes	16 (100.0)	20 (95.2)	–	–
No	**15 (83.3)**	**34 (55.7)**	**3.9**	**1.0–23.2**
M-H adjusted	**–**	**–**	**4.3**	**1.1–16.3**

CI = confidence interval, OR = odds ratio, M-H = Mantel-Haenszel method

The items with statistically significant odds ratios are emphasized with bold font.

intellectual disabilities. The source of the outbreak could not be identified; however, the infection may have spread through the environment contaminated with EHEC. The residents who cleaned a particular restroom at Facility C had 18 times the odds of testing positive for EHEC compared to those who did not, and neither samples from meal remnants nor stool samples from staff who worked in the kitchen yielded EHEC. At Facilities A and B, it is likely that the infection spread via person-to-person contact because those who were unable to wash their own hands were more at risk. Environmental contamination was also supported by the findings that no single peak in the epidemic curve was noted, no episodes were reported in which a possible single source of infection was suspected and limitations in personal and toilet hygiene were confirmed. EHEC spread through contaminated environments has been previously reported;[7] thus our findings are consistent with previous reports.

Infection spread via person-to-person contact is the leading cause of most EHEC outbreaks in institutional settings in Japan and elsewhere, particularly at day cares, schools[13–16] and homes for older people.[17] Foodborne infections[18] and infection spread through the environment were sometimes suspected but were not supported by analytic epidemiology.[13] Thus, this study is unique in that cleaning a certain restroom was implicated by analytical epidemiology as a possible common source.

In this outbreak, about two thirds of cases were asymptomatic. In Japan, active case-finding routinely includes testing asymptomatic contacts.[14,19] According to the national surveillance data, one third of EHEC cases in Japan were asymptomatic.[20] Over three fourths of the cases in our setting were adults, supporting a previous report that the proportion of cases that were symptomatic declined with age.[14] Additionally, the doses of EHEC bacilli were likely small and thus not everyone developed symptoms. Asymptomatic carriers or recovered patients may shed EHEC for more than 30 days;[21] however, humans are not considered as reservoirs.[22] During an outbreak in Australia in 2007, an asymptomatic sibling spread EHEC to another sibling who developed HUS.[23] The role of asymptomatic carriers of EHEC in outbreaks should not be underestimated.

Our study has both strengths and limitations. Since all the residents and staff members of the institution were

tested for EHEC in their stools, we were able to identify infections that were asymptomatic. Although we believe most infections were transmitted through the environment at Facility C, the environmental specimens did not yield the pathogen, most probably because the environment, particularly the door knobs, floor and tables, were disinfected shortly before the environmental samples were collected for bacteriological tests. In addition, residents with intellectual disabilities may have limited ability to provide comprehensive behavioural or risk information, and thus recall and information biases are likely. To minimize these biases, we verified the participants' responses with staff members' records.

We recommend that in institutional settings, particularly those that accommodate people with intellectual disabilities, staff should pay close attention to personal and toilet hygiene of the residents, and restrooms should be cleaned as often as possible to reduce possible infection via contact with contaminated surfaces. The infective dose of EHEC is small (lower than 700 organisms).[24] Institutions should also have a symptomatic surveillance system and monitor trends in diarrhoea incidence among residents. Prefectural governments should strengthen their surveillance systems, including pathogen surveillance with routine PFGE tests, to detect potential outbreaks involving multiple prefectures. Local health offices should provide congregate settings, including health facilities, with training about communicable diseases to prevent outbreaks.

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Conflict of interest

None declared.

References

1. Riley LW, Remis RS, Helgerson SD, McGee HB, Wells JG, Davis BR, et al. Hemorrhagic colitis associated with a rare Escherichia coli serotype. N Engl J Med. 1983 Mar 24;308(12):681–5. doi:10.1056/NEJM198303243081203 pmid:6338386
2. Bell BP, Goldoft M, Griffin PM, Davis MA, Gordon DC, Tarr PI, et al. A multistate outbreak of Escherichia coli O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers. The Washington experience. JAMA. 1994 Nov 2;272(17):1349–53. doi:10.1001/jama.1994.03520170059036 pmid:7933395
3. Bruneau A, Rodrigue H, Ismäel J, Dion R, Allard R. Outbreak of E. coli O157:H7 associated with bathing at a public beach in the Montreal-Centre region. Can Commun Dis Rep. 2004 Aug 1;30(15):133–6. pmid:15315240
4. Carter AO, Borczyk AA, Carlson JA, Harvey B, Hockin JC, Karmali MA, et al. A severe outbreak of Escherichia coli O157:H7–associated hemorrhagic colitis in a nursing home. N Engl J Med. 1987 Dec 10;317(24):1496–500. doi:10.1056/NEJM198712103172403 pmid:3317047
5. Centers for Disease Control and Prevention (CDC). Outbreaks of Escherichia coli O157:H7 associated with petting zoos–North Carolina, Florida, and Arizona, 2004 and 2005. MMWR Morb Mortal Wkly Rep. 2005 Dec 23;54(50):1277–80. pmid:16371942
6. Muto T, Matsumoto Y, Yamada M, Ishiguro Y, Kitazume H, Sasaki K, et al. Outbreaks of enterohemorrhagic Escherichia coli O157 infections among children with animal contact at a dairy farm in Yokohama City, Japan. Jpn J Infect Dis. 2008 Mar;61(2):161–2. pmid:18362413
7. Varma JK, Greene KD, Reller ME, DeLong SM, Trottier J, Nowicki SF, et al. An outbreak of Escherichia coli O157 infection following exposure to a contaminated building. JAMA. 2003 Nov 26;290(20):2709–12. doi:10.1001/jama.290.20.2709 pmid:14645313
8. Michino H, Araki K, Minami S, Takaya S, Sakai N, Miyazaki M, et al. Massive outbreak of Escherichia coli O157:H7 infection in schoolchildren in Sakai City, Japan, associated with consumption of white radish sprouts. Am J Epidemiol. 1999 Oct 15;150(8):787–96. doi:10.1093/oxfordjournals.aje.a010082 pmid:10522649
9. Oita Prefectural Institute of Health and Environment (formerly known as Oita Prefecture Hygiene and Environment Centre) [website]. Oita: Oita Prefectural Government; 2015 (http://www.pref.oita.jp.e.ro.hp.transer.com/site/13002/, accessed on 7 February 2019).
10. Manual for examination and diagnosis of enterohemorrhagic Escherichia coli (EHEC). Tokyo: National Institute of Infectious Diseases; 2017 (https://www.niid.go.jp/niid/images/lab-manual/EHEC20170215.pdf, accessed on 7 March 2018).
11. Terajima J, Izumiya H, Iyoda S, Tamura K, Watanabe H. High genomic diversity of enterohemorrhagic Escherichia coli isolates in Japan and its applicability for the detection of diffuse outbreak. Jpn J Infect Dis. 2002 Feb;55(1):19–22. pmid:11971157
12. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983 Dec;31(12):721–7. doi:10.1111/j.1532-5415.1983.tb03391.x pmid:6418786
13. Bayliss L, Carr R, Edeghere O, Knapper E, Nye K, Harvey G, et al. School outbreak of Escherichia coli O157 with high levels of transmission, Staffordshire, England, February 2012. J Public Health (Oxf). 2016 Sep;38(3):e247–53. doi:10.1093/pubmed/fdv122 pmid:26364319

14. Kanayama A, Yahata Y, Arima Y, Takahashi T, Saitoh T, Kanou K, et al. Enterohemorrhagic Escherichia coli outbreaks related to childcare facilities in Japan, 2010-2013. BMC Infect Dis. 2015 Nov 20;15(1):539. doi:10.1186/s12879-015-1259-3 pmid:26589805

15. Sonoda C, Tagami A, Nagatomo D, Yamada S, Fuchiwaki R, Haruyama M, et al. An enterohemorrhagic Escherichia coli O26 outbreak at a nursery school in Miyazaki, Japan. Jpn J Infect Dis. 2008 Jan;61(1):92–3. pmid:18219147

16. Gouveia S, Proctor ME, Lee MS, Luchansky JB, Kaspar CW. Genomic comparisons and Shiga toxin production among Escherichia coli O157:H7 isolates from a day care center outbreak and sporadic cases in southeastern Wisconsin. J Clin Microbiol. 1998 Mar;36(3):727–33. pmid:9508303

17. Afza M, Hawker J, Thurston H, Gunn K, Orendi J. An outbreak of Escherichia coli O157 gastroenteritis in a care home for the elderly. Epidemiol Infect. 2006 Dec;134(6):1276–81. doi:10.1017/S0950268806006546 pmid:16740198

18. Preston M, Borczyk A, Davidson R, McGeer A, Bertoli J, Harris S, et al. Hospital outbreak of Escherichia coli O157:H7 associated with rare phage type - Ontario. Canadian communicable disease report. 1997;23–05:33-37 (https://pdfs.semanticscholar.org/5972/bd18b94cab06f455754e755e8e89a5cc4c4b.pdf, accessed on 7 February 2019).

19. Yamazaki S, et al. Kansensho yobou hikkei (A handbook for prevention of communicable disease). Tokyo, Japan: Nihon Koshu Eisei Kyokai; 1999. pp. 210–3 (in Japanese).

20. National Institute of Infectious Diseases. Enterohemorrhagic Escherichia coli (EHEC) infection, as of April 2017. Japan Infectious Agent Surveillance Report. 2017;38:87–8 (https://www.niid.go.jp/niid/en/basic-science/865-iasr/7282-447te.html, accessed on 7 February 2019).

21. Swerdlow DL, Griffin PM. Duration of faecal shedding of Escherichia coli O157:H7 among children in day-care centres. Lancet. 1997 Mar 15;349(9054):745–6. doi:10.1016/S0140-6736(05)60196-1 pmid:9074570

22. Beutin L, Martin A. Outbreak of shiga toxin-producing *Escherichia coli* (STEC) O104:H4 infection in Germany causes a paradigm shift with regard to human pathogenicity of STEC strains. J Food Prot. 2012 Feb;75(2):408–18. doi:10.4315/0362-028X.JFP-11-452 pmid:22289607

23. Hanna JN, Humphreys JL, Ashton SE, Murphy DM. Haemolytic uraemic syndrome associated with a family cluster of enterohaemorrhagic Escherichia coli. Commun Dis Intell Q Rep. 2007 Sep;31(3):300–3. pmid:17974224

24. Tuttle J, Gomez T, Doyle MP, Wells JG, Zhao T, Tauxe RV, et al. Lessons from a large outbreak of Escherichia coli O157:H7 infections: insights into the infectious dose and method of widespread contamination of hamburger patties. Epidemiol Infect. 1999 Apr;122(2):185–92. doi:10.1017/S0950268898001976 pmid:10355781

Findings and lessons from establishing Zika virus surveillance in southern Viet Nam, 2016

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Objective: To document the evolution and optimization of the Zika virus (ZIKV) disease surveillance system in southern Viet Nam in 2016 and to describe the characteristics of the identified ZIKV-positive cases.

Methods: We established a sentinel surveillance system to monitor ZIKV transmission in eight sites in eight provinces and expanded the system to 71 sites in 20 provinces in southern Viet Nam in 2016. Blood and urine samples from patients who met the case definition at the sentinel sites were tested for ZIKV using real-time reverse transcription polymerase chain reaction at the Pasteur Institute in Ho Chi Minh City (PI-HCMC). We conducted descriptive analysis and mapped the ZIKV-positive cases.

Results: In 2016, 2190 specimens from 20 provinces in southern Viet Nam were tested for ZIKV at PI-HCMC; 626 (28.6%), 484 (22.1%), 35 (1.6%) and 1045 (47.7%) tests were conducted in the first, second, third and fourth quarters of the year, respectively. Of these tested specimens, 214 (9.8%) were ZIKV positive with 212 (99.1%) identified in the fourth quarter. In the fourth quarter, the highest positivity rate was those in age groups 30–39 years (30.0%) and 40–59 years (31.6%). Of the 214 ZIKV-positive patients, 210 (98.1%) presented with rash, 194 (90.7%) with fever, 149 (69.6%) with muscle pain, 123 (57.5%) with joint pain and 66 (30.8%) with conjunctivitis.

Discussion: The surveillance system for ZIKV disease underwent several phases of optimization in 2016, guided by the most up-to-date local data. Here we demonstrate an adaptable surveillance system that detected ZIKV-positive cases in southern Viet Nam.

In Viet Nam, although Zika virus (ZIKV) disease was not listed as a nationally notifiable disease before 2016, previous literature suggests that it is not a new disease in the country. There has been evidence of possible transmission of ZIKV disease dating as far back as 1954 when neutralizing antibodies against ZIKV were detected in the indigenous population in northern Viet Nam.[1] More recently, a study that retrospectively tested 5617 dengue-negative serum samples collected at seven hospital outpatient departments in 2010–2014 in southern Viet Nam also identified ZIKV-positive cases from 2013.[2] When Zika disease was declared by the World Health Organization (WHO) as a public health emergency of international concern (PHEIC) in 2016,[3] several ZIKV-positive cases of travellers who visited Viet Nam before symptom onset were reported.[4–6]

In response to WHO's declaration of PHEIC, Viet Nam responded swiftly in rolling out Zika surveillance, prevention and control guidelines on 2 February 2016 and the Zika diagnosis and treatment guidelines on 5 February 2016 (see **Fig. 1**).[7,8] In March 2016, two cases of autochthonous transmission of ZIKV infection were detected in Nha Trang and Ho Chi Minh City (HCMC) and reported to WHO.[9] The case in HCMC was a pregnant woman who had fetal demise at week nine of her pregnancy.[10] In June 2016, an infant, born in Dak Lak, Viet Nam,[11] was the first and only known case of microcephaly potentially linked to ZIKV infection in Viet Nam. The ZIKV disease surveillance data are critical to better understand the local outbreak and to guide the appropriate level of response. As with any new surveillance system, adjustments may be needed as part of the

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optimization process. Surveillance for ZIKV infection was initially based on existing dengue virus disease surveillance; however, given the largely asymptomatic and mild clinical presentation of ZIKV disease, an independent surveillance strategy specifically tailored for ZIKV disease was needed. As the local and international situations evolved, Viet Nam also adjusted its surveillance approach and expanded the number of ZIKV disease surveillance sites in southern Viet Nam where the majority of the cases occurred.

The objectives of this paper were to document the evolution and optimization of the ZIKV disease surveillance system in southern Viet Nam in 2016 and to describe the characteristics of the ZIKV-positive cases identified through the surveillance system. We hope that by sharing our lessons we can highlight the practical realities of implementing a new surveillance system for a re-emerging disease in the context of a rapidly evolving international public health emergency and a local ZIKV disease outbreak.

METHODS

Epidemiological surveillance

Surveillance sites

A sentinel surveillance system to monitor ZIKV transmission in southern Viet Nam was established using a phased approach in 2016 (**Fig. 1**). Sentinel sites were gradually expanded from an initial eight sites in eight provinces in February 2016 to 71 sites in 20 provinces by November 2016 (**Fig. 1**). In phase I, the surveillance system was first established using the existing dengue sentinel surveillance system. We targeted eight southern provinces deemed as high-risk areas for active transmission of Zika with the assumption that high-risk areas for dengue transmission would also be high-risk areas for Zika transmission. High-risk areas were selected based on three factors based on the guidance from the Ministry of Health and National Program for Dengue Control: 1) the epidemiology of dengue fever (>100 dengue cases per 100 000 population); 2) the *Aedes aegypti* mosquito density index (>0.5 female mosquito per house per day); and 3) the tourist flow (presence of international and domestic transportation and famous sites frequented by tourists). In each of the eight selected provinces, one existing surveillance site at either a provincial or district hospital was selected and began case finding from 15 February 2016 (**Fig. 1**). One month later, in phase II, sentinel surveillance was rolled out in HCMC, the largest city in southern Viet Nam. The roll-out included all district hospitals in the city (**Fig. 1**). From May 2016, in phase III, the remaining 12 provinces in southern Viet Nam also began implementing the sentinel ZIKV surveillance system in at least one district hospital per province. By November 2016, when ZIKV-positive cases peaked in HCMC, the ZIKV surveillance system had been further expanded to all four city obstetrics hospitals (**Fig. 1**). In addition, eight commune health stations and 15 private clinics participated in the sentinel surveillance system in the fourth quarter of 2016.

Case definitions

All outpatients meeting the case definition at each sentinel hospital were included in our analysis. In 2016, the Viet Nam Ministry of Health issued an initial and a revised official case definitions guided by the international outbreak situation and local data from Viet Nam, as listed in **Table 1**.

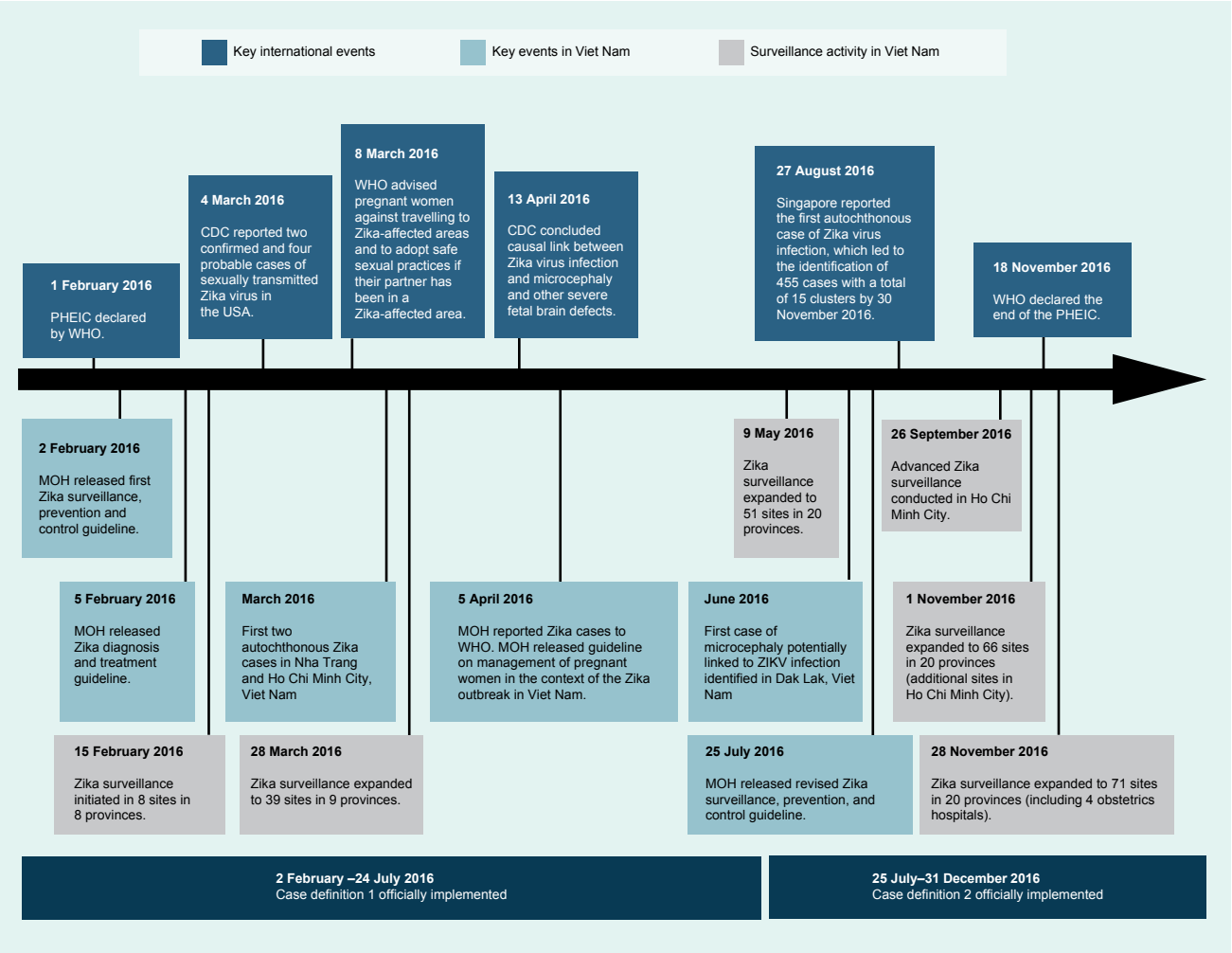
Case investigation

We conducted case investigations and interviewed the patients who met the case definition using a one-page, semi-structured questionnaire to obtain and confirm information on their socio-demographic characteristics, signs and symptoms, dates of symptom onset and travel histories.

Laboratory testing

We collected blood and urine samples from patients who met the case definition. On the same day, we sent the specimens to the Pasteur Institute in HCMC (PI-HCMC) where testing was conducted once per week for ZIKV. A patient was defined as a ZIKV-positive case when ZIKV was detected using real-time reverse transcription polymerase chain reaction (RT–PCR) with Trioplex reagents provided by the United States Centers for Disease Control and Prevention. The ZIKV testing procedure was developed in accordance with the primer and probe sequences as described previously by Lanciotti et al.[12]

Fig. 1. **Timeline of key events related to the ZIKV outbreak internationally and in Viet Nam, 2016**



CDC, Centers for Disease Control and Prevention (United States); PHEIC, public health emergency of international concern; WHO, World Health Organization; USA, United States of America; MOH, Ministry of Health (Viet Nam); ZIKV, Zika virus.

Data collection and analysis

Questionnaire data and test results were first collected on paper forms and later entered and analysed in Microsoft Excel. We conducted descriptive analysis to examine the data by person, place and time. Spot mapping was conducted using ArcGIS (ESRI, Redlands, CA, USA) to look at the geographical spread of ZIKV-positive cases over time.

Ethical approval

The data presented in this manuscript were for public health surveillance[13] and not research; therefore, approval from an ethics committee was not sought.

RESULTS

In total, 2190 specimens from 20 provinces in southern Viet Nam were tested for ZIKV at PI-HCMC in 2016; 626 (28.6%) tests were performed in quarter 1; 484 (22.1%) tests in quarter 2; 35 (1.6%) tests in quarter 3; and 1045 (47.7%) tests in quarter 4. Two distinct waves of ZIKV-positive cases occurred in 2016 (**Fig. 2**). A total of 214 (9.8%) of the 2190 tested specimens were positive for ZIKV. Of the 214 ZIKV-positive specimens, the majority were identified in quarter 4 (n = 212, 99.1%). The positivity rate was 0.2% in quarter 1 (1 positive among 626 samples tested), 0% in quarter 2 (0 positive among 484 samples tested), 2.9% in quarter 3 (1 positive among 35 samples tested) and 20.3% in quarter 4 (212 positive among 1045 samples tested).

Table 1. **ZIKV surveillance case definitions used in Viet Nam, February–December 2016**

Case definition 1 **Date of national guideline implemented: 2 February 2016**
Suspected case Any patient presenting with fever, rash AND at least one of the following: • Conjunctivitis • Joint pain, muscle pain • Headache AND • Travel in/to/from a Zika-affected area within 12 days before symptom onset.
Confirmed case Suspected cases confirmed with ZIKV infection by laboratory diagnostic tests including molecular biology technique, virus isolation, or serology.
Case definition 2 **Date of national guideline implemented: 25 July 2016**
Suspected case Any patient presenting with rash AND at least two of the following symptoms: • Fever ≤ 38.5 °C • Non-purulent conjunctivitis • Joint pain, swelling around the joints • Muscle pain.
Probable case Any patient who meets the criteria for a suspected case AND has Zika IgM antibodies, with no evidence of infection with other flaviviruses.
Confirmed case Any patient who meets the criteria for a suspected or probable case AND has laboratory confirmation of recent ZIKV infection through: • Culture of ZIKV isolates, or • Identification of the specific gene fragment of ZIKV by molecular biology technique, or • Detection of Zika IgM antibodies AND plaque reduction neutralization (PRNT90) for ZIKV with titres ≥ 20 and ZIKV titre ratio ≥ 4 compared to other flaviviruses.

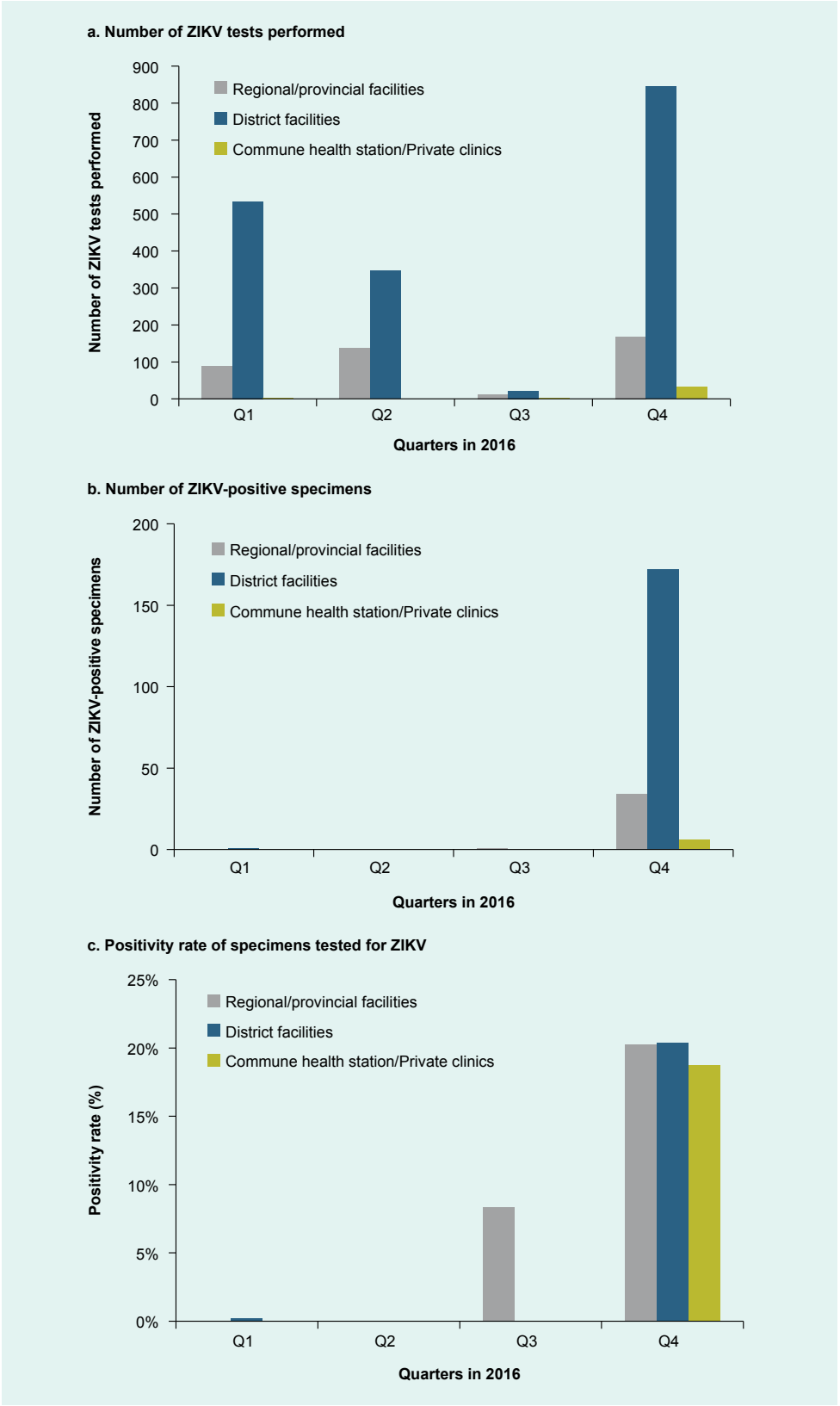
ZIKV, Zika virus.

Most (n = 1749; 79.9%) of the specimens were collected at district hospitals where 173 (9.9%) tested positive; 407 (18.6%) specimens were collected at regional and provincial facilities where 35 (8.6%) specimens tested positive for ZIKV. These facilities included infectious disease hospitals, obstetrics and gynaecology hospitals, paediatric hospitals, provincial general hospitals and provincial preventive medicine centres. During the quarter with the highest incidence (quarter 4), a small number (n = 32; 1.5%) of specimens were obtained from one commune health station (n = 5; 0.2%) and private clinics (n = 27; 1.2%) in one of the sentinel districts (District 2); of these 32 specimens, 6 (18.8%) tested positive (1 [3.1%] from commune health stations and 5 [15.6%] from private clinics.) The positivity rate in quarter 4 was similar across levels of facilities: 20.2% at regional and provincial facilities, 20.4% at district facilities and 18.8% at commune health station and private clinics (**Fig. 2**).

The characteristics of the individuals tested for ZIKV and those tested positive are summarized in **Table 2**. Pregnant women had relatively high positivity rates compared to others tested during the year (22.9%) and in quarter 4 specifically (24.6%). In children and non-pregnant women, the positivity rate in quarter 4 was more than double that of the year as a whole. The positivity rates in non-pregnant women and men were similar (8.7% versus 8.0% in the whole year; 18.8% versus 20.2% in quarter 4). Those in age groups 30–39 and 40–59 had the highest positivity rate at 16.5% and 14.8% in the whole year and 30.0% and 31.6% in quarter 4, respectively. Fewer children under 15 years of age were tested than adults, and the positivity rate for children was 0.7% during the whole year and 3.4% in quarter 4. Of the 145 children aged 5–9 years old who were tested, none tested positive for ZIKV.

The positivity rate was higher in HCMC than in other provinces in southern Viet Nam in 2016 (13.6% versus 2.8%) and in quarter 4 (24.4% versus 8.6%) (**Table 2**). Within HCMC, the positive cases were concentrated in certain districts (**Fig. 3**): Binh Thanh District, District 2 and District 12 had the highest number of positive cases detected in 2016 and in quarter 4.

Fig. 2. **Number of ZIKV tests performed, number of specimens tested positive, and positivity rate by administrative level of facility, Southern Viet Nam, 2016**



ZIKV, Zika virus.

All ZIKV tests were performed at the Pasteur Institute in HCMC. The regional and provincial facilities include infectious disease hospitals, obstetrics and gynaecology hospitals, paediatric hospitals, provincial general hospitals, and provincial preventive medicine centres. The district facilities include district hospitals.

Table 2. **Demographics of individuals tested for ZIKV and those with laboratory-confirmed ZIKV infection, southern Viet Nam, 2016**

	Quarters 1 – 4			Quarter 4		
	Number tested	Number positive	Percentage positive (%)	Number tested	Number positive	Percentage positive (%)
Population group						
Pregnant women	205	47	22.9	187	46	24.6
Other women	1143	100	8.7	526	99	18.8
Men	842	67	8.0	332	67	20.2
Children (<15 years old)	280	2	0.7	59	2	3.4
Age (years)						
< 5	135	2	1.5	28	2	7.1
5–9	145	0	0	31	0	0
10–19	350	27	7.7	147	27	18.4
20–29	844	79	9.4	474	78	16.5
30–39	417	69	16.5	227	68	30.0
40–59	209	31	14.8	98	31	31.6
60+	65	6	9.2	26	6	23.1
Unknown	25	0	0	14	0	0
Location of detection						
Ho Chi Minh City	1422	194	13.6	788	192	24.4
Other provinces	716	20	2.8	232	20	8.6
Unknown	52	0	0	25	0	0
Total	**2190**	**214**	**9.8**	**1045**	**212**	**20.3**

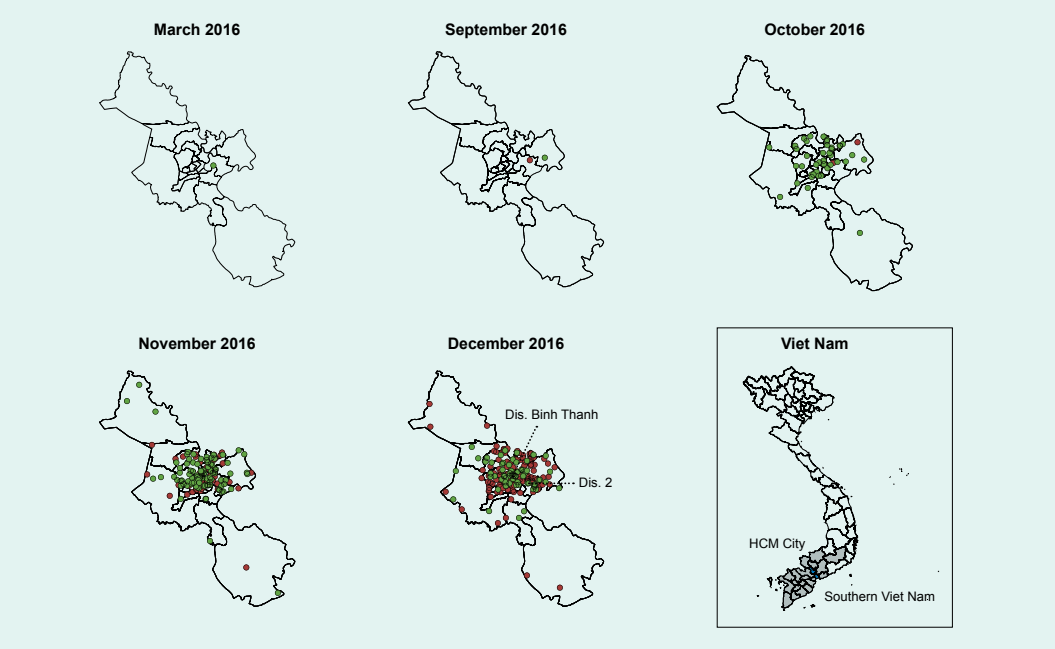
ZIKV, Zika virus.

A patient can often present with multiple symptoms. Of the 214 patients who were positive for ZIKV infection, 210 (98.1%) presented with rash, 194 (90.7%) with fever, 149 (69.6%) with muscle pain, 123 (57.5%) with joint pain and 66 (30.8%) with conjunctivitis (data not shown).

DISCUSSION

In this article, we presented initial efforts to roll out and optimize the surveillance system for ZIKV disease in southern Viet Nam in 2016 and described our early surveillance data. The surveillance system for ZIKV disease underwent several phases of optimization in 2016, guided by the most up-to-date local data. In phase I, PI-HCMC had initially explored integrating ZIKV testing with the existing dengue surveillance. Inpatients with clinically suspected dengue who tested negative for dengue by nonstructural protein 1 or viral culture in 2015 were tested for ZIKV using RT–PCR. All 96 dengue-negative patients were negative for ZIKV (unpublished data). Based on this data, in phase II we decided to implement a dedicated surveillance system for ZIKV that focused on the outpatient ward where patients with milder clinical presentations seek medical care. We believed that this approach was more appropriate than integrating ZIKV surveillance into existing dengue surveillance that is primarily focused on more severe cases from inpatient wards. Focusing on mild cases was also supported by evidence that everyone diagnosed with ZIKV disease outside of Viet Nam after travelling to the country had only mild symptoms.[4–6] In phase III, after successfully detecting ZIKV-positive cases in outpatient departments, particularly at district hospitals, ZIKV surveillance was gradually expanded throughout southern Viet Nam, focusing on outpatient services at district hospitals in HCMC. In addition, the surveillance case definition was adjusted based on our initial analysis of symptoms associated with ZIKV-positive patients, and guided by the latest literature, which showed a high prevalence of rash in ZIKV-positive patients relative to fever, joint pain, muscle pain and conjunctivitis.[14] Our approaches were

Fig. 3. **Spot map of confirmed ZIKV-positive cases identified through the ZIKV surveillance system, Ho Chi Minh City, Southern Viet Nam, 2016**



Dis., district; HCM, Ho Chi Minh; ZIKV, Zika virus.
Green spots: cases of the current month; Red spots: cases from the start of the outbreak in February 2016 to the previous month.

in line with those proposed by the *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies*,[15] which suggests surveillance systems should be effective, efficient, flexible and promptly adaptable to new available information and needs before, during and after events. In the rapidly changing contexts of an ongoing outbreak, Viet Nam demonstrated flexibility by shifting sampling sites from inpatient to outpatient services and revising case definitions as new knowledge became available. Here, we demonstrate that the surveillance system established during the event in 2016 successfully detected ZIKV-positive cases in southern Viet Nam.

The number of ZIKV-positive results increased markedly in quarter 4, likely reflecting an actual increase in ZIKV transmission during this period. However, the increase could also be due to other contributing factors, including those that may have enhanced the ability of the surveillance system to more efficiently detect ZIKV infections. First, since fewer specimens were tested in quarter 3 due to resource constraints, ZIKV infections may have been under-detected in that quarter, leading to a more dramatic increase in ZIKV infections in quarter 4. Second, the number of surveillance sites doubled from 32 in March to 71 in November, alongside a gradual decentralization of surveillance sites, which resulted in a higher proportion of specimens being collected from district facilities. Third, a new case definition with rash being the primary symptom was first introduced in some district hospitals in March 2016 and was formally implemented across all surveillance sites from August 2016 after accumulating evidence suggested that this could be a better case definition to identify more ZIKV-positive cases. Evolution of the surveillance system may have led to increased efficiency in detecting ZIKV-positive cases.

Data from quarter 4 showed that the positivity rate was similar across regional, provincial and district-level facilities. This result suggests that people with ZIKV infection are attending various types of health facilities, and our ability to detect ZIKV infection might be similar across different levels of health facilities. In one of the sentinel districts (District 2), sample collection was experimentally decentralized to the commune health station and private clinics in quarter 4. The decentralized sample collection had a similar positivity rate of ZIKV infection. However, the large majority of cases in 2016 in HCMC were from district hospitals. Therefore, we expect that district-level facilities will continue to play a central role in the surveillance system for ZIKV disease in southern Viet Nam.

Our data suggested the number of the reported cases differed considerably among districts and the reported cases concentrated in certain districts in HCMC. Careful interpretation is needed to understand such results since several factors could influence the level of case detection to varying degrees. It would be reasonable to consider that there were clusters of active transmission in certain districts. However, the geographical differences could also be due to other factors such as the selection of sentinel sites and the case definition not being applied consistently across hospitals by different clinicians. In addition, intensified guidance from national and local authorities following the ZIKV disease outbreak in Singapore in September 2016 may have raised clinicians' awareness levels and made it more likely for them to collect and test specimens for ZIKV infections.

Our results showed that adults, especially those aged 30–59 years, were more affected by ZIKV infection than children. This finding is consistent with previous literature that suggests that children with ZIKV infections generally experience mild symptoms.[16] However, our results contrast with the age distribution of dengue infection, showing that children are more affected by dengue than adults in southern Viet Nam.[18] One possible explanation is that the adult population of southern Viet Nam may have largely developed immunity against dengue, which has been hypothesized to enhance ZIKV infection through antibody-dependent enhancement.[19] Ongoing ZIKV seroprevalence surveys in southern Viet Nam may provide a better understanding of population immunity against ZIKV.

The first year of ZIKV surveillance in southern Viet Nam provided critical evidence that will inform surveillance and response efforts in Viet Nam and other countries, and offered important lessons in optimizing ZIKV surveillance systems. Viet Nam's approach of focusing on outpatient services of health care facilities effectively detected ZIKV-positive cases. However, both the fluctuation in the number of tests performed and the change in case definition made it challenging to interpret trends in local transmission. In addition, given that the ZIKV-positive cases were identified based on the symptoms listed in the case definition, the symptoms of the ZIKV-positive cases shown here may not be representative of all ZIKV-infected individuals.

Moving forward, it may be necessary to prioritize the surveillance approach based on resource availability, especially given the high cost of the current molecular testing methodology using ZIKV PCR. Based on our data, we believe there may be two future directions for ZIKV surveillance to achieve two separate but interrelated objectives. First, Viet Nam may consider monitoring transmission trends by establishing sentinel sites to detect all individuals who meet the case definition, irrespective of age and sex. Based on the system described here, which was developed in response to WHO's PHEIC declaration for Zika, the Ministry of Health of Viet Nam developed guidelines in 2017 for an ongoing, integrated Chikungunya-Dengue-Zika (CDZ) sentinel surveillance system.[20] Second, depending on resource availability, it is important to prioritize Zika testing and surveillance for pregnant women presenting with symptoms consistent with the case definition, regardless of whether they are from sentinel sites or other health facilities to better detect pregnancies that are at risk for microcephaly. In 2017, Viet Nam developed guidelines for all obstetric clinics and hospitals to register, investigate and report pregnancy courses and outcomes of mothers with confirmed ZIKV and babies with microcephaly;[21] however, fewer laboratory samples than expected have been collected and tested for ZIKV to date. Therefore, it would be pertinent to continue to strengthen the implementation of the guidelines. In addition to the ZIKV surveillance activities, we believe full genome sequencing of selected specimens in southern Viet Nam may also shed light on the phylogenetic lineage of circulating ZIKV in the country.

CONCLUSIONS

In our interconnected world, all countries are becoming increasingly aware of the borderless nature of emerging and re-emerging infectious diseases. Monitoring a new disease in the population requires establishing a surveillance system in the context of many unknowns while ensuring flexibility of surveillance systems to adapt to changing information and needs. Here, we demonstrate an adaptable sentinel surveillance system for ZIKV disease in Viet Nam, where it was optimized in a phased approached in 2016, using the most up-to-date local data. We hope that in sharing Viet Nam's experiences with ZIKV surveillance we can document what is often missing in the literature: the real-world challenges faced in public health and the practical solutions needed to conquer these obstacles.

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Conflicts of interest

The authors have no competing interests or financial conflicts.

References

1. Pond WL. Anthropod-borne virus antibodies in sera from residents of South-East Asia. Trans R Soc Trop Med Hyg. 1963 Sep;57(5):364–71. doi:10.1016/0035-9203(63)90100-7 pmid:14062273
2. Quyen NTH, Kien DTH, Rabaa M, Tuan NM, Vi TT, Van Tan L, et al. Chikungunya and Zika virus cases detected against a backdrop of endemic dengue transmission in Vietnam. Am J Trop Med Hyg. 2017 Jul;97(1):146–50. doi:10.4269/ajtmh.16-0979 pmid:28719300
3. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations – 1 February 2016. Geneva: World Health Organization; 2016 (https://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/).
4. Hashimoto T, Kutsuna S, Tajima S, Nakayama E, Maeki T, Taniguchi S, et al. Importation of Zika virus from Vietnam to Japan, November 2016. Emerg Infect Dis. 2017 Jul;23(7):1223–5. doi:10.3201/eid2307.170519 pmid:28445122
5. Katanami Y, Kutsuna S, Taniguchi S, Tajima S, Takaya S, Yamamoto K, et al. Detection of Zika virus in a traveller from Vietnam to Japan. J Travel Med. 2017 Sep 1;24(5). doi:10.1093/jtm/tax031 pmid:28498965
6. Meltzer E, Lustig Y, Leshem E, Levy R, Gottesman G, Weissmann R, et al. Zika virus disease in traveler returning from Vietnam to Israel. Emerg Infect Dis. 2016 Aug;22(8):1521–2. doi:10.3201/eid2208.160480 pmid:27331627
7. Guidelines on surveillance and prevention and control of Zika virus disease - 2 February 2016. Hanoi: Ministry of Health of the Socialist Republic of Viet Nam; 2016 (https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Quyet-dinh-3792-QD-BYT-huong-dan-giam-sat-phong-chong-benh-do-vi-rut-Zika-2016-317999.aspx, accessed 12 Apr 2019).
8. Guidelines on diagnosis and treatment of Zika virus disease - 5 February 2016. Hanoi: Ministry of Health of the Socialist Republic of Viet Nam; 2016 (https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Quyet-dinh-439-QD-BYT-Huong-dan-chan-doan-dieu-tri-benh-do-vi-rut-Zika-302367.aspx, accessed 12 Apr 2019).
9. Zika virus infection - Viet Nam - 12 April 2016. Geneva: World Health Organization; 2016 (https://www.who.int/csr/don/12-april-2016-zika-viet-nam/en/).
10. Lan PT, Quang LC, Huong VTQ, Thuong NV, Hung PC, Huong TTLN, et al. Fetal Zika virus infection in Vietnam. PLoS Curr. 2017 Sep 5;9:9. pmid:29188136
11. Moi ML, Nguyen TTT, Nguyen CT, Vu TBH, Tun MMN, Pham TD, et al. Zika virus infection and microcephaly in Vietnam. Lancet Infect Dis. 2017 Aug;17(8):805–6. doi:10.1016/S1473-3099(17)30412-7 pmid:28741545
12. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis. 2008 Aug;14(8):1232–9. doi:10.3201/eid1408.080287 pmid:18680646
13. WHO guidelines on ethical issues in public health surveillance. Geneva: World Health Organization; 2017 (https://www.who.int/ethics/publications/public-health-surveillance/en/).
14. Musso D, Gubler DJ. Zika virus. Clin Microbiol Rev. 2016 Jul;29(3):487–524. doi:10.1128/CMR.00072-15 pmid:27029595
15. Asia Pacific strategy for emerging diseases and public health emergencies (APSED III): advancing implementation of the International Health Regulations (2005). Manila: WHO Regional Office for the Western Pacific; 2017 (http://iris.wpro.who.int/bitstream/handle/10665.1/13654/9789290618171-eng.pdf).
16. Goodman AB, Dziuban EJ, Powell K, Bitsko RH, Langley G, Lindsey N, et al. Characteristics of children aged <18 years with Zika virus disease acquired postnatally - U.S. states, January 2015-July 2016. MMWR Morb Mortal Wkly Rep. 2016 Oct 7;65(39):1082–5. doi:10.15585/mmwr.mm6539e2 pmid:27711041
17. Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, Mallet HP, et al. Zika virus, French Polynesia, South Pacific, 2013. Emerg Infect Dis. 2014 Jun;20(6):1085–6. doi:10.3201/eid2006.140138 pmid:24856001
18. Dengue - fact sheet [2 February 2018]. Ha Noi: WHO Representative Office in Viet Nam; 2018 (http://www.wpro.who.int/vietnam/topics/dengue/factsheet/en/).
19. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with Zika virus. Nat Immunol. 2016 Sep;17(9):1102–8. doi:10.1038/ni.3515 pmid:27339099
20. Guidelines on the integrated Chikungunya-Dengue-Zika (CDZ) sentinel surveillance system – 3 July 2017. Hanoi: Ministry of Health of the Socialist Republic of Viet Nam; 2017 (https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Quyet-dinh-3091-QD-BYT-2017-giam-sat-long-ghep-sot-xuat-huyet-Dengue-vi-rut-Zika-Chikungunya-353831.aspx, accessed 12 Apr 2019).
21. Guidelines on the surveillance of microcephaly in foetus and the infants exposed to Zika – 13 April 2017. Hanoi: Ministry of Health of the Socialist Republic of Viet Nam; 2017 (https://thuvienphapluat.vn/van-ban/The-thao-Y-te/Quyet-dinh-1425-QD-BYT-giam-sat-hoi-chung-dau-nho-o-thai-nhi-va-tre-so-sinh-do-vi-rut-Zika-2017-346513.aspx, accessed 12 Apr 2019).

Dengue in Fiji: epidemiology of the 2014 DENV-3 outbreak

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Introduction: Dengue virus serotype-3 caused a large community-level outbreak in Fiji in 2013 and 2014. We aimed to characterize the demographic features of affected individuals and to determine dengue mortality during the outbreak.

Methods: All laboratory-confirmed dengue cases and deaths were included in this study. Incidence and mortality were calculated according to demographic variables.

Results: A total of 5221 laboratory-confirmed cases of dengue were included in this analysis. The majority of patients were male (54.5%) and indigenous Fijians (iTaukei) (53.5%). The median age was 25 years old. The overall incidence was 603 per 100 000 population. The age-specific incidence was highest among people between 20 and 24 years of age (1057 per 100 000) for both sexes. The major urban and peri-urban areas of Suva and Rewa subdivisions reported the highest incidence of >1000 cases per 100 000 population.

A total of 48 deaths were included in this analysis. The majority of dengue-related deaths occurred in males (62.5%) and in the iTaukei (60.4%) population. The median age at death was 35 years old. The overall dengue-related deaths was estimated to be 5.5 deaths per 100 000 population. Dengue mortality was higher for males (6.8 per 100 000) than females. The highest age- and sex-specific mortality of 18 per 100 000 population was among males aged 65 years and older.

Discussion: Dengue morbidity and mortality were highest among males, indigenous people and residents of urban and peri-urban locations. Effective and integrated public health strategies are needed to ensure early detection and appropriate outbreak control measures.

Dengue is one of the most common vector-borne diseases of public health importance globally. The disease is endemic in more than 100 countries,[1] and it is estimated that 390 million dengue infections occur annually.[2] Dengue has emerged as a significant public health problem in Pacific island countries, including Fiji, causing large outbreaks in recent years.[3–5]

Dengue is endemic in Fiji, and its epidemiology has showed dynamic changes over the last four decades.[6–8] Dengue distribution is characterized by low endemic levels of transmission, usually dominated by a single serotype with cyclical patterns of outbreaks following introduction of a new serotype.[4,7] In non-outbreak years, the estimated incidence in Fiji ranged from 0.34 to 51.15 per 100 000 population.[9] Historical reports documented two nationwide outbreaks in 1971 and 1975,[10,11] after which there was no major outbreak for over a decade. Since 1988, outbreaks have occurred with increasing frequency, with six major outbreaks reported between 1998 and 2017.[6,7,9,12,13] Major outbreaks have occurred in a cyclical pattern of approximately every four to five years.

In 2013, dengue serotype-3 virus (DENV-3) re-emerged in the South Pacific after 18 years, causing concurrent outbreaks in several Pacific island countries.[3–5] Before then, DENV-3 had last circulated in Fiji in 1989 and 1990, causing a large community-level outbreak. At the end of 2013, dengue cases began to increase in Fiji, and an outbreak was declared that continued into 2014. During this outbreak, over 15 000 cases (1733 per 100 000) were reported nationwide with a record number of deaths.[9] We investigated demographic patterns of incidence and mortality during the 2014 outbreak period that could provide important information for the prediction and control of future outbreaks. We aimed to characterize dengue cases and to determine the magnitude of mortality in 2014.

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METHODS

Dengue surveillance in Fiji includes notification of laboratory-confirmed and clinically suspected cases. Confirmatory testing is primarily performed at the national public health laboratory. The laboratory tests used in Fiji at the time of the outbreak were enzyme-linked immunosorbent assay and non-structural protein antigen. All confirmed cases are reported to the Fiji Centre for Communicable Disease Control (FCCDC). Laboratory surveillance data include demography (patient's name, hospital number, age, sex, ethnicity, address, health facility), date of reporting, and test results. Information not routinely collected for surveillance purposes are date of onset, signs and symptoms, dengue type (dengue fever or dengue haemorrhagic fever), patient outcome (mortality) and socioeconomic data such as education level, occupation, and income. No established surveillance system for determining circulating serotypes exists; however, during outbreaks, representative blood samples are sent to overseas laboratories to identify the specific dengue virus causing the outbreak.

Health-care services in Fiji are provided by the Ministry of Health and Medical Services (MoHMS) which is divided into four divisions: Central, Northern, Western and Eastern. Each division is further divided into several subdivisions that have secondary-level (subdivisional) hospitals that receive referrals from community-level facilities.[9]

All health-care providers report suspected cases of dengue through the national notifiable disease surveillance schedule (NNDSS). The NNDSS staff monitors a comprehensive list of 46 diseases that medical officers are required to report weekly. The NNDSS only contains data on the number, age and sex of patients. All line lists of laboratory-confirmed cases are also submitted to the NNDSS during outbreaks.

Dengue deaths are reported using the standardized medical cause of death certificates (MCDC) that are completed by medical officers. Dengue must be explicitly stated on the MCDC to be coded as a dengue death. All deaths are registered into the patient information system (PATIS plus) electronic database using MCDC data and further coded according to the International Classification of Diseases, Tenth Revision (ICD 10) through an automated system called Iris (version 4.0).[14]

For our epidemiological review, all laboratory-confirmed dengue cases reported to FCCDC in 2014 were included. Duplicate entries of patients who were cases more than once within an incubation period were removed. Deaths attributed to dengue were obtained from PATIS plus. Three additional laboratory-confirmed dengue deaths in 2014 identified in another study[15] were added in the mortality analysis, even though they were not in the official record.

Data analysis was performed using Microsoft Office Excel 2010 and SPSS software version 24. Descriptive statistics were used for the demographic profile (sex, ethnicity and age) of laboratory-confirmed dengue cases and dengue-related deaths.

All descriptive analysis results were calculated as proportions and medians with interquartile ranges.

Overall and specific incidence and mortality, stratified by demographic variables, were computed using population projections provided by the Fiji Bureau of Statistics (FBOS) for 2014 (FBOS 2014, projected population, unpublished). Since FBOS data are not disaggregated for medical divisions, incidence and mortality by medical divisions and subdivisions were calculated using the 2014 population estimates from the MoHMS.[9] Incidence and mortality are expressed per 100 000 population. The geographic distribution of dengue patients was evaluated using the location of the treating health facilities since patients' home addresses were not systematically recorded.

Ethical approval was given by the College Health and Research Ethics Committee, College of Medicine, Nursing and Health Science, Fiji National University and the National Health Research and Ethics Review Committee (2016.110.N.W.).

RESULTS

A total of 5249 laboratory-confirmed cases of dengue were reported in 2014 (FCCDC, unpublished). After excluding 28 duplicates, 5221 cases were included in this analysis. Most of the cases were male (54.5%), were iTaukei (indigenous Fijians) (53.5%) and were residents of the Central Division (65.5%) (**Table 1**). The median age (interquartile range [IQR]) was 25 years (16–35). The majority of cases (80%) were reported during the

Table 1. **Demographic characteristics of laboratory-confirmed and dengue mortality cases**

	Confirmed dengue cases (*n* = 5221) *n* (%)	Dengue deaths (*n* = 48) *n* (%)
Sex		
Male	2848 (54.5)	30 (62.5)
Female	2373 (45.5)	18 (37.5)
Ethnicity		
iTaukei	2794 (53.5)	22 (60.4)
Indian descent	2248 (43.1)	16 (33.3)
Others	179 (3.4)	3 (6.3)
Age group		
0–4	190 (3.6)	5 (10.4)
5–14	852 (16.3)	4 (8.3)
15–24	1464 (28.0)	9 (18.8)
25–34	1211 (23.2)	6 (12.5)
35–44	594 (11.4)	4 (8.3)
45–54	408 (7.8)	6 (12.5)
55–64	208 (4.0)	8 (16.7)
65+	123 (2.4)	6 (12.5)
Unknown	171 (3.3)	0
Median (IQR)	35 (18–57)	25 (16–35)
Division		
Central	3418 (65.5)	20 (40.7)
Western	1080 (20.7)	18 (37.5)
Northern	711 (13.6)	9 (18.8)
Eastern	12 (0.2)	1 (2.1)

IQR, interquartile range.

first quarter with the highest number of cases occurring during epidemiologic week 7 from 23 February to 1 March 2014 (614 cases).

The overall incidence of laboratory-confirmed dengue was 603 cases per 100 000 population. The incidence was higher in males (674 per 100 000) compared with females (577 per 100 000). Age-specific incidence progressively rose after the age of 10 years and reached its highest among people between 20 and 24 years of age (1057 per 100 000) for both sexes, and it steadily declined in the age group 50 years and above (**Fig. 1**). Further analysis of the incidence by geographical location showed the highest burden in the Central Division (912 per 100 000) followed by the Northern and Western Divisions (542.8 per 100 000 and 278.6 per 100 000, respectively). The major urban and peri-urban subdivisions, within the Central Division (Suva and Rewa), reported the highest incidence of >1000 per 100 000 population (**Fig. 2**).

A total of 45 deaths attributed to dengue were reported to MoHMS (PATIS plus, unpublished). Three additional dengue-related deaths were found during another study.[15] A total of 48 deaths were included in this analysis. The majority of reported deaths occurred in males (62.5%), iTaukei (60.4%) and residents of the Central Division (40.7%). The median IQR age at death was 35 years (18–57), and five (10%) deaths were among children under the age of 5 years. Overall mortality was estimated to be 5.5 deaths per 100 000 population. Dengue mortality was higher for males (6.8 per 100 000) compared to females (4.2 per 100 000). Mortality increased steadily with age: the highest mortality was among men aged more than 65 years (18 per 100 000) (**Fig. 3**). The lowest recorded mortality was for boys aged between 5 and 14 years. Those under 5 years of age had higher mortality (5.6 per 100 000) compared to children between 5 and 14 years of age (2.4 per 100 000). The Northern Division had the highest dengue mortality (6.9 per 100 000) followed by the Central (5.3 per 100 000) and Western Divisions (4.6 per 100 000). Two subdivisions in the North (Bua and Macuata) reported the highest mortality (12 per 100 000). Among notified deaths (n = 45), the underlying cause of death was reported as dengue fever in most (62.2%). The remaining 37.8% were reported as dengue haemorrhagic fever.

DISCUSSION

Dengue has emerged as a significant public health problem in Fiji and the South Pacific, causing large outbreaks in recent years.[3,16] A better understanding of the epidemiology of dengue is essential to appropriately allocate limited resources for dengue control and to better evaluate the impact of control activities. We conducted a retrospective review of dengue cases in Fiji during the 2014 DENV-3 outbreak to characterize the demographic features and to determine the magnitude of dengue-related mortality.

In this study, the median age of infection was 25 years, and age-specific incidence was highest among people between the ages of 15 and 34 years. The predominance among those in these age strata may be

Fig. 1. **Age- and sex-specific incidence of laboratory-confirmed dengue in Fiji in 2014**

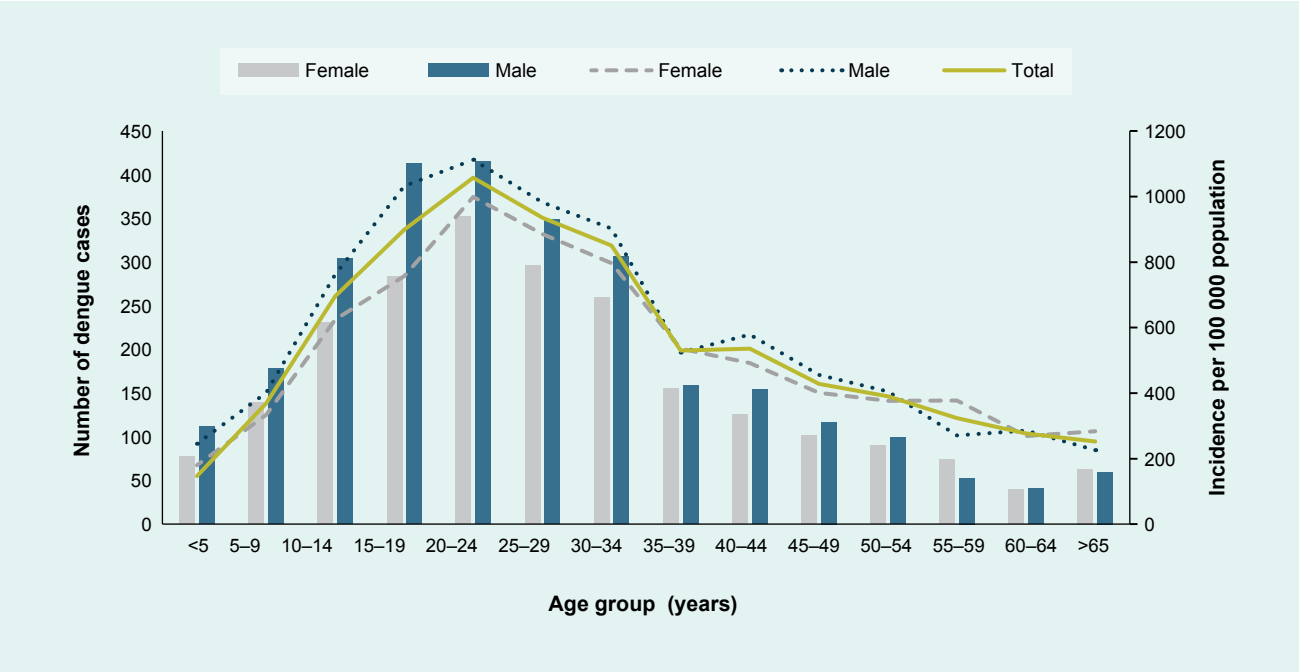


Fig. 2. **Dengue incidence by medical subdivision in Fiji in 2014**

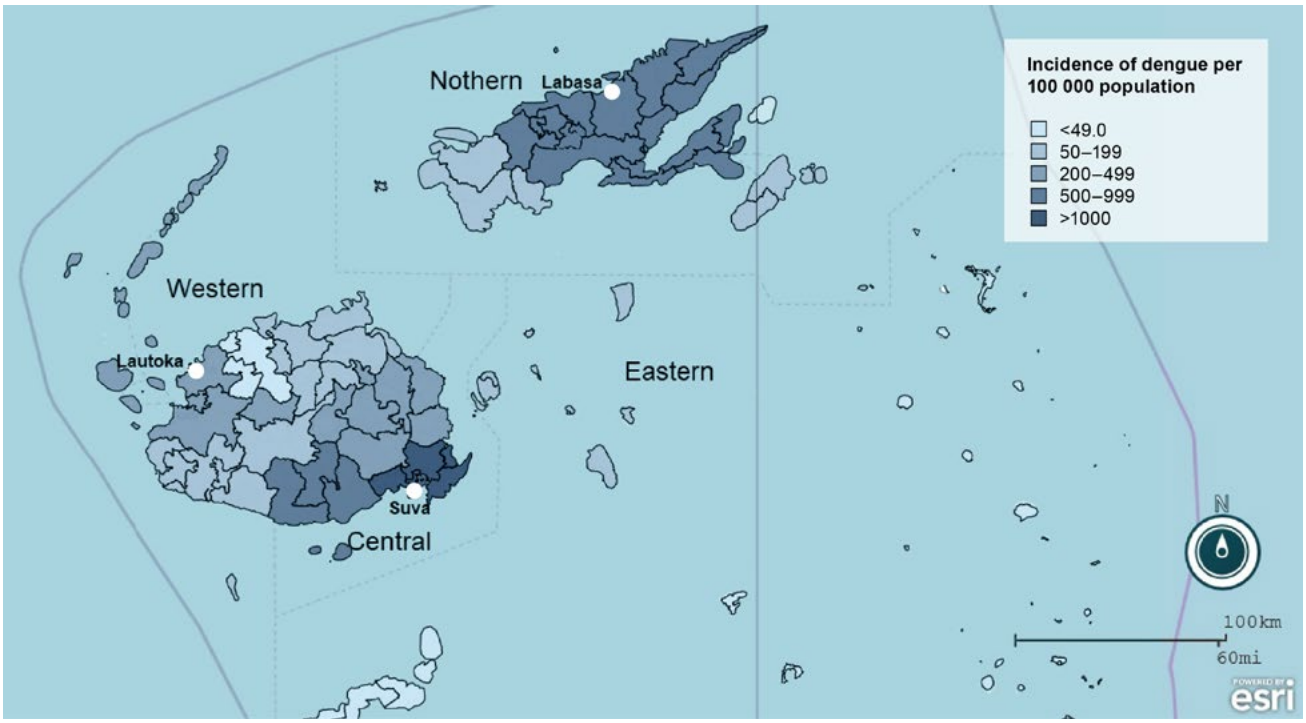
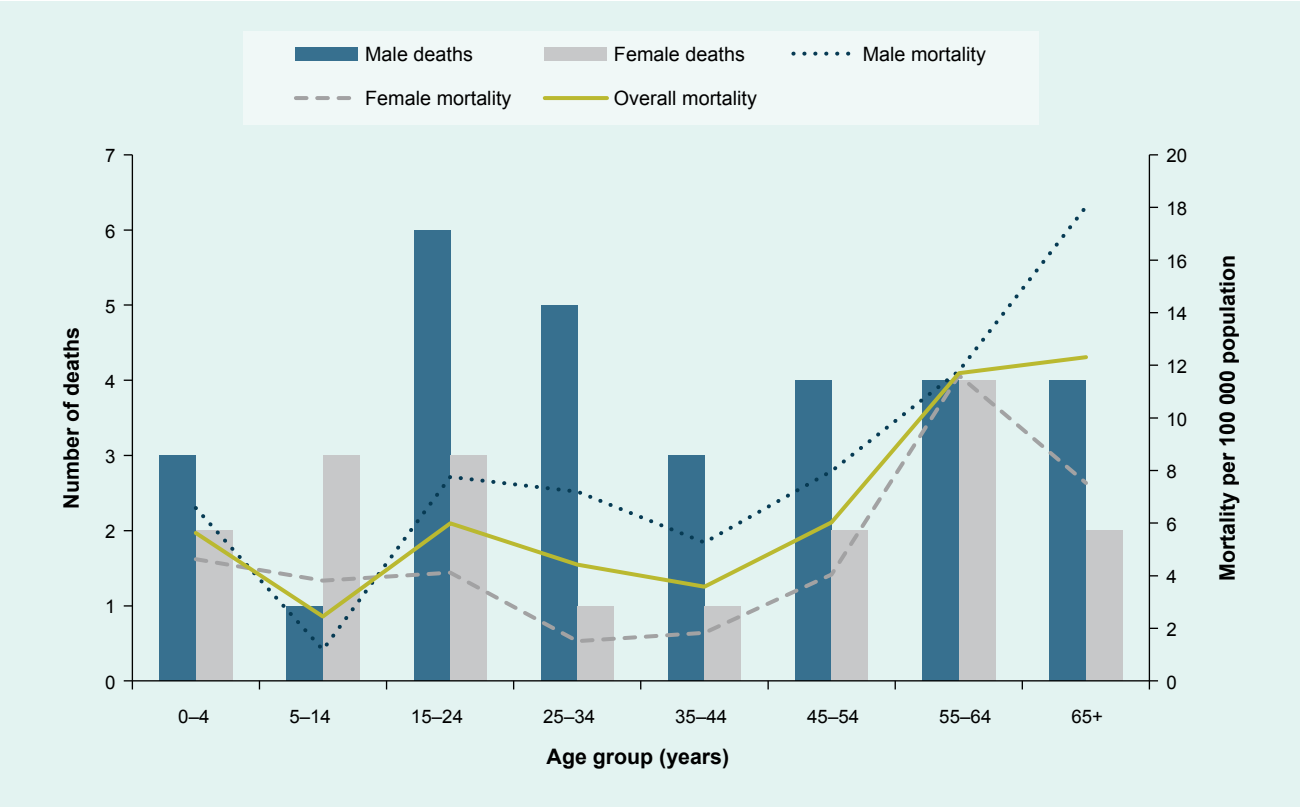


Fig. 3. **Dengue mortality in 2014 outbreak in Fiji, by age group and sex**



explained by their vulnerability to DENV-3, which last circulated in the country 24 years prior. Our findings are consistent with reports from previous outbreaks in Fiji that showed higher morbidity among adolescents and young adults,[6,8,10,11] which differs from patterns seen in hyperendemic countries in Asia where dengue is mainly reported among young children.[17] However, a shift in age groups has been demonstrated in some countries such as Singapore, Malaysia and Thailand, when dengue outbreaks occurred after the introduction of a new serotype mainly affecting the adult population.[18–20]

Males had a higher disease burden than females, as demonstrated by the increased absolute number and incidence among the male population. Previous outbreak and non-outbreak reports also demonstrated male preponderance in Fiji[6,8,11] and other countries.[20,21] We did not investigate the reason for the observed difference in incidence by sex, but possible reasons include increased risk of infection among men due to occupational exposure.

We report high dengue incidence in the main urban and peri-urban areas of Fiji. In the Central Division, Suva (the capital city) and Nausori, the adjacent peri-urban hub, reported the highest incidence with over 1000 cases per 100 000 population. Previous studies in Fiji reported a higher number of dengue cases and mosquito vectors in urban and peri-urban areas.[8,22,23] Increased reporting from urban areas could be due to greater availability of health services and access to testing. Urban and peri-urban areas in Fiji are characterized by expansive informal settlements with high population density and limited sanitation and public services.[22,24] The Suva–Nausori corridor in the Central Division has the largest concentration of informal settlements where access to clean water and sanitation may be an issue.[25] Globally, urban and peri-urban centres are identified as high-risk areas for dengue.[2] Increased risk of spread in these areas is attributed to population movement, travel,[2,23,26] overcrowding, increased vector breeding sites,[26] poor sanitation facilities and hygiene[22] and limited access to health care.[19] Dengue-prevention strategies in Fiji should consider the social determinants of health and include broader socioeconomic influences of better urban planning and improved sanitation to reduce the overall transmission risk factors.

During the 2014 outbreak, the majority of cases were reported in the first three months of the year. Previous outbreaks and surveillance reports showed similar seasonal patterns of dengue from November to April, coinciding with the warm and wet season.[11,23] This time period also overlaps with the cyclone season, when localized dengue outbreaks have been reported following heavy rain and flooding.[27] A previous study demonstrated a significant correlation between the incidence of dengue with high temperatures and increased rainfall in three study sites in Fiji.[23]

Mortality in the 2014 DENV-3 outbreak was higher than that of previously reported outbreaks in Fiji. The 1997–1998 DENV-2 outbreak[7] reported 13 deaths with an estimated mortality of 1.7 deaths per 100 000 population (based on the 1996 census). A review of the 1989–1990 DENV-1 outbreak[6] reported an estimated mortality of 2.1 deaths per 100 000 population (for the estimated population size in 1990). Our findings show higher mortality compared to other endemic and hyperendemic countries in South-East Asia and South America where dengue mortality during outbreak and non-outbreak years ranges from 0.1 to 0.5 per 100 000 population.[28,29] Literature suggests dengue deaths have increased over the last few decades in some countries and regions.[28–30] Increased mortality has also been attributed to greater health-seeking behaviour and increased sensitivity of surveillance for detecting dengue deaths.[28]

The higher mortality among males has been reported previously[31] and is thought to be due largely to differences in health-seeking behaviour.[30] In this study, mortality progressively increased after the age of 55 years, particularly for males. The high mortality among elderly patients has been attributed to decreased immunity, compromised organ function, underlying co-morbidities and prolonged hospitalizations, which increase the risk of hospital-acquired infection or secondary infection.[32,33] This trend is likely to continue as the population ages and the burden of noncommunicable diseases grows.

We found higher mortality in the Northern Division despite the relatively lower incidence. The Division is served by one divisional hospital (Labasa Hospital) and three subdivisional hospitals located in the main urban and peri-urban areas. While no studies have evaluated access to health services and quality of care in the Division, it has the highest poverty rate in the country and poor health indicators.[25] Health-seeking behaviours of the Northern Division population are likely limited by socioeconomic, geographic and infrastructure barriers, especially for rural communities. Labasa Hospital has few specialist doctors and a smaller intensive care unit compared to other divisional hospitals, which could impact the quality of care for critically ill patients, resulting in higher mortality. We cannot substantiate the quality of care and access to health services from the surveillance data. Further studies are warranted to determine the possible reasons of the increased mortality and to address health system-related issues.

In addition, the ethnic distribution of dengue mortality requires further investigation. Reports from a previous outbreak showed increased frequency of haemorrhagic manifestations in the iTaukei people; however, a larger proportion of deaths occurred in Fijians of Indian descent.[6] In contrast, in this outbreak, a large proportion of deaths occurred among the iTaukei people. A global review suggests that ethnic disparities in dengue severity remain unexplained.[30] One study shows that these differences may be largely due to socioeconomic factors that can be addressed by public health interventions.[30]

A review of the global literature on dengue mortality has highlighted underreporting and the difficulties associated with attributing dengue as a cause of death as factors challenging the understanding of mortality trends. In addition, heterogeneity in reporting of mortality and its predictors limits comparisons between studies.[30]

Limitations

This study has several limitations. We limited our analysis to 2014 data to ensure a systematic line listing of cases. It is expected that given the broad clinical spectrum of dengue, many cases would not have been reported, particularly early in the outbreak (end of 2013). Between March and June 2014, only clinically suspected dengue patients were tested due to a shortage of dengue laboratory testing kits. Therefore, the numbers used in this study are likely to significantly underestimate the actual number of dengue cases and deaths that occurred in Fiji during this outbreak. In addition, incomplete case information (such as patient residential address, date of onset) further limits epidemiological analysis. Although residential address information was not available, geographical location of the treating health facility was considered appropriate as patients generally use the health facility closest to their

residents. Health-care providers should systematically differentiate and specify the cause of dengue-related deaths, such as dengue shock and dengue haemorrhagic fever, for appropriate coding of underlying causes of death.

Conclusions and recommendations

Vector-borne diseases remain a significant public health challenge in Pacific island countries and are expected to remain so due to a combination of environmental, climatic and socioeconomic factors. These factors increase the risk of transmission of dengue and emerging arboviral diseases such as chikungunya and Zika.[3] The high incidence and mortality described in this study indicate a need for continued surveillance of dengue in Fiji with regular assessments of its epidemiology to inform broad prevention strategies. We suggest that there is a need to integrate disease and vector surveillances to identify outbreaks earlier in high-risk areas. In addition, vector surveillance needs to be improved to provide real-time data on vector density in high-risk areas and to identify circulating serotypes before seasonal outbreaks occur. This will allow for early interventions to reduce breeding sites in targeted areas and inform risk communication strategies.

Early detection and prompt case management are crucial to reduce dengue mortality. We reported high mortality among males, indigenous people and residents of urban and peri-urban areas. This information needs to be incorporated into assessing high-risk patients and interventions for prevention. Further studies are required to identify specific risk factors for mortality among dengue patients in Fiji.

The 2014 DENV-3 outbreak in Fiji demonstrated the increasing risk of a large-scale community outbreak with increased mortality following introduction of a new dengue serotype.

Effective and integrated public health strategies are needed to ensure early detection and implement outbreak control measures.

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Conflict of interest

None.

References

1. Dengue and severe dengue. Geneva: World Health Organization; 2017 (https://www.who.int/mediacentre/factsheets/fs117/en/, accessed 5 January 2018).
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504–7. doi:10.1038/nature12060 pmid:23563266
3. Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, et al. Concurrent outbreaks of dengue, chikungunya and Zika virus infections - an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. Euro Surveill. 2014 Oct 16;19(41):20929. doi:10.2807/1560-7917.ES2014.19.41.20929 pmid:25345518
4. Cao-Lormeau VM, Roche C, Musso D, Mallet HP, Dalipanda T, Dofai A, et al. Dengue virus type 3, South Pacific Islands, 2013. Emerg Infect Dis. 2014 Jun;20(6):1034–6. doi:10.3201/eid2006.131413 pmid:24856252
5. Nogareda F, Joshua C, Sio A, Shortus M, Dalipanda T, Durski K, et al. Ongoing outbreak of dengue serotype-3 in Solomon Islands, January to May 2013. West Pac Surveill Response. 2013 Jul 30;4(3):28–33. doi:10.5365/wpsar.2013.4.2.013 pmid:24319611
6. Fagbami AH, Mataika JU, Shrestha M, Gubler DJ. Dengue type 1 epidemic with haemorrhagic manifestations in Fiji, 1989-90. Bull World Health Organ. 1995;73(3):291–7. pmid:7614660
7. Prakash G, Raju AK, Koroivueta J. DF/DHF and its control in Fiji. Dengue Bull. 2001;21:21–7 (https://apps.who.int/iris/bitstream/handle/10665/163682/dbv25p21.pdf).
8. Erenavula JIJ, Ledua KS, Naicker P, Tukana VL, Kishore K. Dengue fever in Fiji: incidence from 2003–2009. Fiji Journal of Public Health. 2012;1(1):37–9 (https://www.health.gov.fj/eJournal/index.php/2016/02/18/dengue-fever-in-fiji-incidence-from-2003-2009/).
9. Ministry of Health & Medical Services annual report 2014: Suva: Fiji Ministry of Health and Medical Services; 2014 (https://www.health.gov.fj/PDFs/Annual%20Report/Annual%20Report%202014.pdf, accessed 19 February 2016).
10. Maguire T, Miles JAR, Macnamara FN, Wilkinson PJ, Austin FJ, Mataika JU. Mosquito-borne infections in Fiji. V. The 1971-73 dengue epidemic. J Hyg (Lond). 1974 Oct;73(2):263–70. doi:10.1017/S0022172400024116 pmid:4529580
11. Reed D, Maguire T, Mataika J. Type 1 dengue with hemorrhagic disease in Fiji: epidemiologic findings. Am J Trop Med Hyg. 1977 Jul;26(4):784–91. doi:10.4269/ajtmh.1977.26.784 pmid:889018
12. Dengue fever situation in the Pacific island countries and territories, 30 September 2008. Noumea: Secretariat of the Pacific Community; 2008 (http://www.pphsn.net/ENGLISH/Publications/InformACTION/IA29/Selected_articles_per_disease-2.htm#dengue, accessed 19 December 2017).
13. Pacific syndromic surveillance report, week 33, ending 20 August 2017. Manila: WHO Regional Office for the Western Pacific; 2017 (http://www.wpro.who.int/southpacific/programmes/communicable_diseases/disease_surveillance_response/PSS-20-August-2017/en/).
14. International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Geneva: World Health Organization; 2010 (https://apps.who.int/classifications/icd10/

browse/2016/en, accessed 3 March 2016).

15. Getahun A, Batikawai A, Khan S, Nand D, Naidu R, Ram R, et al. Factors associated with dengue fatality in Fiji: a hospital-based case control study. Pacific Health Dialog. 2019;21(3):139–147. doi: 10.26635/phd.2019.603
16. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization; 2009 (https://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf, accessed 3 February 2016).
17. Bravo L, Roque VG, Brett J, Dizon R, L'Azou M. Epidemiology of dengue disease in the Philippines (2000-2011): a systematic literature review. PLoS Negl Trop Dis. 2014 Nov 6;8(11):e3027. doi:10.1371/journal.pntd.0003027 pmid:25375119
18. Limkittikul K, Brett J, L'Azou M. Epidemiological trends of dengue disease in Thailand (2000-2011): a systematic literature review. PLoS Negl Trop Dis. 2014 Nov 6;8(11):e3241. doi:10.1371/journal.pntd.0003241 pmid:25375766
19. Mohd-Zaki AH, Brett J, Ismail E, L'Azou M. Epidemiology of dengue disease in Malaysia (2000-2012): a systematic literature review. PLoS Negl Trop Dis. 2014 Nov 6;8(11):e3159. doi:10.1371/journal.pntd.0003159 pmid:25375211
20. Ler TS, Ang LW, Yap GS, Ng LC, Tai JC, James L, et al. Epidemiological characteristics of the 2005 and 2007 dengue epidemics in Singapore - similarities and distinctions. West Pac Surveill Response. 2011 May 20;2(2):24–9. doi:10.5365/wpsar.2010.1.1.011 pmid:23908885
21. Liew SM, Khoo EM, Ho BK, Lee YK, Omar M, Ayadurai V, et al. Dengue in Malaysia: factors associated with dengue mortality from a national registry. PLoS One. 2016 Jun 23;11(6):e0157631. doi:10.1371/journal.pone.0157631 pmid:27336440
22. Raju AK. Community mobilization in *Aedes aegypti* control programme by source reduction in peri-urban district of Lautoka, Viti Levu, Fiji Islands. New Delhi: WHO Regional Office for South-East Asia; 2003 (https://www.who.int/iris/handle/10665/163791).
23. Oli K, McNamara K.E. Dengue and climate change: exploring the relationships and risks in Fiji. Fiji Journal of Public Health. 2015;4(1):1–7 (https://www.health.gov.fj/pdfs/Fiji%20Journal%20of%20Public%20Health%20Vol4Issue1.pdf).
24. Greenwell J, McCool J, Kool J, Salusalu M. Typhoid fever: hurdles to adequate hand washing for disease prevention among the population of a peri-urban informal settlement in Fiji. West Pac Surveill Response. 2013 Jan 10;4(1):41–5. doi:10.5365/wpsar.2012.3.4.006 pmid:23908955
25. Children in Fiji: an atlas of social indicators. Suva: UNICEF in the Pacific; 2011 (https://www.unicef.org/pacificislands/Fiji_Equity_Atlas_Web_version.pdf, 23 February 2018).
26. Singh N, Kiedrzynski T, Lepers C, Benyon EK. Dengue in the Pacific–an update of the current situation. Pac Health Dialog. 2005 Sep;12(2):111–9. pmid:18181502
27. Ministry of Health annual report 2012. Suva: Fiji Ministry of Health and Medical Services; 2012 (https://www.health.gov.fj/PDFs/Annual%20Report/Annual%20Report%202012.pdf, 15 July 2017).
28. Wartel TA, Prayitno A, Hadinegoro SR, Capeding MR, Thisyakorn U, Tran NH, et al. Three decades of dengue surveillance in five highly endemic South East Asian countries. Asia Pac J Public Health. 2017 Jan;29(1):7–16. doi:10.1177/1010539516675701 pmid:28198645
29. Paixão ES, Costa MC, Rodrigues LC, Rasella D, Cardim LL, Brasileiro AC, et al. Trends and factors associated with dengue mortality and fatality in Brazil. Rev Soc Bras Med Trop. 2015 Jul-Aug;48(4):399–405. doi:10.1590/0037-8682-0145-2015 pmid:26312928
30. Carabali M, Hernandez LM, Arauz MJ, Villar LA, Ridde V. Why are people with dengue dying? A scoping review of determinants for dengue mortality. BMC Infect Dis. 2015 Jul 30;15(1):301. doi:10.1186/s12879-015-1058-x pmid:26223700
31. Moraes GH, de Fátima Duarte E, Duarte EC. Determinants of mortality from severe dengue in Brazil: a population-based case-control study. Am J Trop Med Hyg. 2013 Apr;88(4):670–6. doi:10.4269/ajtmh.11-0774 pmid:23400577
32. Leo YS, Thein TL, Fisher DA, Low JG, Oh HM, Narayanan RL, et al. Confirmed adult dengue deaths in Singapore: 5-year multi-center retrospective study. BMC Infect Dis. 2011 May 12;11(1):123. doi:10.1186/1471-2334-11-123 pmid:21569427
33. Lee IK, Liu JW, Yang KD. Clinical and laboratory characteristics and risk factors for fatality in elderly patients with dengue hemorrhagic fever. Am J Trop Med Hyg. 2008 Aug;79(2):149–53. doi:10.4269/ajtmh.2008.79.149 pmid:18689614

Health facility use by dengue patients in the Klang Valley, Malaysia: a secondary analysis of dengue surveillance data

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Background: Dengue patients in Malaysia have the choice to seek care from either public or private sector providers. This study aims to analyse the pattern of health facility use among dengue patients to provide input for the ongoing policy discussion regarding public–private integration. The focus of this study is in the Klang Valley, which has a high dengue burden as well as a high number of private facilities.

Methods: This is a cross-sectional study using an available secondary data source – the Malaysian national dengue passive surveillance system, e-Dengue registry. A total of 61 455 serologically confirmed dengue cases from the Klang Valley, registered in year 2014, were included. We retrospectively examined the relationship between demographic factors and the choice of health-care sector by logistic regression.

Results: The median age of the cohort was 26 (interquartile range: 17 to 37) years. More private facilities (54.4%) were used for inpatient care; more public facilities (68.2%) were used for outpatient care. The Chinese and urban populations showed significantly higher use of the private health-care sector with an adjusted odds ratio of 4.8 [95% confidence interval (CI): 4.6–5.1] and 2.3 (95% CI: 2.2–2.4), respectively.

Conclusion: Both public and private health facilities bear significant responsibilities in delivering health-care services to dengue patients. The workload of both sectors should be included in future health policy planning by public agencies.

Dengue is a fast emerging mosquito-borne viral disease in all World Health Organization (WHO) regions.[1] It poses substantial socioeconomic burden to the endemic countries. A recent study reported that both fatal and non-fatal dengue cases contributed to 1.14 million disability-adjusted life years globally in 2013.[2] The disability-adjusted life years is a measure of disease burden, expressed as the sum of years of potential life lost due to ill-health, disability or premature mortality. Furthermore, a prospective study involving three countries in Asia (Cambodia, Malaysia and Thailand) and five countries in the Americas (Brazil, El Salvador, Guatemala, Panama and Venezuela) found that the average cost for an ambulatory dengue case was US$ 514, while the cost for a hospitalized case was US$ 1394.[3]

Dengue infection is hyperendemic in Malaysia. Its incidence doubled from 146 per 100 000 population in 2013 to 328 per 100 000 population in 2016.[4] It was estimated that Malaysia spent about US$ 175.7 million annually on treatment and dengue prevention activities.[5] The Klang Valley, with an estimated population of 7.9 million in the state of Selangor, the Federal Territory of Kuala Lumpur and the Federal Territory of Putrajaya in 2014, has been targeted as the focus for reduction of dengue cases as it has consistently contributed more than half of the national dengue burden.[4,6–8]

The Malaysian health-care system is a mixture of public and private systems; the public and private sectors complement each other in the delivery of health-care services. Public health-care providers serve both rural and urban populations; private health-care providers mainly concentrate in high-density urban areas, especially along the west coast of Peninsular Malaysia.[9] The public health-care system is mainly financed through taxation

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and general revenue collected by the federal government. Additionally, the Employees Provident Fund and Social Security Organization also contributed to health-care funding for the public sector.[10] The private sector is mainly funded through private employers, private insurance and out-of-pocket payments.[10] To facilitate efficient health policy planning and resource allocation we need to estimate the disease burden in both health-care sectors and understand the factors associated with the pattern of health facility use. In Malaysia, the performance and workload of the private sector were seldom taken into consideration in health policy planning by public agencies. This situation may lead to inefficiencies in the health sector and underutilization of expertise.

Studies related to health facility use in Malaysia are limited. Hence, this study aimed to analyse the pattern of health facility use among dengue patients in the Klang Valley by using the data captured in the national dengue surveillance system, e-Dengue registry.

METHODS

Study setting and populations

This is a cross-sectional study that is based entirely on an available secondary data source in Malaysia. A secondary data analysis was performed using the data captured in the e-Dengue registry, a national dengue passive surveillance system in Malaysia. All confirmed dengue cases from the Klang Valley registered in the e-Dengue registry from 1 January 2014 to 31 December 2014 were included in the analysis.

We assumed the health facilities that notified cases to the e-Dengue registry were the first medical facilities to be used by dengue patients. For cases with missing information on the name of the medical facility, the full addresses of the health-care facilities were mapped on Google Maps to identify the facilities. Then the facility names were matched with a list of public and private health-care facilities. A list of the Klang Valley public health-care facilities was obtained from the Development Division, Ministry of Health (MoH) Malaysia. The list comprised 18 public hospitals and 89 public clinics. A list of private health-care facilities was obtained from the Medical Practice Division, MoH Malaysia. There were 92 private hospitals and 2205 private clinics in the Klang Valley during the study period.

The e-Dengue registry and case definition

The e-Dengue registry was established in Malaysia in 2009 under the National Dengue Strategic Plan 2009–2013.[7] In Malaysia, it is mandatory for health-care practitioners to notify all clinically suspected or serologically confirmed dengue cases through an online notification system (e-Notice). The diagnosis is verified by district health officers according to the WHO 1997 classification.[11] Dengue fever is defined as any case with "acute febrile illness with two or more clinical presentations (myalgia, arthralgia, retro-orbital pain, headache, rash, leukopenia and haemorrhagic manifestations) in additional to supportive serology or occurrence at the same location and time as other confirmed dengue cases. A confirmed dengue case is one that was confirmed through laboratory testing such as dengue virus isolation, virus antigen detection, virus genomic sequence detection and/or a fourfold rise in antibody titer."[11] Only confirmed dengue cases were entered into the e-Dengue registry by the district health officers.

Statistical analysis

The background characteristics of all dengue patients in the Klang Valley and the pattern of health facility use were described through descriptive analyses. Logistic regression was used to examine the relationship between demographic factors and patients' choices of health-care sectors. The two-sided statistical significance level was set at $P < 0.05$. Statistical Package for Social Science (version 22.0; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Ethics approval and consent to participate

This article is research involving secondary data. All cases included in this study were anonymized. The study was registered under the National Medical Research Registry (NMRR-17–544–34899) and approved by the Medical Research Ethics Committee (MREC), MoH Malaysia.

RESULTS

Demographic profiles

This study included 61 445 serologically confirmed dengue cases reported within the Klang Valley area in 2014. Patients' ages ranged from less than one month

to 98 years. The age was non-normally distributed, with Kolmogorov–Smirnov normality test showing $P < 0.001$. There were eight cases with missing age. The median age was 26 (interquartile range: 17 to 37) years (**Table 1**). The majority of the cases (77.5%) were adults aged 15–59 years; 18.9% of the cases were children aged below 15 years. Those aged 60 years and above contributed only 3.6% of the total cases. More than half of the cohort were male (57.1%). The majority of the cohort were Malay (54.1%) followed by Malaysian Chinese (25.4%) and Indian (10.3%). In 2014, 8.4% of the registered dengue cases in the Klang Valley were non-Malaysian with the majority from Bangladesh (26.7%) followed by Nepal (23.1%), Indonesia (12.1%), India (6.1%), China (5.3%), Myanmar (5.3%), Pakistan (4.9%) and other countries. Ethnicity information was missing from 778 (1.3%) cases.

Table 1. **Demographic profiles of confirmed dengue cases in the Klang Valley, 2014**

Characteristics	Dengue patients (n = 61 445)	
Age in years* (median, IQR)	26	17, 37
Gender	***n***	**%**
Male	35 108	57.1
Female	26 337	42.9
Ethnicity§		
Malay	33 236	54.1
Malaysian Chinese	15 606	25.4
Indian	6354	10.3
Indigenous population	309	0.5
Non-Malaysian	5162	8.4
Area of residence		
Urban	52 899	86.1
Rural	8546	13.9

* Eight cases with missing data.

§ 778 cases with missing data.

Health facility utilization by dengue patients in Klang Valley

There were 3158 cases with missing information on the health-care sector use. The use of private and public health-care facilities by dengue patients in the Klang Valley was 51% and 49%, respectively. When comparing the use of public and private health-care facilities within the districts, differences of more than 65% were noted for Hulu Selangor district, Kuala Langat district and Sabak Bernam district (**Table 2**). At least 85% of the patients from these districts were using public health-care facilities instead of private health-care facilities. Dengue patients from the Federal Territory of Kuala Lumpur, Petaling district and Hulu Langat district used private health facilities more than public ones. **Fig 1** shows a map of the Klang Valley.

The utilization rate of hospitals was about five times higher than that of clinics for the whole study population (83% versus 17%). When the utilization of health-care sectors was stratified by type of facility (private versus public), an inverse picture was observed between inpatient and outpatient cases. For hospitalized cases, the use of private facilities (54.4%) was about 10% higher than that of public facilities (45.6%). For cases who presented to outpatient care, the use of private clinics (31.8%) was two times lower than that of public clinics (68.2%).

The association of patients' demographic profiles and the choice of health-care sectors was tested (**Table 3**). Cases with missing information on health-care sector, age and/or ethnicity (n = 3900) were excluded from this analysis. Multivariate analysis showed that females have higher private health care use than males ($P < 0.001$). Compared to the Malay, the Malaysian Chinese were 4.8 times more likely to use private health-care facilities; both the indigenous group and foreigners had lower odds than Malay, with the adjusted odds ratio of 0.2 and 0.5, respectively ($P < 0.001$). The adjusted odds of the urban population choosing private health-care facilities was 2.3 times higher than the rural population ($P < 0.001$).

DISCUSSION

To the best of our knowledge, this is the first study focused on the pattern of health facility use among dengue patients in Malaysia. We observed similar overall usage of private and public health-care facilities by dengue patients in the Klang Valley. Our finding differs from that reported by Zara AL et al. in which the use of public health-care facilities was two times higher than private health-care facilities among dengue patients in Brazil.[12] This difference could be attributed to differences in health-care systems and health-seeking behaviours between Malaysians and Brazilians.

Stratification by the type of health-care facility showed dengue patients in the Klang Valley used more

Table 2. **Use of health-care facilities of different districts in the Klang Valley**

District	Use of health-care facilities, *n* (%)		
	Public sector	Private sector	Difference of public/private*
Gombak	4183 (59.2)	2885 (40.8)	1298 (18.4)
Hulu Langat	5132 (45.5)	6155 (54.5)	–11 023 (–9.0)
Hulu Selangor	1065 (84.8)	191 (15.2)	874 (69.6)
Klang	4493 (73.8)	1597 (26.2)	2896 (47.6)
Kuala Langat	726 (86.0)	118 (14.0)	608 (72.0)
Kuala Selangor	553 (70.4)	232 (29.6)	321 (40.9)
Petaling	9245 (39.5)	14 180 (60.5)	–4,935 (–21.0)
Sabak Bernam	243 (97.2)	7 (2.8)	236 (94.4)
Sepang	328 (64.6)	180 (35.4)	148 (29.2)
Kuala Lumpur	2712 (41.2)	3875 (58.8)	–1,163 (–17.6)
Putrajaya	123 (65.8)	64 (34.2)	59 (31.6)

* Negative values denote more private sector usage than public sector usage.

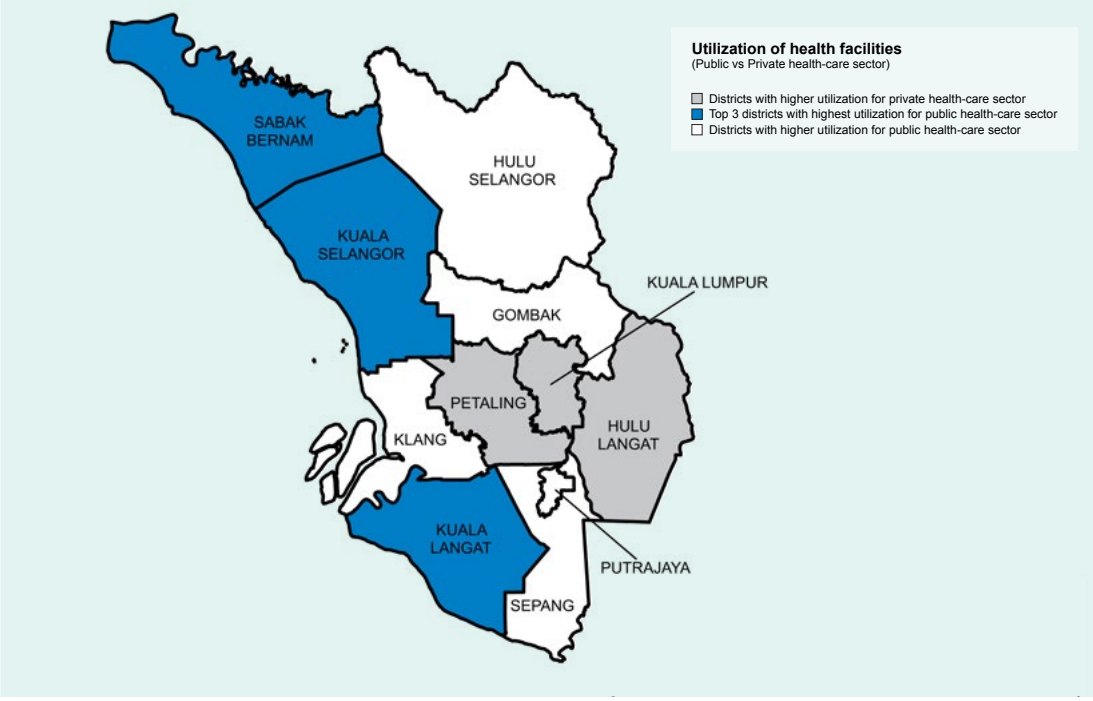
Table 3. **Analysis of demographic profile with use of private compared with public health-care facilities**

Characteristics	Univariate		Multivariate*	
	Crude OR	95% CI	Adjusted OR	95% CI
Age group (years)				
0–9	0.7	(0.5–1.1)	1.0	(0.7–1.6)
10–19	0.5	(0.3–0.7)	0.6	(0.4–0.9)
20–29	0.4	(0.3–0.6)	0.6	(0.4–0.9)
30–39	0.7	(0.5–1.0)	1.0	(0.6–1.5)
40–49	0.9	(0.6–1.3)	1.0	(0.7–1.6)
50–59	0.7	(0.5–1.1)	0.7	(0.5–1.2)
60–69	0.6	(0.4–0.9)	0.6	(0.4–0.9)
70–79	0.6	(0.4–1.0)	0.5	(0.3–0.9)
Above 80	1 (ref.)		1 (ref.)	
Gender				
Male	0.8	(0.8–0.8)	0.9	(0.9–0.9)
Female	1 (ref.)		1 (ref.)	
Ethnicity				
Malaysian Chinese	4.8	(4.6–5.1)	4.8	(4.6–5.1)
Indian	1.1	(1.0–1.1)	1.1	(1.0–1.1)
Indigenous	0.2	(0.2–0.3)	0.2	(0.2–0.3)
Non-Malaysian	0.6	(0.5–0.6)	0.5	(0.5–0.6)
Malay	1 (ref.)		1 (ref.)	
Area of residence				
Urban	2.2	(2.1–2.3)	2.3	(2.2–2.4)
Rural	1 (ref.)		1 (ref.)	

* Analysed with stepwise binary logistic regression, which the model includes age, gender, ethnicity and area of residence; total number of excluded from analysis in view of missing information: 3900 (6.3%).

CI: confidence interval; OR: odds ratio; Ref = reference category used for respective variable in logistic regression.

Fig. 1. **Map of the Klang Valley and the pattern of health facility use**



private inpatient care and public outpatient care. The opposite was observed in the National Health Morbidity Survey (NHMS) 2015, which demonstrated a higher utilization of public inpatient care and private outpatient care among the Klang Valley population.[13] NHMS is a population survey that targets all types of diseases when collecting information regarding the use of health-care services.[13] However, our study involved only confirmed dengue cases. Therefore, the use pattern of health-care services may differ when we focus only on a single medical condition, dengue fever.

Our finding demonstrates that hospital utilization was nearly five times higher than clinic utilization among dengue patients in the Klang Valley. According to a published report, dengue fever is the third and fourth most common discharge diagnosis made in private and public hospitals, respectively, in Malaysia.[9] However, Brazil reported the opposite where the majority (81.4%) of the dengue patients used outpatient services.[12] The nature of private health insurance and its coverage may influence patients' health-seeking behaviour. The private insurance policies offered in Malaysia usually cover the cost of hospital admission but not the cost of outpatient care.[9] This may have influenced the health-seeking behaviour and caused a propensity for hospital use. The fact that the Klang Valley has the highest percentage of private health insurance coverage[13] could possibly explain the higher use of private hospital care.

Similar to the NHMS 2015, we found that private health-care facilities were used most by Malaysian Chinese regardless of the types of facility; the indigenous population had the least private health-care utilization among all. This could be related to the income distribution across the ethnic groups in Malaysia. Malaysian Chinese are generally in a higher income group as compared to other ethnicities,[14] and nearly half of Malaysian Chinese were covered by private health insurance.

Malaysia has a mixed public–private provision of health-care services for primary, secondary and tertiary care. Public health-care services are more evenly distributed in urban and rural areas; private facilities tend to be available only in urban areas.[9] The population in urban areas may have a higher socioeconomic status and are able to afford private services more than those in the rural population. This may also explain why the urban population has higher use of private health care.

Our study has a few limitations. First, this study only focused on data captured within the Klang Valley, so it might not be suitable to generalize the findings to the whole of Malaysia. Second, as the study was conducted

using data from year 2014, the pattern of health facility use might be different now. Third, as the e-Dengue registry only captures confirmed dengue cases, the preference of health-care facilities among the undiagnosed and clinical dengue cases remains unanswered. Fourth, a majority of dengue patients are asymptomatic and might not seek medical attention. Therefore, the high hospital use as observed in this study might be associated with a more severe form of dengue infection. Additionally, we noted the new dengue classification published by WHO in 2009; however, the 1997 WHO dengue classification was the case definition used in the surveillance system at the time of data collection. As this is secondary research, we do not have control over the case definition used by the system. However, a published systemic review concluded no study had formally compared the 1997 WHO dengue classification with the 2009 classification in the area of surveillance and research.[15] Therefore, the applicability of either classification in the surveillance system remains unknown. As the e-Dengue registry has limited variables, we were unable to study other factors such as disease severity, economic factors, geographical factors, organizational factors and cultural factors that could potentially play an important role in determining use of health-care facilities. Lastly, as we used the health-care facilities that notified the cases as the proxy for dengue patients' preferences, it might not reflect the true preference of patients. Nevertheless, this study has a large sample size compared to other studies with similar objectives, and it was the first study in Malaysia to analyse disease-specific health facility use. This study shed light on the big picture of health facility use among dengue patients in the Klang Valley.

CONCLUSIONS

Our results showed both public and private health facilities bear significant responsibilities in delivering health-care services to dengue patients in the Klang Valley. Malaysian Chinese, females and urban populations have higher utilization for private health-care facilities. Future health service and policy planning related to dengue infection should take into account the workload of both public and private sectors.

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Conflicts of interest

None.

References

1. Global strategy for dengue prevention and control 2012–2020. Geneva: World Health Organization; 2012 (https://www.who.int/denguecontrol/9789241504034/en/).
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016 Jun;16(6):712–23. doi:10.1016/S1473-3099(16)00026-8 pmid:26874619
3. Suaya JA, Shepard DS, Siqueira JB, Martelli CT, Lum LC, Tan LH, et al. Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. Am J Trop Med Hyg. 2009 May;80(5):846–55. doi:10.4269/ajtmh.2009.80.846 pmid:19407136
4. iDengue. Kuala Lumpur: Kementerian Sains Teknologi dan Inovasi (MOSTI); 2014 (http://idengue.remotesensing.gov.my/idengue/index.php, accessed 5 April 2017) (in Malay).
5. Packierisamy PR, Ng CW, Dahlui M, Inbaraj J, Balan VK, Halasa YA, et al. Cost of dengue vector control activities in Malaysia. Am J Trop Med Hyg. 2015 Nov;93(5):1020–7. doi:10.4269/ajtmh.14-0667 pmid:26416116
6. Balvinder SG. History and epidemiology of dengue. Putrajaya: MyHEALTH; 2017 (http://denggi.myhealth.gov.my/history-and-epidemiology-of-dengue/?lang=en).
7. Dengue Prevention and Strategic Plan, 2009-2013. Putrajaya: Vector Control Unit, Ministry of Health, Malaysia; 2009 (https://books.google.com.my/books?id=PuZcDwAAQBAJ&lpg=PA21&dq=pelan%20strategik%20denggi%20kebangsaan%202009-2013&pg=PA21#v=onepage&q=pelan%20strategik%20denggi%20kebangsaan%202009-2013&f=true, accessed 5 April 2018).
8. Dengue Prevention and Strategic Plan, 2015-2020. Putrajaya: Vector Control Unit, Ministry of Health, Malaysia; 2014 (https://www.cdc.gov.tw/File/Get/TSS-3tfl58rn9U7cNZ8JCg, accessed 5 April 2018).
9. Malaysia health systems research volume 1, contextual analysis of the Malaysian Health System, March 2016. Putrajaya: Ministry of Health, Malaysia and Boston: Harvard T.H. Chan School of Public Health, Harvard University; 2016 (http://www.moh.gov.my/moh/resources/Vol_1_MHSR_Contextual_Analysis_2016.pdf, accessed 18 April 2018).

10. Malaysia national health accounts: health expenditure report, 1997-2016. Putrajaya: Malaysia National Health Accounts Unit, Planning Division, Ministry of Health, Malaysia; 2018 (https://www.aidsdatahub.org/sites/default/files/publication/Malaysia_Health_Expenditure_Report_1997-2016_07122018.pdf, accessed 26 March 2018).

11. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: World Health Organization; 1997 (https://www.who.int/csr/resources/publications/dengue/Denguepublication/en/).

12. Zara AL, Martelli CM, Siqueira JB Jr, Parente MP, Braga C, Oliveira CS, et al. Health services utilization by dengue patient in Brazil, 2012-2013: A multicenter study. Value Health. 2015 11;18(7):A529. doi:10.1016/j.jval.2015.09.1642 pmid:26532966

13. National health morbidity survey 2015 Vol. V. Putrajaya: Ministry of Health, Malaysia; 2015 (http://iku.moh.gov.my/index.php/research-eng/list-of-research-eng/iku-eng/nhms-eng/nhms-2015, accessed 29 March 2018).

14. Household income and basic amenities survey report 2012. Putrajaya: Department of Statistics, Malaysia; 2012 (https://www.dosm.gov.my/v1/index.php?r=column/cone&menu_id=UlVlbUxzUWo0L3FEaWZmUVg4ZFQzZz09, accessed 19 April 2017).

15. Horstick O, Jaenisch T, Martinez E, Kroeger A, See LLC, Farrar J, et al. Comparing the usefulness of the 1997 and 2009 WHO dengue case classification: a systematic literature review. Am J Trop Med Hyg. 2014 Sep;91(3):621–34. doi:10.4269/ajtmh.13-0676 pmid:24957540

Seroprevalence of Middle East respiratory syndrome coronavirus (MERS-CoV) in public health workers responding to a MERS outbreak in Seoul, Republic of Korea, in 2015

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The first case of Middle East respiratory syndrome coronavirus (MERS-CoV) in the Republic of Korea was confirmed in May 2015 after a traveller returned from the Middle East.[1] There were 186 cases, including 38 deaths, within two months.[1] The potential of a single MERS-confirmed patient to result in such a large MERS outbreak constitutes a serious global health concern.[2]

During this MERS outbreak, massive public health containment measures were enacted at various levels; these included epidemiological investigations, isolation of suspected and confirmed cases, contact tracing and home quarantine of contacts. Local public health centre (LPHC) and emergency medical services (EMS) personnel responded to the outbreak by conducting initial interviews with suspected cases, transporting patients and specimens and managing contacts. Responders in contact with patients used different levels of personal protective equipment (PPE). Full-protection PPE includes a gown, N95 respirator, gloves and goggles. As the transmissibility of MERS is unclear,[3] it is possible that responders were infected by being exposed to MERS patients.

We conducted a cross-sectional study in January 2016 to assess whether LPHC and EMS workers were infected and to determine their degree of exposure. The participants had contact with MERS-confirmed patients or their specimens during the outbreak and volunteered to participate in this study. The survey, which was a face-to-face interview, examined subjects' general characteristics, professional responsibilities, contact history, symptoms after exposure and use of PPE.

Contact was defined as meeting at least one of the following four criteria:[4] being within 2m of a confirmed patient, staying in the same space as a confirmed patient for over 5 minutes, contact with a patient's respiratory or digestive secretions and contact with specimens from confirmed patients before the sample was packaged. Contact within the same space was graded into four levels according to distance of contact and wearing of PPE. Without full PPE protection: Grade 1 was defined as contact within 2m, and Grade 2 was defined as contact at over 2m. With full PPE protection: Grade 3 was defined as contact within 2m, and Grade 4 was defined as contact at over 2m.

Serum collected from all participants was screened for the presence of MERS-CoV IgG using enzyme-linked immunosorbent assays (ELISAs). One sample with borderline results and five samples with negative ELISA results were retested using indirect immunofluorescence

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(IIFT) and plaque reduction neutralization (PRNT) tests for confirmation. The indirect ELISA and MERS-CoV IIFT used commercial MERS-CoV IIFT slides (EUROIMMUN, Lübeck, Germany) and followed the manufacturer's protocol. Analysis was performed using a DE/Axio Imager M1 immunofluorescence microscope (Zeiss, Jena, Germany). The PRNT was performed as previously described.[5] The number of plaques per well were counted; reductions in plaque counts of 50% (PRNT50) and 90% (PRNT90) were calculated using the Spearman-Kärber formula.[5]

Thirty-four workers participated in the study (**Table 1**): 31 from 11 LPHCs and three from two EMS units. Twenty (58.8%) responders were male; their mean age was 44 (34–56.7) years. Twenty-five participants (73.5%) occupied health-related positions: 11 (32.4%) general health-care staff, 6 (17.6%) nurses, 4 (11.8%) doctors, 3 (8.8%) paramedics and 1 medical laboratory technologist (2.6%). Nine participants (26.5%) were non-health-related workers: 5 (14.7%) technicians, 2 (5.9%) administrators, 1 (2.9%) agricultural worker and 1 (2.9%) unknown.

Based on the highest risk contact for each participant, seven (20.6%) of the responders were classified as Grade 1; they were partially protected with at least gloves and an N95 respirator (**Table 1**). They contacted asymptomatic or symptomatic patients, and symptomatic patients wore surgical masks. After MERS-CoV had been confirmed in a patient, all staff were fully protected when in contact with the patient. The closest contact occurred when touching and holding patients during transport. One responder wearing full PPE had a mild fever (37.5 °C) after contact with a symptomatic patient who was later confirmed as infected. Since the response system had not expanded in the early days of the outbreak, she was not tested but was isolated with self-monitoring.

Serum samples were obtained from all 34 participants at an average of 7.3 months (range: 6.7–8.1 months) after exposure. On ELISA, there were 33 (97.1%) negative results and one borderline result. The results of six samples, including one with borderline ELISA results, were negative in the IIFT and PRNT.

In our study, we could not find evidence of MERS infection in the public health providers after direct contact with confirmed patients. This may be because there was a lower risk of transmission when participants were transporting or counselling patients outside of the hospital compared to providing medical assistance within the hospital. In other MERS outbreaks, secondary infections were related to health-care settings.[1,6] Although the exact route of infection transmission is unknown, aerosolizing procedures in crowded rooms with inadequate infection prevention and control measures were observed in health-care settings.[7] In the 2015 Republic of Korea outbreak, some health-care workers without proper PPE were infected in tertiary hospitals, thus emphasizing the

Table 1. **Exposure to MERS-confirmed patients (*n* = 34)**

Exposure	*n*	(%)
Grade of contact		
Grade 1	7	(20.6)
Grade 2	3	(8.8)
Grade 3	20	(58.8)
Grade 4	4	(11.8)
Longest period of contact		
< 30 minutes	13	(38.2)
30 minutes to 1 hour	10	(29.4)
1 to 2 hour(s)	6	(17.6)
2 to 5 hours	5	(14.7)
Activity (*n* = 67)*		
Patient transport	24	(35.8)
Patient counselling	10	(14.9)
Ambulance disinfection	10	(14.9)
Specimen transportation	8	(11.9)
Respiratory specimen collection	7	(10.4)
Taking vital signs	4	(6.0)
Discarding exposed goods	3	(4.5)
Other	1	(1.5)
Symptoms after contact		
Yes	1	(2.9)
No	33	(97.1)
PPE education		
Received	29	(85.3)
Not received	5	(14.7)
Training in wearing PPE		
Received	20	(58.8)
Not received	13	(38.2)
Unknown	1	(2.9)

* The 34 study participants performed multiple activities.

PPE: personal protective equipment.

optimal use of PPE to prevent MERS infection.[8] Moreover, since the participants did not contact any spreaders except one participant who contacted a patient that caused two secondary infections, the risk of transmission from the contacted patients was likely low.

This study had several limitations. First, the survey was conducted 7.3 months after the MERS outbreak, making recall bias possible. Second, it is possible that we missed some mild or asymptomatic cases. Furthermore, because the serological tests were performed several months post-exposure, pre-existing MERS antibodies may have decreased or disappeared in the interval, potentially leading to underestimation. While asymptomatic MERS infection had been detected using RT–PCR testing at the time of outbreak,[9] a Saudi Arabian study showed the longevity of MERS-CoV antibodies in MERS patients varied in the severity of illness. For example, antibodies in severely infected patients persisted after 18 months, but milder and subclinical cases detected no antibodies even early on in the disease.[10] Third, the number of participants was relatively small and may not be representative or generalizable. Despite these limitations, this study suggests that the risk of MERS transmission to public health professionals responding to MERS outside the hospital setting (i.e. patients' homes) was low, particularly for those who wore some level of PPE such as masks and gloves. Further study is needed to prospectively survey public health responders including symptomatic or asymptomatic cases to conduct genetic test and serologic test during an outbreak.

In conclusion, the public health providers in our study did not have evidence of MERS transmission after direct contact with confirmed patients when PPE was used properly.

Ethics

Ethical approval for the study was obtained from the institutional review board of Seoul National University Hospital in Seoul (IRB No. C-1512–049–727).

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Conflicts of interest

None.

References

1. Oh MD, Park WB, Park S-W, Choe PG, Bang JH, Song K-H, et al. Middle East respiratory syndrome: what we learned from the 2015 outbreak in the Republic of Korea. Korean J Intern Med (Korean Assoc Intern Med). 2018 Mar;33(2):233–46. doi:10.3904/kjim.2018.031 pmid:29506344
2. Petersen E, Hui DS, Perlman S, Zumla A. Middle East respiratory syndrome - advancing the public health and research agenda on MERS - lessons from the South Korea outbreak. Int J Infect Dis. 2015 Jul;36:54–5. doi:10.1016/j.ijid.2015.06.004 pmid:26072036
3. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015 Sep 5;386(9997):995–1007. doi:10.1016/S0140-6736(15)60454-8 pmid:26049252
4. Interim US guidance for monitoring and movement of persons with potential Middle East respiratory syndrome coronavirus (MERS-CoV) exposure. Atlanta, GA: Centers for Disease Control and Prevention; 8 April 2018 (https://www.cdc.gov/coronavirus/mers/hcp/monitoring-movement-guidance.html).
5. Cohen BJ, Audet S, Andrews N, Beeler J; WHO working group on measles plaque reduction neutralization test. Plaque reduction neutralization test for measles antibodies: Description of a standardised laboratory method for use in immunogenicity studies of aerosol vaccination. Vaccine. 2007 Dec 21;26(1):59–66. doi:10.1016/j.vaccine.2007.10.046 pmid:18063236
6. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al.; KSA MERS-CoV Investigation Team. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013 Aug 1;369(5):407–16. doi:10.1056/NEJMoa1306742 pmid:237821617.
7. WHO MERS-CoV global summary and assessment of risk 2018. Geneva: World Health Organization; 2018 (https://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf).
8. Kim CJ, Choi WS, Jung Y, Kiem S, Seol HY, Woo HJ, et al. Surveillance of the Middle East respiratory syndrome (MERS) coronavirus (CoV) infection in healthcare workers after contact with confirmed MERS patients: incidence and risk factors of MERS-CoV seropositivity. Clin Microbiol Infect. 2016 Oct;22(10):880–6. doi:10.1016/j.cmi.2016.07.017 pmid:27475739
9. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, et al. 2014 MERS-CoV outbreak in Jeddah–a link to health care facilities. N Engl J Med. 2015 Feb 26;372(9):846–54. doi:10.1056/NEJMoa1408636 pmid:25714162
10. Alshukairi AN, Khalid I, Ahmed WA, Dada AM, Bayumi DT, Malic LS, et al. Antibody response and disease severity in healthcare worker MERS survivors. Emerg Infect Dis. 2016;22(6):1113. pmid: 27192543

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