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Zika preparedness and response in Viet Nam

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This article describes Viet Nam Ministry of Health's (VMoH) activities to prepare for and respond to the threat Zika virus (ZIKV), including the adaptation of existing surveillance systems to encompass ZIKV surveillance.

On 1 February 2016, the World Health Organization (WHO) declared the Zika epidemic a Public Health Emergency of International Concern (PHEIC).[1] Following this declaration, the VMoH developed a national ZIKV preparedness and response plan that encompassed coordination, prevention, surveillance, care and treatment, communication, logistics and international cooperation. The national emergency operations centre (EOC) at the General Department of Preventive Medicine (GDPM), using Global Health Security Agenda (GHSA) resources, served as the nerve centre for these activities. The GDPM, the central public health agency within the VMoH, created the ZIKV response plan, including training health-care workers to recognize and report ZIKV infection, strengthening surveillance and building ZIKV diagnostic testing capacity. The plan was implemented by the four Vietnamese regional public health institutes (RPHI) that serve as the regional surveillance and laboratory lead for outbreak preparedness and response. A task force comprising epidemiologists, laboratorians, health communications specialists, local government leaders and clinicians was established in each region.

Teams made up of trainers from the GDPM, the Medical Services Administration, the Maternal and Child Health Department, the Health Communication and Education Department and international experts from WHO and the United States Centers for Disease Control and Prevention (CDC) were deployed to each region to train clinicians to recognize and report ZIKV. Training included a training-of-trainers component and was followed by a series of cascading workshops to lower administrative levels. Three ZIKV informational trainings were conducted covering all 63 provinces within the country, educating a total of 637 local health-care providers and authorities. Additionally, guidance for clinicians regarding early diagnosis, services, and care of pregnant women was developed and disseminated to health-care providers.

An existing sentinel surveillance system for the dengue virus was expanded in eight southern provinces to include ZIKV, as the clinical presentations of the two diseases are very similar. In each province, one existing surveillance hospital site was selected and began screening individuals who met the dengue case definition for ZIKV, starting 15 February 2016. Later, surveillance for ZIKV was extended to four hospitals in the northern regions, six hospitals in the central coast regions and four hospitals in the central highlands region. All participating sites collected blood and urine samples for ZIKV testing

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from inpatients and outpatients who met the dengue case definition. Laboratory testing was performed on more than 2000 specimens from the south and central regions between May and August 2016. An additional 221 dengue-negative specimens that were collected by the dengue surveillance system in 2015 were tested for ZIKV to detect historical infections. Two cases of ZIKV were identified in the contemporaneous blood samples, while none was identified in the historical samples.

Between May and August 2016, in addition to the two ZIKV cases identified by the sentinel surveillance system,[2] four cases were identified by the WHO Event Management System (EMS) in travellers who developed symptoms returning home from Viet Nam.[3] In response to these cases, public health workers were deployed to the areas where the six case-patients either lived or travelled to search for other possible cases. Intensive mosquito control efforts, including reduction of mosquito breeding grounds, were carried out in these areas.

The Government of Viet Nam was able to increase capacity for surveillance and response through its collaborations and partnerships with WHO, CDC and other organizations and its commitment to the GHSA. GHSA was launched in 2014 as a collaboration between multiple institutions and nations with the aim to improve countries' abilities to respond to public health emergencies.[4,5] One of the early GHSA investments in Viet Nam was the creation of a national EOC in Hanoi. The national EOC was able to receive, analyse, interpret and share information in real time with national, regional and international partners during the ZIKV response. Partnerships between Vietnamese public health responders and outside organizations, including WHO and CDC, provided training opportunities for laboratorians and epidemiologists. Laboratorians from the four RPHIs attended a CDC ZIKV laboratory training workshop in Taiwan, China, while on-the-ground epidemiology training was provided by international experts. In addition, resources such as primer/probe sequences and positive control RNAs were shared from outside institutions. Together, these collaborations and partnerships allowed Viet Nam to rapidly respond to the ZIKV threat.

The ZIKV PHEIC allowed Viet Nam to test its newly enhanced response system and identify areas that needed to be modified or expanded. Several lessons were learnt. First, while the GDPM led surveillance efforts at the national level, the mode of implementation was determined at the regional level. This practice led to variations in surveillance strategies in different regions, making it challenging to relate the data. In future responses, it would be useful to create a unified implementation plan for surveillance that could be consistently applied throughout the country. Second, while co-opting an existing surveillance system meant a new surveillance system could be established rapidly, it resulted in the creation of an inadequate response. In this response, the dengue surveillance system was initially used as the base for ZIKV surveillance. The dengue system was focused on inpatient surveillance. This turned out to be a poor fit for ZIKV surveillance given that most ZIKV patients have a mild clinical course. Finally, although a system for analysing and visualizing data was available at the national level, surveillance data were recorded and reported manually at the district and regional levels, resulting in a significant delay between data collection and data analysis and reporting.

Currently the VMoH is working to improve data accessibility by creating data warehouses to integrate data sources and building three additional regional EOCs. All EOCs will be networked and be able to collect, analyse, display and share data in real time. The networked data warehouses at the EOCs will integrate data from notifiable diseases and sentinel surveillance systems, as well as from laboratory and immunization databases. These advances are being supported through the GHSA and by collaborating partners. It is expected that these continued improvements will greatly facilitate future responses to emerging threats in Viet Nam.

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An outbreak investigation of paediatric severe acute respiratory infections requiring admission to intensive care units – Fiji, May 2016

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Introduction: Influenza-associated severe acute respiratory infections (SARI) are a major contributor to global morbidity and mortality. In response to a cluster of SARI cases and deaths in pregnant women, with two deceased cases testing positive for influenza A(H1N1)pdm09, an investigation was initiated to determine whether there was an increase of paediatric SARI cases admitted to divisional hospital intensive care units in Fiji in may 2016 compared to May 2013–2015.

Methods: Retrospective case finding was conducted at the paediatric intensive care units (PICUs) in Fiji's three divisional hospitals. Data were collected from 1 January 2013 to 26 May 2016. Cases were identified using a list of clinical diagnoses compatible with SARI.

Results: A total of 632 cases of paediatric SARI with complete details were identified. The median age of cases was 6 months (Interquartile range: 2–14 months). Children aged less than 5 years had a higher rate of paediatric SARI requiring admission to a divisional hospital PICU in May 2016 compared to May 2013–2015 (Incidence rate ratio: 1.7 [95% CI: 1.1–2.6]). This increase was not observed in children aged 5–14 years. The case-fatality ratio was not significantly different in 2016 compared to previous years.

Conclusion: The investigation enabled targeted public health response measures, including enhanced SARI surveillance at divisional hospitals and an emergency influenza vaccination campaign in the Northern Division.

Influenza-associated severe acute respiratory infections (SARI) are a major contributor to global morbidity and mortality, particularly among high-risk groups such as pregnant women and children. In 2008, the World Health Organization (WHO) estimated that there were 90 million new cases of seasonal influenza globally and 20 million cases of influenza-associated acute lower respiratory infections in children less than 5 years.[1] Influenza outbreaks typically occur during winter months in countries with temperate climates. In Pacific island countries, influenza outbreaks can occur throughout the year with less seasonal variation.[2] Influenza vaccination is an effective method for the prevention of influenza infection and subsequent complications.[3] WHO recommends influenza vaccination for pregnant women and children aged 6 months to 5 years to prevent severe disease requiring hospitalization.[1]

Fiji is a tropical archipelago in the South Pacific Ocean with an estimated population of 865 611.[4] National surveillance systems in Fiji capture information on influenza-like illness; however, surveillance for SARI is limited.[5] Fiji does not currently have a seasonal influenza vaccination policy; however, vaccination is recommended for high-risk groups including health-care workers, pregnant women, elderly persons and those with chronic illnesses.[3] Influenza vaccination is not publicly funded under Fiji's national immunization programme, yet

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vaccines may be purchased privately from health-care providers.[6] Uptake of the influenza vaccine in Fiji has previously been reported as low.[7]

In May 2016, the Ministry of Health and Medical Services (MoHMS) in Fiji identified an increase in adult hospital admissions due to severe respiratory infections. In addition, a small cluster of pregnant women developed SARI, four of whom died. Two of the four deceased cases tested positive for the influenza A(H1N1)pdm09 virus.[8] In response to the increased SARI activity in adults, an investigation was conducted to determine if there was an increase in paediatric SARI cases requiring admission to divisional hospital paediatric intensive care units (PICUs) in Fiji in May 2016 compared to May 2013–2015 and to implement appropriate control measures. The investigation was led by the Fiji Centre for Communicable Disease Control (FCCDC) with support by WHO. This paper reports the findings of the investigation.

METHODS

We conducted retrospective case finding on 26–27 May 2016 at the three divisional hospital PICUs in Fiji: Colonial War Memorial Hospital (covering Central and Eastern Divisions), Labasa Divisional Hospital (Northern Division) and Lautoka Divisional Hospital (Western Division). Patient registers were reviewed to identify cases clinically compatible with SARI. Data from January 2013 to May 2016 were collected to ensure sufficient historical data to calculate baseline rates of disease.

A case-patient was defined as a child aged 0–14 years admitted to a divisional hospital PICU from 1 January 2013 to 26 May 2016 with any of the following diagnoses: pneumonia, severe pneumonia, acute respiratory distress syndrome, influenza, lower respiratory tract infection, upper respiratory tract infection or severe acute respiratory infection.

Data were collected on patients' date of admission, age, diagnosis and outcome. Population data were calculated by applying estimated growth rates to 2007 Fiji census data.[9] Incidence rates were calculated for the month of May by division and paediatric age groups available from the census data (0–4 years, 5–9 years and 10–14 years). Incidence rate ratios (IRR) and Fisher's exact 95% confidence intervals (CI) were calculated to compare incidence rates for May 2016 and May 2013–2015. The frequency and proportion of SARI cases were tabulated with a further breakdown of age for children less than 5 years (0–5 months, 6–11 months, 12–23 months, 24–35 months, 36–47 months and 48–59 months) as well as the 5–9 year and 10–14 year age categories. Case-fatality ratios (CFRs) were calculated for January–May 2016 and January–May 2013–2015. A Fisher's exact two-sided p-value was calculated to compare the 2016 and baseline case-fatality ratios. The month of May 2016 in this paper refers to data collected up to 26 May 2016 (date of the investigation); data were collected and analysed for whole months in prior years. All analyses were conducted using Stata 14.1 (StataCorp LP, College Station, USA) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, USA).

RESULTS

We identified 632 cases of paediatric SARI with complete details requiring admission to divisional hospital PICUs between January 2013 and May 2016 (**Fig. 1**). The median age of paediatric SARI cases during the investigation period (January 2013–May 2016) was 6 months (Interquartile range: [IQR] 2–14 months). Ninety-three per cent (n = 586) of all cases identified during the investigation were in children aged less than 5 years. Moreover, 85% (n = 540) were in children aged less than 2 years.

Fig. 1 shows the number of cases admitted by month and year of the investigation period. The rate of paediatric SARI in children less than 5 years was higher during the month of May 2016 when compared to the same period in 2013–2015 (IRR: 1.7 [95% CI: 1.1–2.6]) (**Table 1**). The rate increase in children less than 5 years was not statistically significant when stratified by division (**Table 1**).

The CFRs were not significantly different for cases of paediatric SARI requiring admission to divisional hospital PICUs in January–May 2016 (12.5%) compared to the same period in 2013–2015 (9.1%) (P = 0.343).

Outbreak response

The FCCDC established enhanced SARI surveillance at divisional hospital PICUs to ensure continued monitoring. In addition, the FCCDC, with support from the WHO Emerging Diseases Clinical Assessment and Response Network, conducted critical care training with a particular focus on SARI for PICU staff in August 2016.

Fig. 1. **Cases of paediatric severe acute respiratory infection (SARI) admitted to divisional hospital paediatric intensive care units (PICUs) by division and month of admission, Fiji, January 2013 to May 2016 (*n* = 632)**

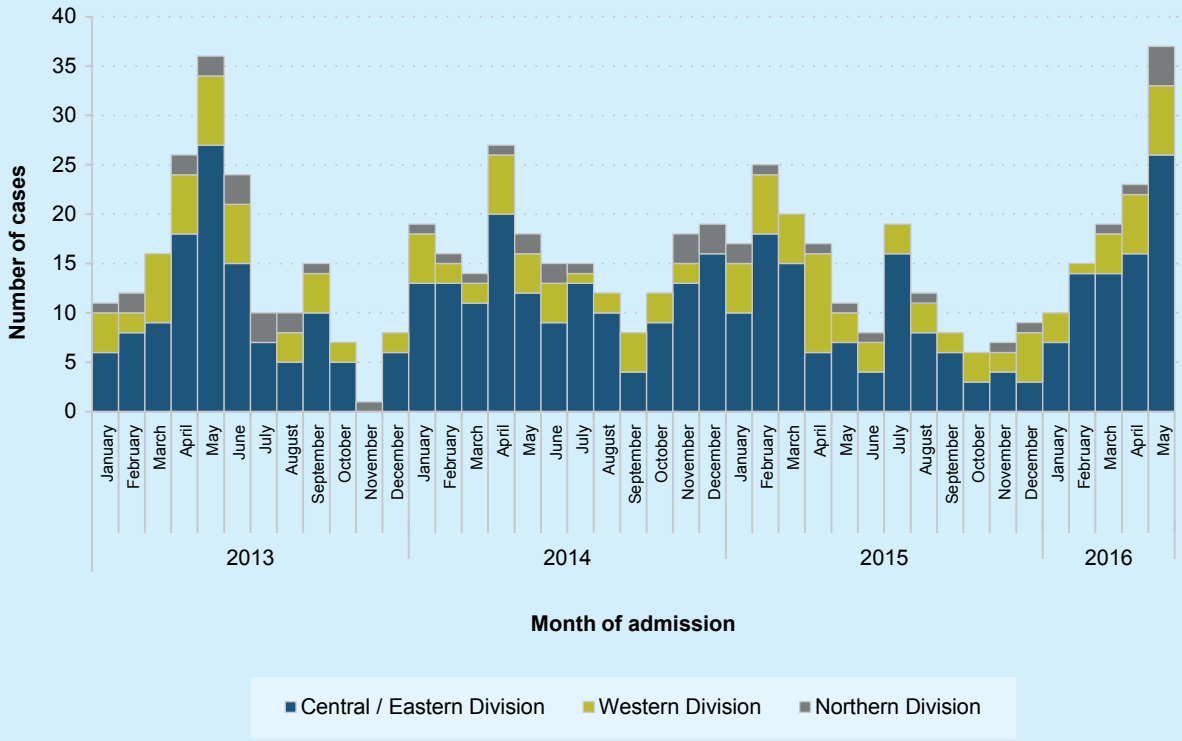

Table 1. **Incidence rate per 10 000 population and incidence rate ratio of paediatric SARI requiring admission to divisional hospital PICUs, Fiji, May 2016 and May 2013–2015**

	May 2016 IR*	May 2013–2015 IR*	IRR (95% CI)†
Central/Eastern Division			
0–4 years	5.6	3.5	1.6 (0.9–2.7)
5–9 years	0.3	0.2	1.5 (0.0–28.2)
10–14 years	0.2	-	-
Western Division			
0–4 years	2.2	1.3	1.7 (0.6–4.8)
5–9 years	-	0.2	-
10–14 years	-	-	-
Northern Division			
0–4 years	2.9	1.2	2.4 (0.5–11.2)
5–9 years	-	-	-
10–14 years	-	-	-
Divisions combined			
0–4 years	4.0	2.3	1.7 (1.1–2.6)
5–9 years	0.1	0.2	0.7 (0.0–7.5)
10–14 years	0.1	-	-
All years (0–14)	1.4	0.9	1.7 (1.1–2.6)

* Monthly incidence rates were calculated for May in each year.

† Incidence rate ratios could not be calculated for some groups because of zero counts.

CI: confidence interval, IR: incidence rate, and IRR: incidence rate ratio

Paediatric SARI activity in the Central/Eastern and Western divisions had been increasing in the months before the investigation (**Fig. 1**). However, the increase appeared to be delayed in the Northern Division, allowing an opportunity to implement preventive measures. In anticipation of an increase in paediatric SARI cases in the Northern Division, the MoHMS and WHO Division of Pacific Technical Support facilitated a donation of 6000 doses of paediatric influenza vaccine. An emergency influenza vaccination campaign in the Northern Division was jointly coordinated by the Northern Division Public Health Team, the Fiji Expanded Programme on Immunization (EPI) and Labasa Divisional Hospital from July to September 2016. The vaccination campaign targeted children aged 6–12 months and achieved 84% coverage (Fiji EPI, unpublished data, 2016).

DISCUSSION

We found that children aged less than 5 years experienced a higher rate of SARI requiring admission to divisional hospital PICUs in the month of May 2016 compared to the same month in 2013–2015. The majority of SARI cases in the investigation period occurred in children aged less than 2 years (85%), which confirms that this age group is at a high risk of severe influenza-associated respiratory infections.[1,10]

Three months before the outbreak, Fiji was struck by one of the strongest tropical cyclones recorded in the southern hemisphere. Tropical Cyclone Winston resulted in 44 deaths and caused severe damage and displacement throughout Fiji.[11] Populations in crisis have a higher risk of outbreaks of acute respiratory infections, and this may have influenced the increase in paediatric SARI requiring PICU admissions among children aged less than 5 years in May 2016.[12]

The increased incidence of paediatric SARI in May 2016 may also have been influenced by circulating influenza A viruses. Influenza A was predominant in Fiji during April–May 2016, with A(H1N1)pdm09, A(H3) and some B viruses detected.[13] The April–May period began with more notifications of A(H1N1)pdm09; however, A(H3) was predominant overall.[13] Globally, the 2015–2016 influenza season was also marked by an early predominance of the influenza A(H1N1)pdm09 virus with influenza A(H3N2) predominant later in the global season.[14,15]

Several limitations were identified in the investigation. We only measured severe disease requiring admission to paediatric intensive care units; this paper does not provide a comprehensive estimate of paediatric SARI incidence. The investigation case definition was based on clinical diagnoses, which may have resulted in some misclassification of SARI cases. The etiology of SARI was not systematically investigated as suspected cases of influenza are not routinely confirmed by microbiological testing in Fiji; the assumption that the increase in paediatric SARI was due to influenza cannot be confirmed. CFRs should be interpreted in the context of PICU admissions rather than all paediatric SARI hospitalizations. Since the investigation was conducted in May 2016, CFRs were calculated for the period January–May for each year (2013–2016) and incidence rates for the month of May only (2013–2016). Small case numbers in some divisions and age groups may have influenced the results.

While recognizing there are competing priorities for health resources, the introduction of a seasonal influenza vaccination policy for high-risk groups, as per WHO recommendations, should be considered to address the ongoing burden of paediatric SARI in Fiji.[1,3]

CONCLUSION

This investigation provided valuable information on the burden of paediatric SARI requiring admission to divisional hospital PICUs in Fiji in May 2016. The data were used to implement targeted public health response measures and enhance surveillance for paediatric SARI in divisional hospitals in Fiji.

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Epidemiology of tuberculosis in Papua New Guinea: analysis of case notification and treatment-outcome data, 2008–2016

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Papua New Guinea has strengthened its surveillance system for tuberculosis (TB) under the National TB Program. This paper provides an overview of TB surveillance data at the national and subnational levels from 2008 to 2016.

TB case notification has consistently increased since 2008 with 6184 cases (93 per 100 000 population) in 2008 to 28 598 (359 per 100 000 population) in 2014 and has stabilized since 2014 with 28 244 cases (333 per 100 000 population) in 2016. The population-screening rate for TB rose from 0.1% in 2008 to 0.4% in 2016. Notified cases were dominated by extra-pulmonary TB (EP-TB, 42.4% of all cases in 2016). The proportion of pulmonary TB cases with no sputum test results was high with a national average of 26.6%. The regional variation of case notifications was significant: the Southern Region had the highest number and rate of notified TB cases. Of the nationally reported cases, 26.7% occurred in children. Treatment success rates remained low at 73% for bacteriologically confirmed TB and 64% for all forms of TB in 2016, far below the global target of 90%. For all forms of TB, 19% of patients were lost to follow-up from treatment.

An analysis of TB data from the national surveillance system has highlighted critical areas for improvement. A low population-screening rate, a high proportion of pulmonary TB cases without sputum test results and a low treatment success rate suggest areas for improvement in the National TB Program. Our additional subnational analysis helps identify geographical and programmatic areas that need strengthening and should be further promoted to guide the programme's direction in Papua New Guinea.

Papua New Guinea has high burdens of tuberculosis (TB), multidrug-resistant TB (MDR-TB) and TB/HIV co-infection.[1] The estimated TB incidence in Papua New Guinea in 2016 was 432 cases per 100 000 population.[1]

Papua New Guinea initiated directly observed treatment, short-course (DOTS), a global TB control strategy, in 2008. While other countries have adopted newer global strategies, Papua New Guinea is facing challenges in adapting and implementing basic DOTS. With external support, DOTS was expanded nationwide, and the standardized-routine-surveillance system was strengthened, resulting in the capturing of TB reports nationwide since 2012.

This paper provides an overview of national and subnational TB surveillance data in Papua New Guinea, from the inception of the DOTS strategy in 2008 to 2016. The results are expected to facilitate better understanding of TB epidemiology in Papua New Guinea, help identify programmatic gaps and inform actions.

METHODS

We conducted a retrospective descriptive analysis of TB cases and treatment outcomes using routine surveillance data from the national TB database for the period 2008–2016. TB laboratory results, case notifications, HIV testing results and treatment outcomes were analysed by disease category, geographic areas and demographic variables. Papua New Guinea has a decentralized health-care system; TB services are delivered by provincial and local governments under policies set by the National Department of Health.[2] The National TB Program defined a basic management unit (BMU) as the initial point of TB data collection. There are approximately 275 BMUs and 114 laboratories with TB testing capacities with varying catchment populations across 22 provinces. Recording and reporting formats are in line with WHO recommendations.[3] The BMU reports are consolidated into a standardized report that is submitted quarterly to the provincial health office and to the National TB Program at the National Department of Health. The aggregated national database is maintained in Excel.

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We obtained case-notification and treatment-outcome data from the aggregated national database. Population data were projected using 2000 and 2011 census data;[4,5] age- and sex-disaggregated population data for 2015 were sourced from LivePopulation.com.[6] To assess case-finding efforts, we calculated a population-screening rate,[7] which we defined as the number of people with presumptive TB examined by smear microscopy divided by the total population in each year. The smear-positivity rate was defined as the number of smear-positive patients divided by the total number of people examined for TB. Treatment outcomes were classified as per WHO definitions as cured, treatment completed, treatment failed, died, lost to follow-up and not evaluated. Treatment success was defined as the sum of cured and treatment completed.[3] R version 3.4.1 was used for data analysis and visualization. QGIS version 2.18 was used to produce maps.

Ethics statements

As this report used routinely available data and no personal identifying information was collected, ethical clearance was not required according to local regulations.

RESULTS

In 2016, 0.4% of the national population was screened for TB, and 15% of those screened were smear positive; the percentages varied across regions and provinces (**Fig. 1**). Low levels of both indicators were observed in the Highlands Region (0.22% screened, 7.6% positive), low screening with high positivity was observed in the Islands Region (0.34% screened, 17.9% positive), and moderate screening with high positivity was observed in the Momase Region (0.44% screened, 17.9% positive) and the Southern Region (0.78% screened, 15.8% positive). While national population screening increased over time, from 0.1% in 2008 to 0.4% in 2016, smear positivity did not decrease proportionately (17% in 2008 and 15% in 2016) (**Fig. 2**).

In 2016, the case notification rate for all forms of TB was 333 per 100 000 population (n = 28 244). The number and rate of case notifications of all forms of TB increased during 2008–2014 but stabilized during 2015–2016 (**Fig. 3**). The total TB caseload was driven mainly by extra pulmonary TB (EP-TB) (n = 11 984, 42% in 2016) and pulmonary TB cases without sputum test results (either the test was not done or the result was not available) (n = 7527, 27% in 2016). Among all TB cases and pulmonary TB cases, 15.6% and 25.9% were bacteriologically confirmed, respectively.

Case notification of new smear-positive TB was highest in the 15–24-year-old age group (**Fig. 4**). Case notification rates show two peaks in the 25–34-year old age group (for both males and females) and in the 55–64-age group (for males only). Case notification rates were equally high in younger males and females (15–34 years old), whereas higher rates were observed in men in older age groups.

We observed variations in case notification among the four regions (**Fig. 5** and **6A**). The Southern Region had the highest rate (615 per 100 000 population) in 2016, with an increasing annual trend since 2008 and a peak in 2014 (802 per 100 000 population). The rate in the regions of Momase and Islands increased during the study period to over 300 per 100 000 population in 2016, while the rate in the Highlands plateaued at around 200 per 100 000 population in 2013. EP-TB was the main contributor to the overall case notifications in the Momase, Highlands and Southern regions during 2016 (37%, 60% and 46%, respectively), followed by pulmonary TB cases without sputum test results (29%, 21% and 20%, respectively). The proportion of pulmonary TB cases without sputum test results declined in the Highlands Region (from 39% in 2011 to 21% in 2016) and the Southern Region (from 35% in 2012 to 20% in 2016). In the Islands Region, pulmonary TB cases without sputum test results were most commonly reported, and they sharply increased from 28% in 2014 to 47% in 2016. In all regions, the proportion of new smear-positive TB cases remains low at below 20%.

At the provincial level, high case notification rates of more than 600 per 100 000 population were reported in the National Capital District (NCD), Western, Gulf and West New Britain provinces in 2016 (**Fig. 6B**). Ten provinces contributed to 76% of the reported TB burden: NCD, Western, Gulf, Oro, East Sepik, Madang, Morobe, Eastern Highlands, Chimbu, and West New Britain.

Paediatric TB cases (age ≤14 years old) constituted 26.7% (n = 7541) of all notified TB cases in 2016. Most of the provinces reported proportions of paediatric TB cases between 20% and 30% (**Fig. 7**). Four provinces—

Manus, Jiwaka, Southern Highlands and Western Highlands—reported proportions of paediatric cases of less than 20%. Four provinces—Sandaun, Hela, Oro and West New Britain—reported proportions of paediatric cases of more than 30%; particularly high proportions were reported in Hela (51%) and West New Britain (48%) (**Fig. 7**).

In 2016, the proportion of pulmonary TB among total TB notifications was 27.3% nationally. New smear-positive cases accounted for 15.6% of TB notifications nationwide, with the lowest proportion found in the Highlands Region (8%) (**Table 1**). EP-TB contributed 42.4% of the total notifications in 2016, with the highest proportion reported in the Highlands Region (60.4%). The proportions of pulmonary TB cases without sputum test results ranged from 19.8% in the Southern Region to 47% in the Islands Region as compared to the national average of 26.6%.

Of all TB cases, 34.8% were tested for HIV with variations at the subnational level ranging from 3% in Central Province to 86.4% in Jiwaka Province (**Table 1**). The regional testing rate was highest in the Highlands (45.7%), with two of its provinces (Enga and Jiwaka) achieving an HIV testing rate of ≥80%. The HIV testing rate was the lowest in the Islands (11.4%). In 2016, 7.1% of the notified TB patients who were tested for HIV were HIV positive. HIV positivity ranged from 0% in Sandaun Province to 28.6% in Manus Province. Six provinces had HIV positivity rates of 10% or more: Chimbu, Enga, East New Britain, Manus, Central and Oro (**Table 1**).

The treatment success rate for all TB cases at the national level remained low in comparison to the global standard,[1] ranging between 55% and 65% during the study period (**Fig. 8**). The percentage of patients lost to follow-up declined over time; nevertheless, it remained high at ≥19% in 2016. Loss to follow-up and not evaluated were the major contributing factors towards a low treatment success rate in Papua New Guinea. In 2016, 986 deaths were reported. Loss to follow-up remained a major issue for all regions, with the highest rate in the Islands (27% in 2016). We observed higher treatment success rates in new smear-positive cases (73% in 2016), though the cure rate remained considerably lower than the treatment success rate.

DISCUSSION

In this paper, we report national and subnational TB surveillance data that provide an overview of the TB epidemiological and programmatic situation in Papua New Guinea over nine years. From 2008 to 2012, the country succeeded in expanding DOTS and strengthening the national surveillance system to capture nationwide data. Improved case-finding efforts resulted in a doubling of population screening from 0.2% in 2011 to 0.4% in 2014. The population-screening rate has remained static since 2014, and the rate was found to be low compared to other countries such as Cambodia (1.1% in 2013)[7] and Tajikistan (0.57% in 2013).[8] The programme in Papua New Guinea might not be reaching hard-to-reach populations possibly due to the policy to focus on a limited number of health centres.[9]

In the setting of an effective TB programme, the smear-positivity rate is inversely proportional to the population-screening rate.[7] In Cambodia, the smear-positivity rate declined from 29% in 2001 to 8% in 2013 along with an increased screening rate.[7] In contrast, the smear-positivity rate in Papua New Guinea did not decrease considerably, indicating that improved case detection had a limited impact on reducing infectiousness or that only highly presumptive cases were tested, leading to missed cases. Delayed diagnoses (due to limited access to health facilities and microscopy centres) and low treatment success rates likely contribute to high smear positivity. Papua New Guinea has only 114 microscopy facilities across 275 BMUs with weak referral systems, resulting in overreliance on clinical diagnosis. These health systems gaps can also account for the high proportion of pulmonary TB cases without sputum test results (26.6%) and the low proportion of bacteriologically confirmed TB among pulmonary TB cases (25.9%) compared to 38% in the Western Pacific Region and 57% globally.[1]

In parallel with increased population-screening rates, case notification rates steadily increased from 2008 to 2014, spiked in 2012 and plateaued in 2014. The highest case notification rates were in the 15–64-year-old age group, diverging from the pattern of highest case notification rates in older populations seen in most high-burden countries in the Western Pacific Region.[10] Similarly, the proportion of paediatric TB in Papua New Guinea

(26.7%) was found to be higher than other high-burden countries in the Western Pacific Region.[11] Paediatric TB represents recent transmission and can be a sentinel marker of disease transmission.[12,13] Although over-diagnosis is possible, the large proportion of paediatric TB cases indicates ongoing community transmission. We believe that this calls for improvements in early case finding and appropriate community preventive measures, including contact investigation.

Without additional information, we cannot determine the causes of regional variations in TB case notification. The increased case notification rate in the Southern Region might reflect might reflect increased true TB incidence or improved programme activities, or both. Given Papua New Guinea's rich regional sociocultural diversity, different factors can affect an individual's TB risk and health-seeking behaviours as well as a programme's performance measures in different ways. Ultimately, these differences may lead to regional differences in case notification rates.

The high proportion of pulmonary TB cases without sputum test results is a major barrier in understanding TB epidemiology in Papua New Guinea. Many factors could have contributed to this high proportion, including limited accessibility to a TB laboratory and unreliable sputum transport systems.[14] Without increasing the number of quality-assured functional TB laboratories, the challenge to increase bacteriological confirmation of TB will remain.

Despite the national mandate to test everyone diagnosed with TB for HIV infection, only 34.8% of TB patients were tested; 7% were positive, a percentage comparable to other high-risk populations, such as sex workers (14.9%), men who have sex with men and transgender individuals (8.5%).[15] Among other countries in the Western Pacific Region with a high burden of TB, the percentage of TB patients tested for HIV ranged from 13% in the Philippines to 84% in Cambodia; HIV positivity ranged from <1% in the Philippines to 4% in Cambodia.[1] While the percentage of TB patients tested for HIV in Papua New Guinea is comparable with other high-burden countries in the Region, positivity is higher. Collaboration between TB and HIV programmes and the implementation of integrated service delivery models with proper monitoring are essential to reduce the burden of TB/HIV co-infection.

Treatment success did not improve during the study period; the national average remained around 65%, far below the global target of 90%,[16] and the Western Pacific Region rate of more than 85%.[1,10] None of the regions achieved the >85% treatment success target. Loss to follow-up continues to be a major challenge that has likely resulted in an underreporting of deaths. New smear-positive cases had better outcomes compared to re-treatment cases but did not reach the global target. To improve treatment outcomes, further action is needed to strengthen patient support, including daily treatment, monitoring, counselling and continued efforts to strengthen the health system and address socioeconomic and physical barriers to accessing TB services.[17] Family DOT and self-administration are currently practised in Papua New Guinea but have not led to improved treatment success rates. Revisiting the care modality by strengthening community involvement and using an informal health workforce for treatment support is warranted. To improve access to TB treatment, it is essential not only to increase the number of BMUs but also to advance integrated service delivery through the full network of public health facilities, including aid posts (lowest-level public health facility) in communities.

This report has several limitations. An analysis of drug-resistant (DR-TB) was not included because a nationwide data collection system for DR-TB has not been established. Laboratory data used in the analysis were limited to smear microscopy results since data on GeneXpert and culture tests were not captured in the surveillance system. Data quality might have been an issue, especially as the surveillance system was being established, and the reporting rate was low between 2008 and 2012. Hence, trends in those years should be interpreted with caution. In addition, a high percentage of pulmonary TB cases without sputum test results hindered the interpretation of results.

Despite these limitations, we have provided an overview of TB surveillance data and identified patterns in TB epidemiology and programmatic performance in Papua New Guinea. In particular, subnational-level analysis helped identify geographical and programmatic areas that can be prioritized for improvement.[7,18] The use of subnational data should be further strengthened and routinely performed for operational planning and implementation of effective TB programmes in Papua New Guinea.

Conflicts of interest

The authors have no conflicts of interest.

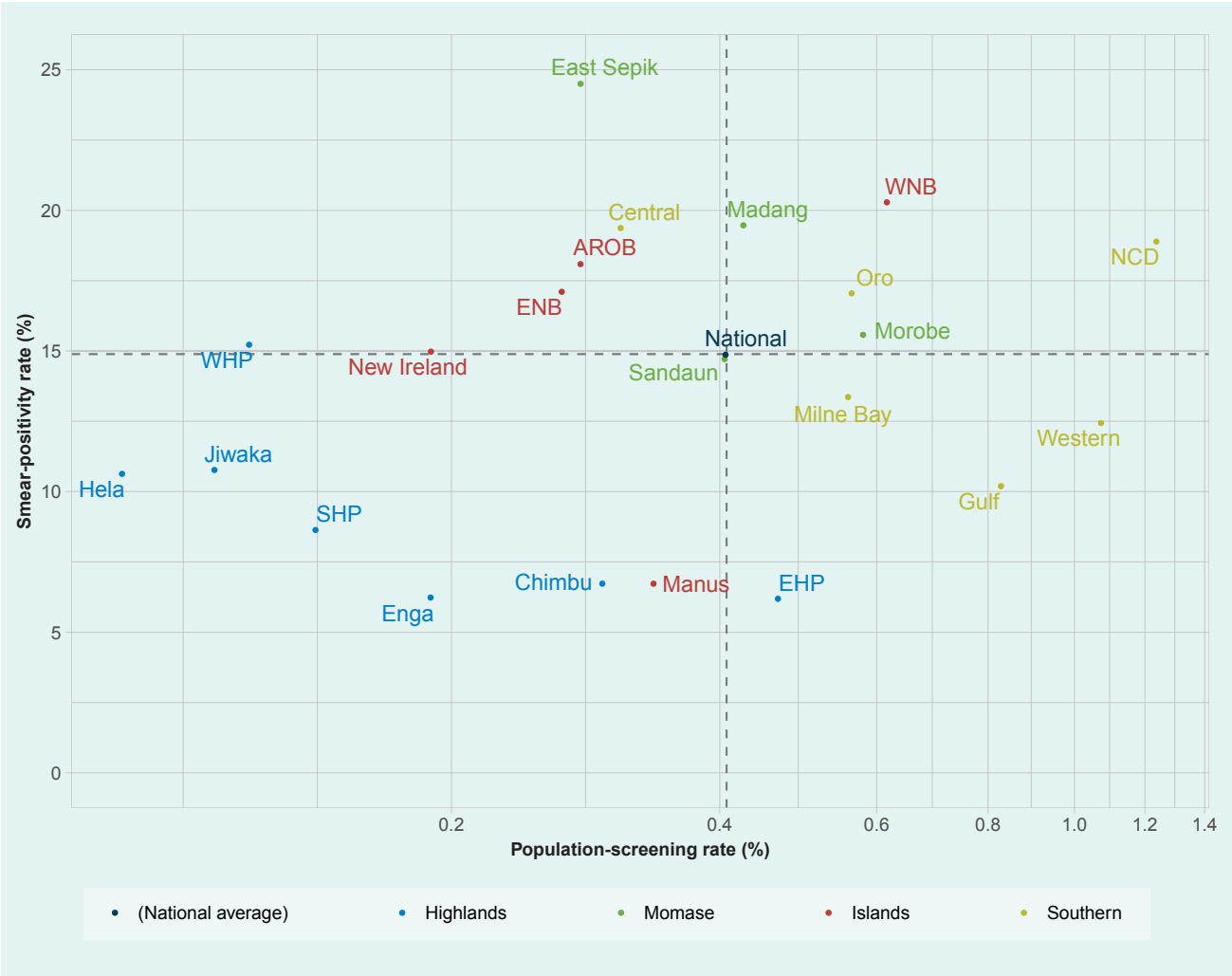
Funding information

None.

Acknowledgements

The authors wish to thank all health-care workers who provide TB diagnosis and treatment services in Papua New Guinea. The authors extend their thanks to all staff members of national and provincial teams working on the National TB Program of Papua New Guinea for their tremendous efforts in data collection and reporting.

Fig. 1. **Population-screening rate vs smear-positivity rate by province, Papua New Guinea, 2016**



Note: A log scale was used for the y-axis. AROB: Autonomous Region of Bougainville, EHP: Eastern Highlands Province, ENB: East New Britain, NCD: National Capital District, SHP: Southern Highlands Province, WHP: Western Highlands Province, WNB: West New Britain.

Fig. 2. **Population-screening rate vs smear-positivity rate, Papua New Guinea, 2008–2016**

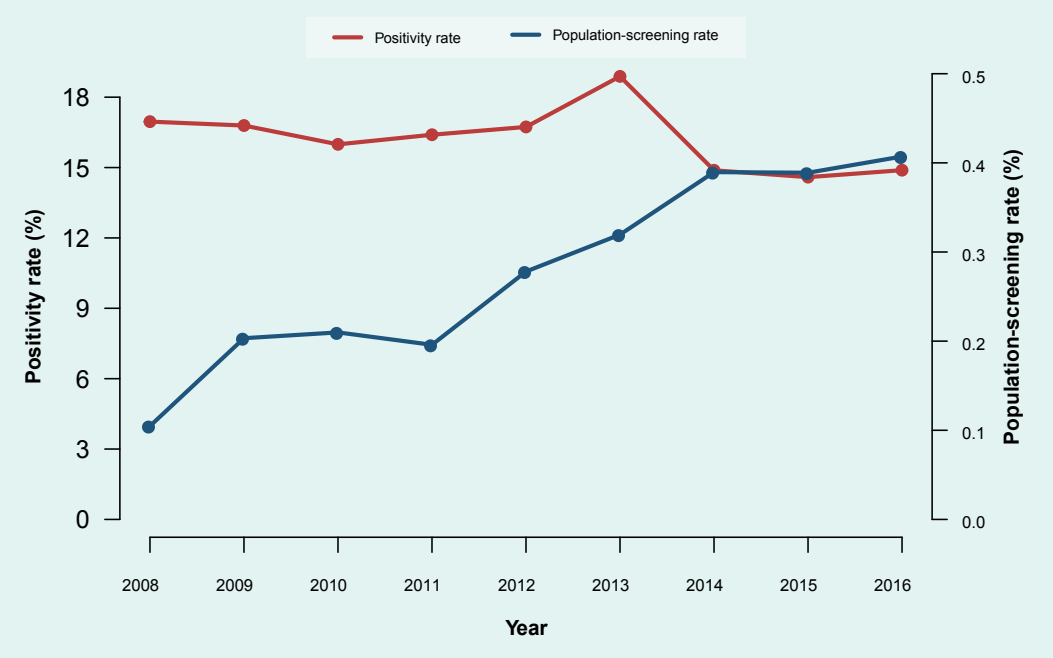
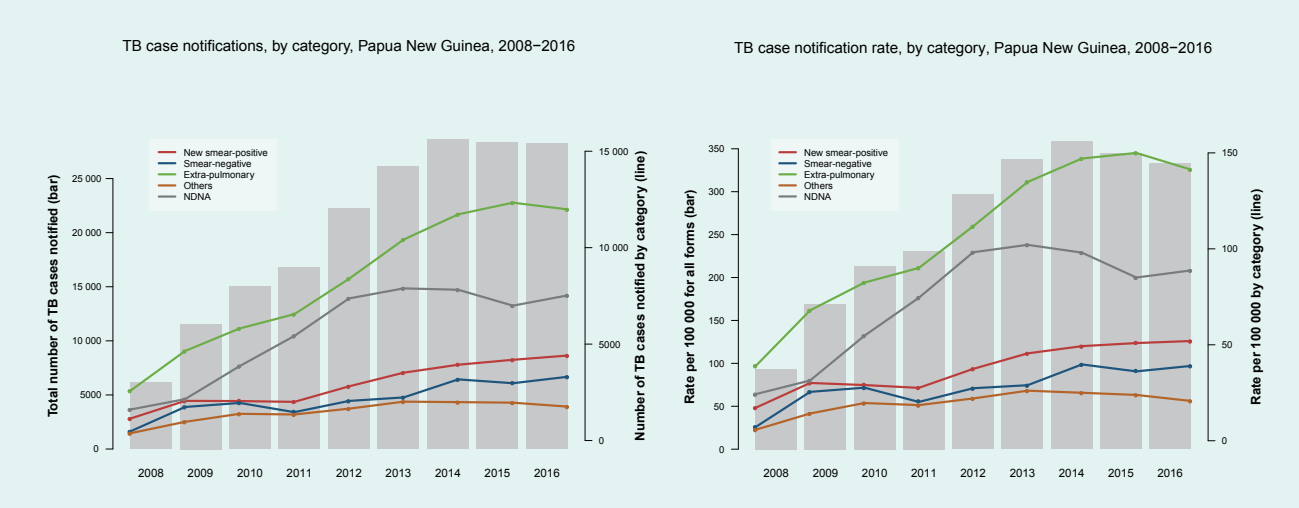
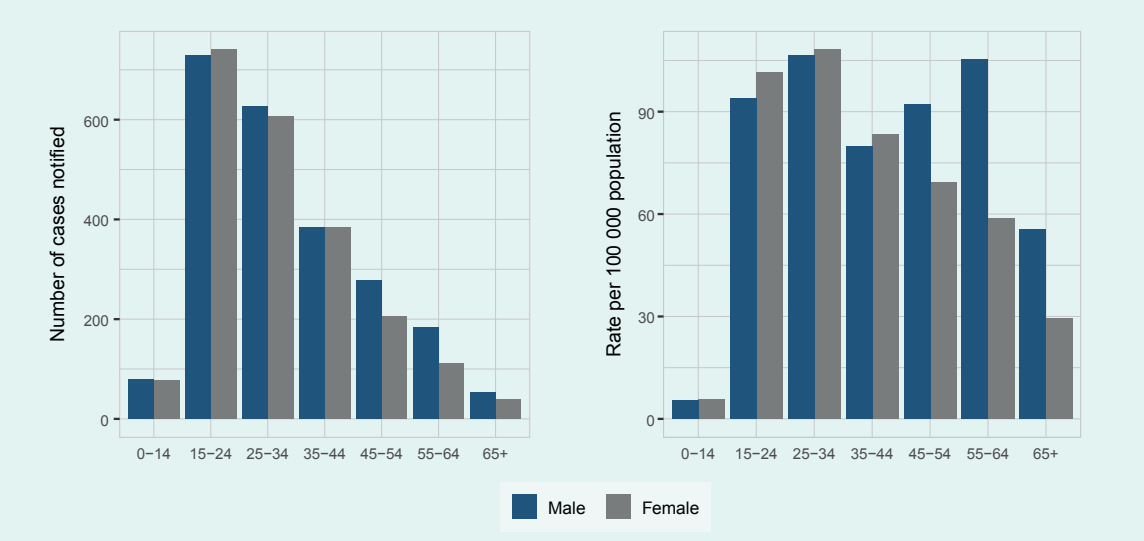


Fig. 3. **TB case notification (absolute number and rate) by diagnostic category, Papua New Guinea, 2016**



NDNA: Sputum smear testing not done or results are not available

Fig. 4. **TB case notification (new smear-positive) by age and sex, Papua New Guinea, 2016**



The age- and sex-disaggregated population data in 2015 were used to calculate case notification rates for 2016.

Fig. 5. **TB case notification (absolute number, rate and percentage) by region, Papua New Guinea, 2008–2016**

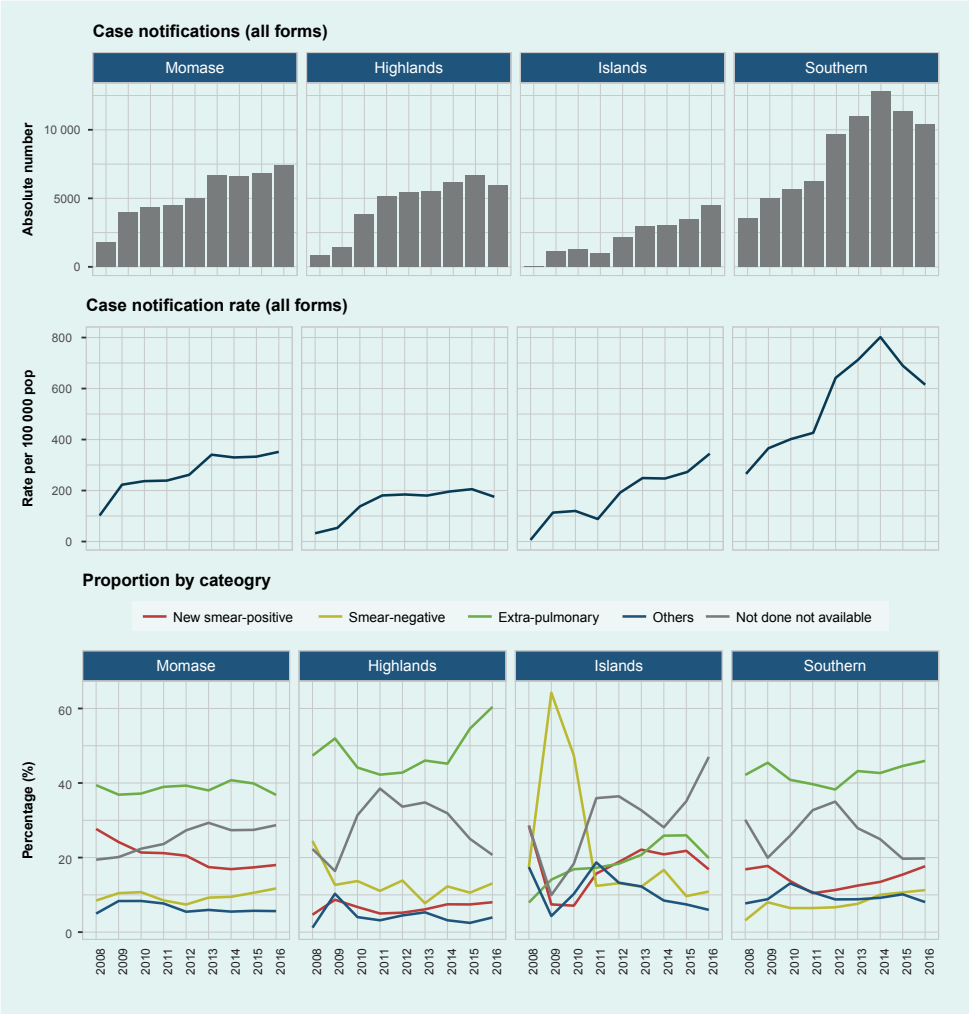


Fig. 6A. **Number of TB case notifications by province, Papua New Guinea, 2016**

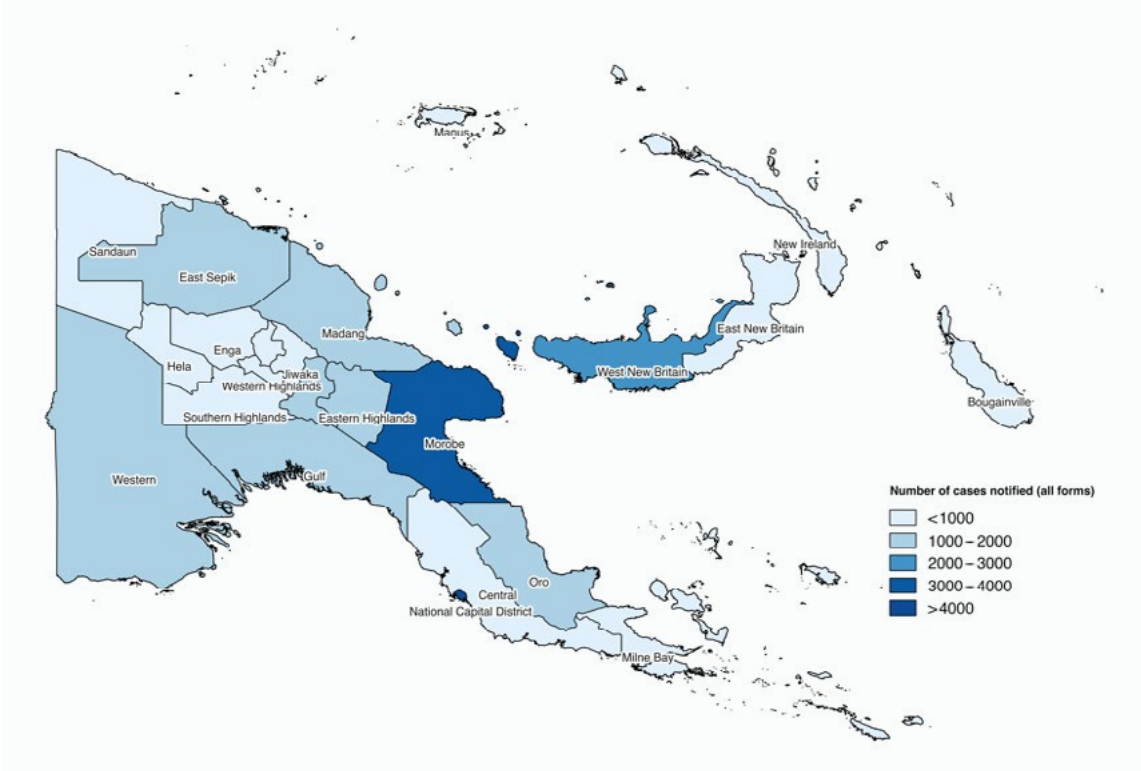


Fig. 6B. **TB case notification rate by province, Papua New Guinea, 2016**

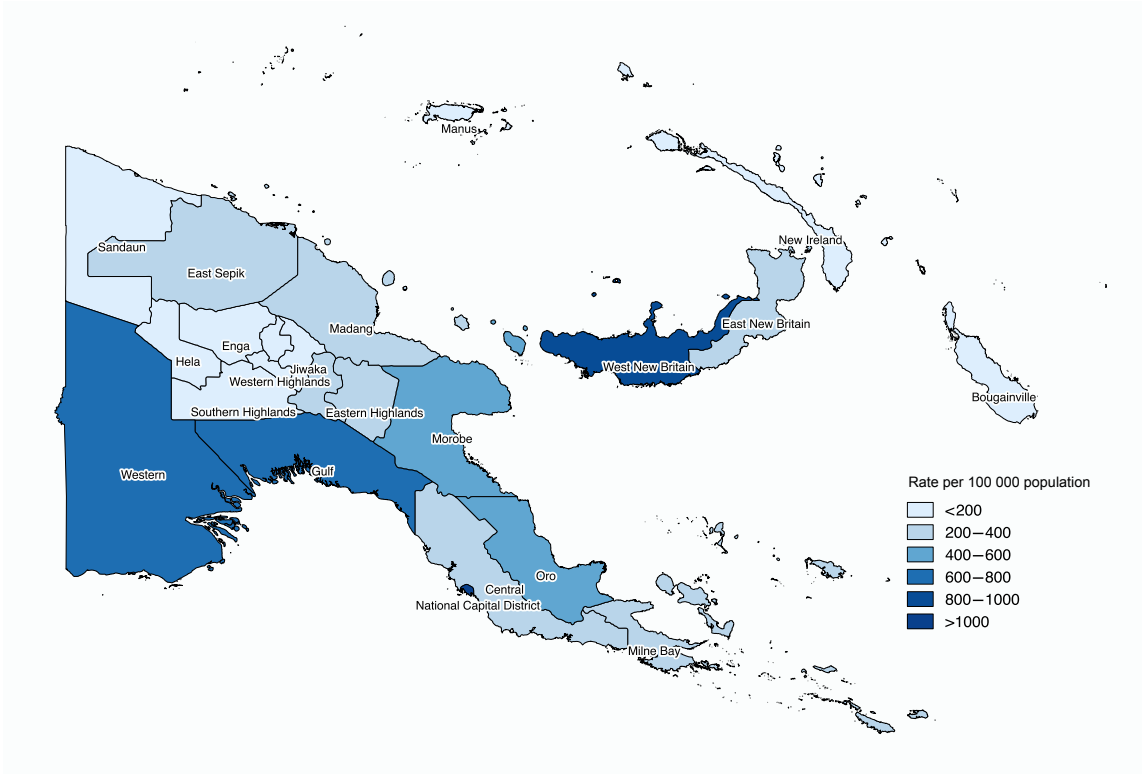
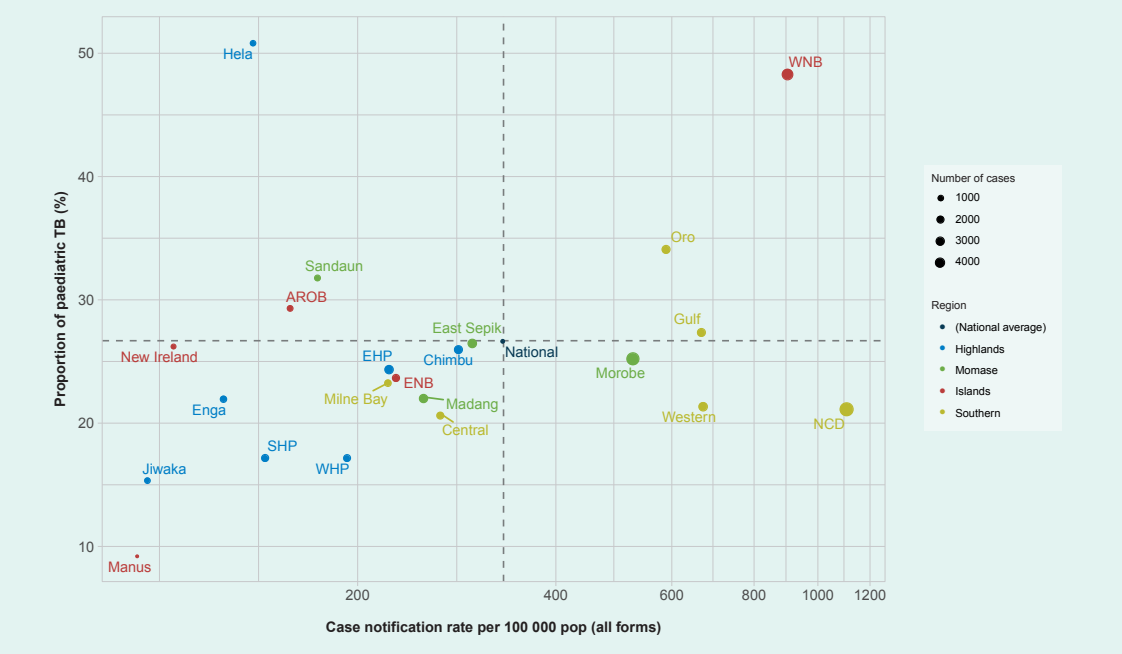


Fig. 7. **Proportion of paediatric TB among all notified TB cases by province, Papua New Guinea, 2016**



Note: A log scale was used for the x-axis. AROB: Autonomous Region of Bougainville, EHP: Eastern Highlands Province, ENB: East New Britain, NCD: National Capital District, SHP: Southern Highlands Province, WHP: Western Highlands Province, WNB: West New Britain

Table 1. **Summary indicators for TB programme, Papua New Guinea, 2016**

Region	Province	Case notification (all forms)		Category of TB					Paediatric cases (%)	TB patients tested for HIV (%)	HIV-positive among patients tested (%)
		Number	Rate per 100 000 population	New smear-positive (%)	Smear-negative (%)	Extra-pulmonary (%)	Others (%)	Not done not available (%)			
Momase		**7393**	**352**	**18.0**	**11.7**	**36.8**	**5.6**	**28.7**	**25.4**	**45**	**5.3**
	East Sepik	1532	301	16.4	5.0	32.1	4.4	42.0	26.6	9.6	9.5
	Madang	1430	253	23.7	16.6	38.8	5.9	15.3	22.1	36.6	5.2
	Morobe	3938	529	15.9	12.7	38.1	6.0	28.7	25.4	63.6	5.4
	Sandaun	493	175	23.1	10.1	34.9	6.1	26	31.8	31.2	0.0
Highlands		**5924**	**175**	**8.0**	**13.1**	**60.4**	**3.9**	**20.7**	**23.6**	**45.7**	**8.9**
	Chimbu	1274	286	5.7	15.7	44.4	4.9	30.9	26.1	22.9	12.7
	Eastern Highlands	1481	225	8.4	13.8	78.5	3.4	18.2	24.4	33.6	5.0
	Enga	645	126	8.8	12.2	63.6	0.3	16.1	22.0	82.3	14.9
	Hela	397	139	5.5	9.8	74.1	2.3	8.3	50.9	34.3	5.9
	Jiwaka	435	96	10.6	14.7	62.5	3.9	8.3	15.4	86.4	4.0
	Southern Highlands	869	145	8.2	13.5	46.8	4.3	28.0	17.3	57.1	7.9
	Western Highlands	823	194	10.0	8.5	56.7	6.8	18.0	17.3	46.2	9.7
Islands		**4502**	**345**	**16.8**	**10.9**	**19.9**	**6.0**	**47**	**39.7**	**11.4**	**8.2**
	Bougainville	463	159	28.1	6.3	27.6	6.9	31.7	29.4	8.9	4.9
	East New Britain	901	230	21.6	18.2	25	7.5	30.1	23.8	24.4	15.0
	Manus	65	93	24.6	12.3	33.8	10.8	18.5	9.2	10.8	28.6
	New Ireland	255	105	25.9	15.3	35.3	6.3	17.3	26.3	47.8	0.8
	West New Britain	2818	907	12.5	8.9	15.2	5.2	58.3	48.4	4.4	3.2
Southern		**10 425**	**615**	**17.7**	**11.3**	**45.9**	**8.1**	**19.8**	**23.7**	**31.3**	**7.3**
	Central	860	268	22.7	6.0	43.8	9.2	20.9	20.7	3.0	19.2
	Gulf	1264	669	14.2	11.6	43.7	10	20.5	27.5	33.9	5.4
	Milne Bay	699	223	28.3	10.7	32.9	8.0	21.6	23.3	19.3	8.9
	National Capital District	4783	1117	17.5	12.5	42.8	8.0	24.4	21.3	42.5	7.6
	Oro	1284	592	15.1	9.1	49.1	8.8	17.9	34.2	20.6	10.6
	Western	1535	674	15.4	12.3	62.1	5.3	4.8	21.4	24.7	4.2
National		**28 244**	**333**	**15.6**	**11.7**	**42.4**	**6.2**	**26.6**	**26.7**	**34.8**	**7.1**

Fig. 8. **Treatment outcomes at national and regional levels, Papua New Guinea, 2008–2016**

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Retrospective use of whole genome sequencing to better understand an outbreak of *Salmonella enterica* serovar Mbandaka in New South Wales, Australia

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Introduction: *Salmonella enterica* serovar Mbandaka is an infrequent cause of salmonellosis in New South Wales (NSW) with an average of 17 cases reported annually. This study examined the added value of whole genome sequencing (WGS) for investigating a non-point source outbreak of *Salmonella* ser. Mbandaka with limited geographical spread.

Methods: In February 2016, an increase in *Salmonella* ser. Mbandaka was noted in New South Wales, and an investigation was initiated. A WGS study was conducted three months after the initial investigation, analysing the outbreak *Salmonella* ser. Mbandaka isolates along with 17 human and non-human reference strains from 2010 to 2015.

Results: WGS analysis distinguished the original outbreak cases (n = 29) into two main clusters: Cluster A (n = 11) and Cluster B (n = 6); there were also 12 sporadic cases. Reanalysis of food consumption histories of cases by WGS cluster provided additional specificity when assessing associations.

Discussion: WGS has been widely acknowledged as a promising high-resolution typing tool for enteric pathogens. This study was one of the first to apply WGS to a geographically limited cluster of salmonellosis in Australia. WGS clearly distinguished the outbreak cases into distinct clusters, demonstrating its potential value for use in real time to support non-point source foodborne disease outbreaks of limited geographical spread.

Salmonella enterica serovar Mbandaka is a relatively uncommon *Salmonella* serovar in New South Wales (NSW) with an average of 17 cases notified per year over the past 10 years.[1] *Salmonella* ser. Mbandaka cases reported in Australia have been acquired locally and overseas in India, Africa, Indonesia, Mexico and China.[2] In Australia, *Salmonella* ser. Mbandaka has been isolated from foods such as chicken, peanut butter, turkey meat and curry powder.[2] Whole genome sequencing (WGS) is a high-resolution typing method that can help foodborne disease investigators distinguish outbreak cases from non-outbreak cases.[3] WGS has been used for public health surveillance in the United States of America, United Kingdom of Great Britain and Northern Ireland, and the European Union.[4–6] In Australia, several jurisdictional reference laboratories are developing WGS capacity and evaluating its utility for routine surveillance of enteric pathogens.[7] This study examined the potential added value of WGS in assisting investigators identify the source of a community outbreak of *Salmonella* ser. Mbandaka with limited geographical spread.

METHODS

In February 2016, an increase in *Salmonella* ser. Mbandaka notifications was noted in the Hunter New England and Central Coast local health districts of NSW. A confirmed case was defined as any resident or visitor to NSW with laboratory-confirmed *Salmonella* ser. Mbandaka infection and symptom onset from 1 January 2016 to 30 April 2016. Individuals meeting the case definition were interviewed by phone, beginning 22 February 2016, using a standard *Salmonella* hypothesis-generating questionnaire to collect demographic, clinical and risk factor information, including travel and food consumption histories during the seven days before illness onset. For

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reference, data from a 2016 Victorian Food Consumption study were used to provide expected food consumption frequencies in a healthy population. This data set contains seven-day food consumption histories of approximately 500 randomly selected healthy individuals in Victoria from January to April 2016, the same time period as the *Salmonella* ser. Mbandaka outbreak. The Victoria data set was used because no equivalent NSW data set exists. Food consumption frequencies of outbreak cases were compared to those from the Victorian Food Consumption study using binomial probability.

Illness onset dates were documented during case interviews or estimated based on specimen collection dates, using the average incubation period from all other cases, for cases lost to follow-up. The WGS study was conducted retrospectively three months after the initial outbreak investigation, analysing the *Salmonella* ser. Mbandaka isolates associated with this outbreak and comparing them with 10 human strains from 2010 to 2015 and six non-human isolates from 2012 to 2015 (primarily egg farm swabs from the NSW Food Authority). WGS was conducted by the NSW Enteric Reference Laboratory, Institute of Clinical Pathology and Medical Research, NSW Health Pathology. For WGS, the DNA was extracted and purified using a DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA quantities were estimated using the Qubit dsDNA HS Assay Kit and the Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. For each purified DNA sample, a 100 bp library was prepared using the NexteraXT kit (Illumina, Inc., San Diego, CA, USA), then pooled and sequenced on the NextSeq500 platform (Illumina). FastQ files were imported into CLC Genomics Workbench v 7.0 (CLC bio, Aarhus, Denmark); reads were trimmed to remove Nextera transposase adaptor sequences and then mapped to the reference genome *Salmonella* ser. Mbandaka str. ATCC 51958 (NCBI GenBank accession: CP019183.1).

Clusters were identified based on sequence similarity between *Salmonella* ser. Mbandaka genomes using single nucleotide polymorphism (SNP) analysis. The SNP phylogenetic tree was generated through the concentrated SNP alignments using MEGA7 sequence analysis software (https://www.megasoftware.net) with a bootstrap value at 100.[8]

The food consumption histories were reanalysed based on the clusters identified by WGS and compared to the data from the 2016 Victorian Food Consumption study. Data were entered and analysed in EpiInfo (Version 7) and Microsoft Excel.

Ethics statement

This work was part of an outbreak investigation and did not require ethical review and oversight by a Human Research Ethics Committee.

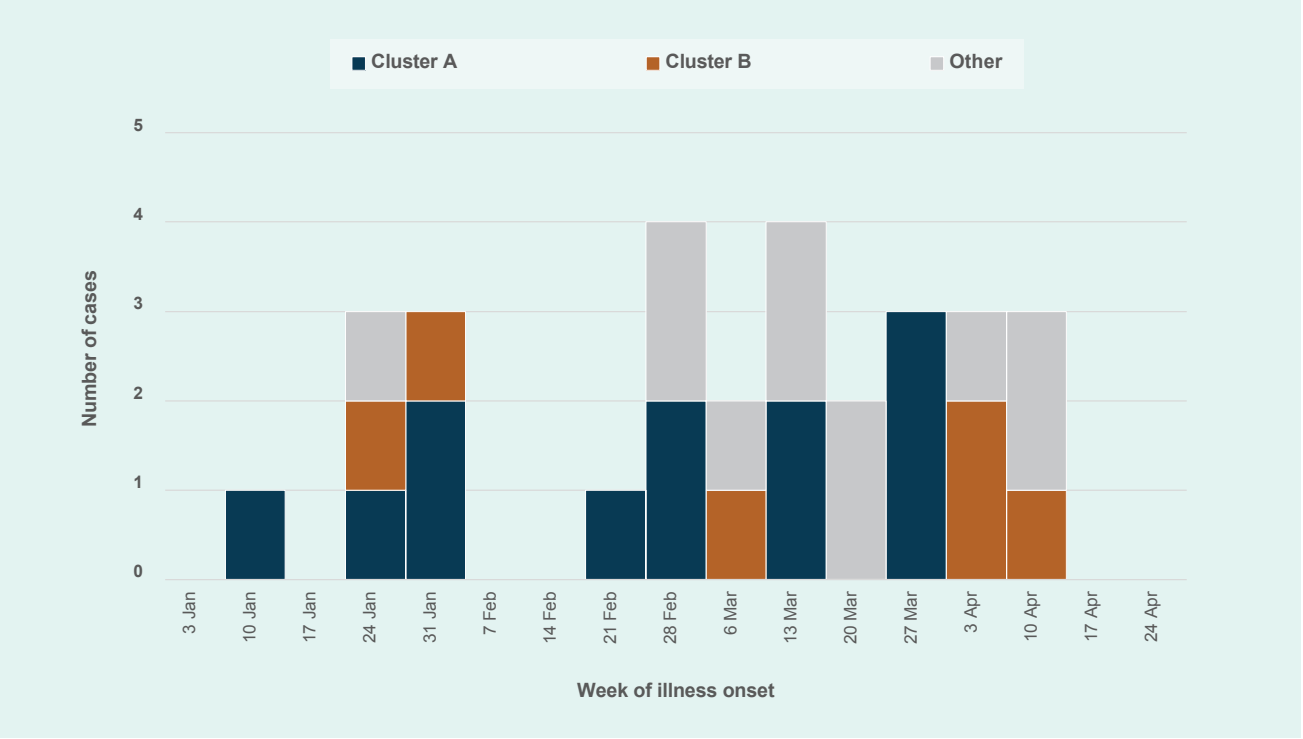
RESULTS

From 1 January 2016 to 30 April 2016, 29 cases of salmonellosis caused by *Salmonella* ser. Mbandaka were notified. The epidemic curve of cases investigated as part of this outbreak is shown in **Fig. 1**. Illness onset dates ranged from 15 January to 14 April 2016. Seven case patients were hospitalized and no patients died. Patients were aged from 1 to 89 years with a median age of 48 years, 14 (48%) lived in the Hunter New England Local Health District, 16 (55%) were male and three (10%) were of Aboriginal origin. Commonly reported symptoms included diarrhoea (n = 21, 95%), lethargy (n = 17, 85%), abdominal pain (n = 14, 64%), fever (n = 13, 62%) and vomiting (n = 12, 55%). Symptoms continued for 1–10 days (median five days).

The initial (pre-WGS) investigation did not identify any common eating establishments or shopping venues among cases. Processed cheese was identified to have a higher-than-expected consumption frequency among cases; it was consumed by 64% of cases when the expected consumption frequencies in a healthy population was 22% (binomial probability [P = 0.0008]). However, on closer analysis, several different brands of processed cheese and places of purchase were indicated, and in the absence of additional cases, no food safety investigation was initiated. Other foods with a higher-than-expected consumption frequency included watermelon (63%, P = 0.0341, P = 0.04), onion (69%, P = 0.0574, P = 0.07) and green capsicum (53%, P = 0.0599, P = 0.07).

WGS analysis distinguished the original outbreak cases into two main clusters: Cluster A, which included 11 cases with an SNP distance between 12 and 82, and Cluster B, which included six cases with an SNP distance

Fig. 1. **Confirmed cases (n = 29) of *Salmonella* ser. Mbandaka in New South Wales by cluster and week of illness onset, 3 January to 30 April 2016**



between 10 and 25 (**Fig. 2**). In addition to the two key clusters, WGS identified smaller clusters and several sporadic cases. The food consumption frequencies re-analysed by the two key clusters are shown in **Table 1**. The consumption of processed cheese among cases in Cluster A increased to 89% ($P < 0.0001$) and decreased in Cluster B to 33%. ($P = 0.5254$) when compared to all cases (**Table 1**).

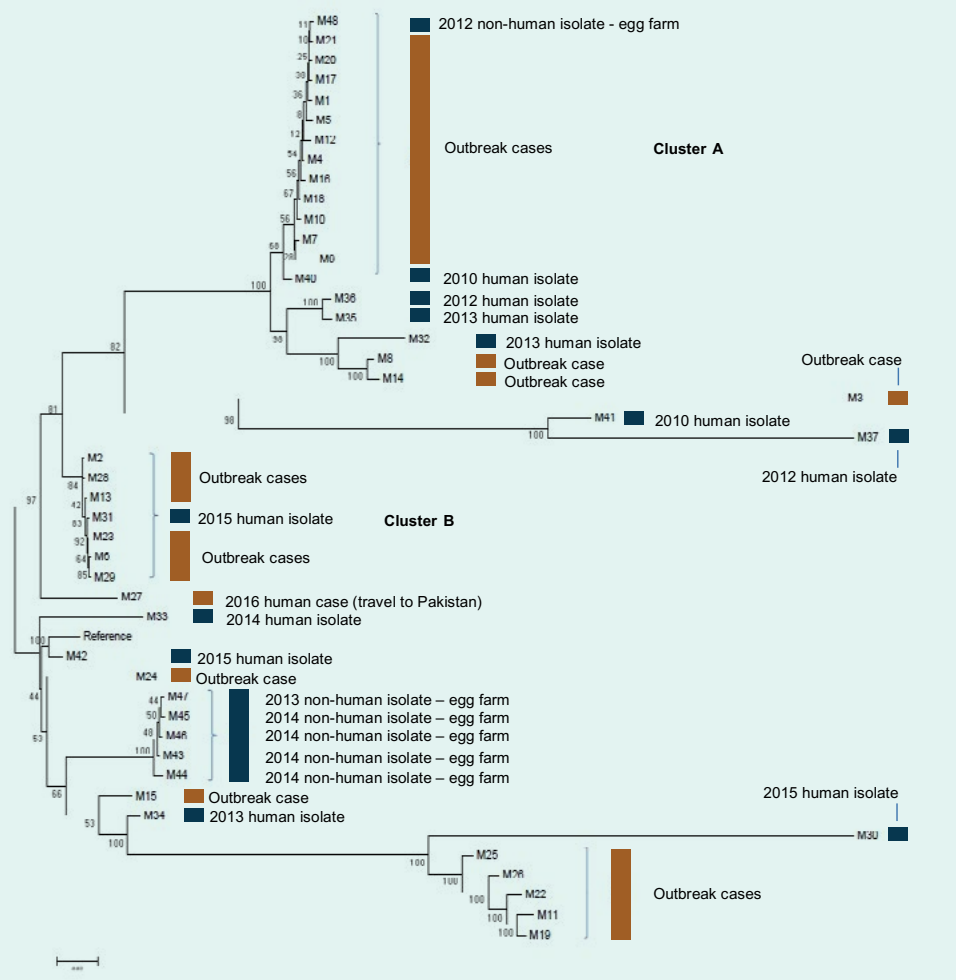
DISCUSSION

Internationally, WGS is increasingly being used for enhanced foodborne disease surveillance and response due to its discrimination power for typing cases and tracing infection sources and its similar turnaround times to other laboratory techniques.[5,6] WGS is also being used to understand disease transmission pathways and determinates of transmission, monitor pathogen evolution and adaptation, identify infections with epidemic potential and refine control strategies.[9]

In the United States, WGS is replacing pulsed-field gel electrophoresis for subtyping foodborne pathogens for outbreak surveillance.[10] WGS of foodborne pathogens is used for regulatory purposes by the US Food and Drug Administration[5] and has proven valuable in outbreak investigations for differentiating sources of contamination.[11,12] In European Union countries and in the United Kingdom, WGS is increasingly being used for foodborne disease outbreak investigations and national surveillance of infectious diseases.[4,6] In Australia, WGS is acknowledged as a promising typing alternative; however, it is not yet in widespread use due to limitations in standardized quality control and data interpretation, cost and infrastructure.[13,14] WGS is being piloted by OzFoodNet, an Australian Department of Health foodborne disease surveillance and response network, and has been successfully applied in multijurisdictional foodborne disease outbreaks and for routine surveillance of *Listeria monocytogenes*.[3,15]

This *Salmonella* ser. Mbandaka study was one of the first in Australia to apply WGS to a geographically limited cluster of *Salmonella*. Although the WGS was not conducted in real time, its potential to support an outbreak investigation was demonstrated. WGS was able to differentiate the outbreak cases of *Salmonella* ser. Mbandaka into distinct clusters and sporadic cases. Analysis of food consumption histories based on

Fig. 2. **Phylogenetic tree generated from whole-genome SNPs for outbreak and non-outbreak cases of *Salmonella* ser. Mbandaka in NSW**



phylogenetic cluster suggests two concurrent outbreaks of *Salmonella* ser. Mbandaka may have occurred in NSW. If WGS had been conducted in real time, affected individuals would have been reinterviewed to collect additional details on food items of interest and further analysis conducted. Our findings support an earlier study in NSW that applied WGS retrospectively to five epidemiologically confirmed community outbreaks of *Salmonella enterica* serovar Typhimurium and found that WGS significantly increased the resolution of investigations. Their study also found that for one of the outbreaks, the food source was contaminated with more than one strain of *Salmonella* ser. Typhimurium, highlighting the need to assess both laboratory and epidemiological information during an investigation.

Data from the Victorian Food Consumption study allowed investigators to estimate expected food consumption frequencies in a healthy population and, using binomial probabilities, compare them to the food consumption frequencies among the outbreak cases. This method allows for rapid hypothesis generation to guide further environmental and epidemiological investigations. The absence of an equivalent NSW food consumption data set was a limitation of this study. It was assumed that food consumption habits and available foods in Victoria and NSW were similar enough to permit hypothesis generation. Given the potential for differences in food habits or food availability between the two populations, the associations derived need to be interpreted with caution and used for hypothesis generating rather than testing. The rapid development in advanced laboratory tools also presents challenges for public health practitioners. As public health reference laboratories have been adopting WGS, clinical laboratories are increasingly relying on culture-independent multiplexed molecular panels to test

Table 1. **Food consumption frequencies among all cases and by key clusters identified by WGS**

Food Item	All cases			WGS – Cluster A			WGS – Cluster B			Reference*		
	Ate food	Total	%	Ate food	Total	%	Ate food	Total	%	Ate food	Total	%
Tomato	11	13	85%	9	9	100%	2	3	67%	497	665	75%
Carrot	12	16	75%	9	10	90%	3	4	75%	534	662	81%
Potato	10	14	71%	9	9	100%	1	3	33%**	546	667	82%
Onion	11	16	69%	8	10	80%**	3	4	75%	307	666	46%
Chicken pieces	11	16	69%	6	10	60%	3	4	75%	406	664	61%
Black pepper	11	16	69%	8	10	80%	3	4	75%	427	666	64%
Processed cheese	9	14	64%**	8	9	89%**	1	3	33%	149	665	22%
Free range eggs	7	11	64%	4	6	67%	2	3	67%	291	446	65%
Eggs (any)	7	11	64%	7	9	78%	3	4	75%	446	665	67%
Watermelon	10	16	63%**	8	10	80%**	2	4	50%	245	667	37%
Apple	10	16	63%	6	10	60%	3	4	75%	446	667	67%
Banana	10	16	63%	6	10	60%	3	4	75%	464	667	70%
Beef mince	8	14	57%	7	8	88%**	1	4	25%	332	663	50%
Green capsicum	8	15	53%	6	9	66%**	2	4	50%	209	667	31%
Grapes	8	15	53%	4	9	44%	3	4	75%	375	666	56%
Red capsicum	8	15	53%	6	9	67%	2	4	50%	304	667	46%
Broccoli	8	15	53%	6	9	67%	2	4	50%	348	665	52%
Cucumber	8	15	53%	5	9	56%	3	4	75%	383	665	58%

* Reference = data from 2016 Victorian Food Consumption study

** Difference from reference statistically significant (< 0.05)

stool specimens for enteric pathogens.[16] The move away from culturing enteric pathogens will reduce the number of isolates available for typing by WGS or other culture-dependent typing methods. In response, scientists are working to develop metagenomic sequencing-based tools to characterize stool specimens without the need for culture.[7,17] As these developments continue to evolve, health practitioners will need to understand how they will impact surveillance systems, outbreak detection and response activities.

In conclusion, this study highlighted the potential value of WGS in supporting epidemiologists to investigate a relatively small, non-point source foodborne disease outbreak in a community. If conducted in real time, WGS could have assisted with potential source detection to guide further investigations and to aid control efforts. The continued application of WGS to support foodborne disease outbreak investigations in Australia will contribute to a global understanding of its potential to control outbreaks in a more timely and efficient manner.

Conflicts of interest

None.

Funding information

None.

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Epidemiology of vaccine-preventable diseases in Japan: considerations for pre-travel advice for the 2019 Rugby World Cup and 2020 Summer Olympic and Paralympic Games

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Introduction: In 2019 and 2020, Japan will host two international sporting events estimated to draw a combined 22 million visitors. Mass gatherings like these ones increase the risk of spread of infectious disease outbreaks and international transmission. Pre-travel advice reduces that risk.

Methods: To assist ministries of health and related organizations in developing pre-travel advice, we summarized national surveillance data in Japan (2000–2016, to the extent available) for rubella, invasive pneumococcal disease, measles, non-A and non-E viral hepatitis, hepatitis A, invasive *Haemophilus influenzae* disease, tetanus, typhoid fever, invasive meningococcal disease, Japanese encephalitis, influenza, varicella, mumps and pertussis by calculating descriptive statistics of reported cases and reviewing trends. (See **Annex A** for details of reviewed diseases.)

Results: Our findings showed notable incidences of rubella (1.78 per 100 000 person-years), influenza (243.5 cases per sentinel site), and mumps (40.1 per sentinel site); seasonal increases for influenza (November–May) and Japanese encephalitis (August–November); and a geographical concentration of Japanese encephalitis in western Japan. Measles cases decreased from 11 013 in 2008 to 35 in 2015, but outbreaks (n = 165 cases) associated with importation occurred in 2016. Though invasive meningococcal disease incidence was only 0.03 per 100 000, international transmission occurred at a mass gathering in Japan in 2015.

Discussion: Ministries of health and related organizations should use these findings to develop targeted pre-travel advice for travellers to the 2019 Rugby World Cup and the 2020 Summer Olympic and Paralympic Games, especially for mumps, measles, rubella, influenza, and meningitis. Travellers with increased exposure risk should also be advised about hepatitis A and Japanese encephalitis.

The 2019 Rugby World Cup will occur from 20 September to 2 November throughout Japan, and the 2020 Summer Olympic and Paralympic Games will happen in Tokyo from 24 July to 6 September. These mass gatherings (MGs) are estimated to attract 22 million visitors to Japan.[1] MGs like these can strain resources of the host country and have been associated with disease outbreaks and the international spread of disease.[2–4]

The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend travellers seek advice from health professionals before travelling to an MG.[5,6] This strategy has been associated with a twofold increase in vaccinations among Hajj pilgrims who seek such advice compared to those who do not.[7]

Up-to-date vaccination for all vaccine-preventable diseases (VPDs) is the best way to prevent illness, outbreaks and the international spread of disease. To assist ministries of health and other organizations in developing targeted pre-travel advice for these MGs, we aimed to summarize the recent epidemiology of selected VPDs in Japan.

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METHODS

We selected diseases based on frequency, severity and potential immunity (i.e. likelihood that foreign travellers to Japan would have developed immunity against the disease before visiting Japan because of wide circulation of the pathogen or global vaccination trends) among visitors to Japan. We obtained data from the National Epidemiological Surveillance of Infectious Diseases (NESID) system for a period of at least eight years up to the latest finalized data (for most diseases 2015; years inclusive unless otherwise noted). National notifiable disease surveillance comprises passive case-based reporting from all health-care facilities in Japan. For this work, we selected rubella, invasive pneumococcal disease, measles, viral hepatitis non-E and non-A, hepatitis A, invasive *Haemophilus influenzae* disease, tetanus, typhoid, invasive meningococcal disease and Japanese encephalitis. NESID also has weekly sentinel surveillance from approximately 3000 paediatric clinics for some diseases. Of these, we selected varicella, mumps, pertussis and influenza. An additional 2000 adult outpatient clinics report influenza.

We gathered data on case totals by sex, age group, prefecture, and week and year of report. When available, we obtained clinical disease classifications (e.g. modified measles), vaccination history, the suspected location or route of infection and laboratory results. For influenza and varicella, we obtained counts of hospitalized cases with laboratory evidence of infection. Influenza cases have been reported from hospitals with more than 300 beds since 2011 and varicella cases from all hospitals since September 2014.

We calculated totals, proportions, ranges, and incidence per 100 000 person-years using annual population estimates from Japan's Statistics Bureau,[8] applying relevant proportions for incomplete years. For sentinel diseases, we calculated mean cases reported per sentinel site because catchment population sizes were unavailable. To further contextualize the findings, we briefly described current vaccination policies. For detailed case definitions and additional disease information, **see Annex B**.

RESULTS

VPDs under national notifiable disease surveillance (non-sentinel)

Rubella (2008–2015)

For the period reviewed, approximately 79% of the reported rubella cases occurred in 2013 (n = 14 344). The 2013 epidemic affected all 47 prefectures and comprised mostly males (76%; n = 10 972) and persons aged 20–44 years (70%; n = 10 055). Cases for the overall period were also mostly male (75%; n = 13 660) and aged 20–44 years (69%; n = 12 440). For 2015, cases with known vaccination history (n = 74; 45%) were typically undervaccinated: 49% (n = 36) unvaccinated, including four individuals too young to vaccinate, and 41% (n = 30) with one dose. The incidence of rubella for the reviewed period was 1.78 cases per 100 000 person-years (n = 18 117) (see **Table 1**).

Since April 2006, the routine vaccination schedule has included two doses of measles-rubella (MR) vaccine: the first dose at 1 year of age and the second dose less than 1 year before entering primary school (typically age 5 or 6). Prior to 2006, a single rubella dose had been routine for 11–12-year-old girls since 1977. Doses for both sexes aged 12–89 months and for boys 11–12 years old were added in 1995.

Invasive pneumococcal disease (IPD) (2013–2015)

Reported cases of IPD were consistently lowest from mid-July to late September. The incidence was 1.5 per 100 000 person-years (n = 5229) from April 2013, when IPD became notifiable, through 2015. Adults aged ≥60 years accounted for 62% (n = 3227) of cases, while children <5 years made up 19% (n = 1017). Males accounted for 60% (n = 3134).

Since November 2013, routine vaccination has included four doses of 13-valent pneumococcal conjugate vaccine (PCV13) for children aged 2–59 months. PCV13 replaced PCV7, which had been subsidized since November 2010 and was routine since April 2013 for children <24 months old. Routine immunization with 23-valent pneumococcal polysaccharide vaccine for adults aged ≥65 years began in October 2014 after having been available on a voluntary basis since 1988.

Table 1. **Incidence and characteristics of selected notifiable (non-sentinel) vaccine-preventable diseases (VPDs), Japan, 2006–2016**

Disease (*n* cases; period reviewed)	Period incidence[a]	Annual incidence range[b]	% Male (*n*)	Predominant age groups in years: % (*n*)	Case reporting	Vaccination schedule[f]
Rubella (18 117; 2008–2015)	1.78	0.07–11.3	75 (13 660)	20–44: 69 (12 440)	Clinical or laboratory	Routine
IPD (5229; 2013[c]–2015)	1.50	1.05–1.9	60 (3134)	<5: 19 (1017); ≥60: 62 (3227)	Clinical and laboratory	Routine (PCV7 and PPSV23)
Measles (13 805; 2008–2016)	1.20	0.03–8.6	57 (7812)	20–39: 58 (95)[d]	Clinical or laboratory	Routine
Viral hepatitis[e] (2454; 2006–2015)	0.19	0.17–0.22	74 (1808)	20–44: 64 (1559)	Clinical and laboratory	Routine (hepatitis B)
Hepatitis A (2245; 2006–2015)	0.18	0.10–0.34	58 (1313)	25–64: 72 (1744)	Laboratory	Voluntary
IHD (560; 2013[c]–2015)	0.16	0.11–0.20	60 (338)	≥70: 52 (293)	Clinical and laboratory	Routine
Tetanus (1158; 2006–2015)	0.09	0.07–0.10	56 (653)	≥55: 85 (984)	Clinical	Routine
Typhoid (330; 2008–2015)	0.03	0.02–0.05	59 (195)	20–39: 59 (194)	Laboratory	Not approved
IMD (94; 2013–2015)	0.03	0.02–0.03	64 (60)	≥50: 59 (55)	Clinical and laboratory	Voluntary (MCV4)
Japanese encephalitis (51; 2006–2015)	0.004	0.002–0.008	63 (32)	≥60: 61 (31)	Clinical and laboratory	Routine

a. Per 100 000 person-years; b. More than 4 consecutive weeks higher than the weekly average of reported cases for the year; c. From April; d. For 2016 (*n* = 165); e. Non-A, non-E: 81% HBV; f. See immunization schedule in Japan (1 October 2016) at https://www.niid.go.jp/niid/images/vaccine/schedule/2016/EN20161001.pdf.

IHD: invasive Haemophilus influenzae disease

IMD: invasive meningococcal disease

IPD: invasive pneumococcal disease

MCV4: Meningococcal Conjugate Vaccine (Quadravalent)

PCV7: Pneumococcal Conjugate Vaccine (7-valent)

PPSV23: Pneumococcal Polysaccharide Vaccine (23-valent)

Measles (2008–2016)

Reports of measles in Japan decreased from 11 013 cases in 2008 to 35 cases in 2015. In 2016, however, 165 cases were reported. Of these, 32% (*n* = 52) were *modified measles* (i.e. laboratory confirmation with less than 3 classic measles symptoms), 58% (*n* = 95) were 20–39 years old and 19% (*n* = 32) were <10 years old. Among the 112 cases in 2016 (68%) with known vaccination history, most were undervaccinated: 42% (*n* = 47) unvaccinated, including eight under vaccine age and 36% (*n* = 40) with one dose. Measles virus was detected in 139 (84%) of the 2016 cases, 25% (*n* = 35) of which had travelled abroad. Genotype was identified for 89% (*n* = 124) of these isolates: 53% (*n* = 66) D8, 46% (*n* = 57) H1 and <1% (*n* = 1) B3. Case-patients with these isolates who had not travelled abroad were linked to international airports in Japan. For the reviewed period, measles incidence was 1.2 per 100 000 person-years (*n* = 13 805).

See rubella vaccination (above). Additionally, a single measles vaccine dose has been available for children aged 12–71 months since 1978 and was expanded to 89 months in 1995.

Viral hepatitis (non-A, non-E) (2006–2015)

Hepatitis B virus (HBV) accounted for 81% (*n* = 1933) of the 2400 (incidence: 0.19 per 100 000 person-years) reported laboratory-confirmed viral hepatitis non-A, non-E cases in Japan for the reviewed period. HBV cases were 78% male (*n* = 1503). Suspected sexual transmission accounted for 70% of HBV cases (*n* = 1349). Of the 1091 male case-patients reporting sexual transmission, 66% (*n* = 715) reported heterosexual contact, 21% (*n* = 226) reported homosexual contact, 2% (*n* = 20) reported heterosexual and homosexual contact and 16% (*n* = 170) gave no response.

The routine schedule has included three doses of hepatitis B vaccine for infants aged <12 months since October 2016. Voluntary maternal vaccination is also available.

Hepatitis A (2006–2016)

Hepatitis A cases peaked in 2006 (n = 320), 2010 (n = 347) and 2014 (n = 433) with higher frequencies during the first half of each year. Males were 58% of all cases (n = 1313) and persons aged 25–64 years were 72% (n = 1744). Domestic infection was suspected for 80% (n = 1185) of cases from 2010 to 2015 (prior data not reviewed) without regional clustering. Total incidence for the reviewed period was 0.18 per 100 000 person-years (n = 2245).

Since March 2013, two-dose inactivated hepatitis A vaccination has been available on a voluntary basis for all ages. Previously it had been available for those aged ≥16 years.

Invasive Haemophilus influenzae *disease (IHD) (2013–2015)*

The number of reported IHD cases increased from 108 in 2013 (IHD became notifiable in April 2013) to 200 in 2014 and 252 in 2015. Males accounted for 60% (n = 338) of the cases. Over half (52%; n = 293) of the cases were aged ≥70 years and 17% (n = 95) were <5 years old. The incidence of IHD was 0.16 per 100 000 person-years (n = 560) from April 2013 through 2015.

Since April 2013, four doses of *H. influenzae* type b vaccine have been routine for those aged <59 months. Voluntary vaccination for children <5 years had been approved since December 2008; government financial assistance was added in November 2010.

Tetanus (2006–2015)

Between 89 and 128 cases of tetanus were reported each year with consistent increases during epidemiologic weeks 19–29. Cases were mostly aged ≥55 years (85%; n = 984). All prefectures reported cases. The incidence of tetanus in Japan for the reviewed period was 0.09 per 100 000 person-years (n = 1158).

Four doses of diptheria, tetanus, acellular pertussis, and inactivated polio vaccine (DTaP–IPV) between age 3 months and 7½ years and one diptheria and tetanus (DT) dose at age 11 or 12 are included in the routine schedule.

Typhoid fever (2008–2015)

Most cases of typhoid fever reported in Japan (72%; n = 238) were acquired outside Japan. The annual percentage of domestically acquired cases decreased from 38% (n = 25) in 2013 to 11% (n = 4) in 2015. Domestic cases appeared mostly sporadically with no known cause; however, in August 2014, an outbreak of eight cases was linked to salad consumption at a restaurant in Tokyo.[9] The incidence of typhoid fever for the reviewed period was 0.03 per 100 000 person-years (n = 330).

No vaccine has been approved for typhoid fever in Japan. Individual physicians may import and administer the vaccine without government reimbursement or, in the case of adverse events, patient compensation.

Invasive meningococcal disease (IMD) (2013–2015)

There were 23–37 cases of IMD reported each year from April 2013 (when meningococcal sepsis was added to the list of conditions requiring mandatory reporting for IMD) through 2015 with no seasonality. Most cases were male (64%; n = 60) and aged ≥50 years (59%; n = 55). IMD incidence in Japan was 0.03 per 100 000 (n = 94).

The meningococcal conjugate vaccine (MCV4) became available for voluntary use in May 2015.

Japanese encephalitis (JE) (2006–2015)

Of the 47 prefectures in Japan, five in western Japan (Fukuoka, Kumamoto, Nagasaki, Shimane and Ehime) accounted for 43% (n = 22) of reported JE cases for the reviewed period; 22 prefectures did not report any cases. Reports were consistently higher during epidemiologic weeks 35–47. Males were 63% (n = 32) and persons aged ≥60 years were 61% (n = 31) of all cases. JE incidence in Japan was 0.004 per 100 000 person-years (n = 51) with 2–10 cases reported each year.

Four doses of inactivated JE vaccine are included in the routine schedule: three between 6 months and 7½ years of age and one between 9 and 13 years of age.

VPDs under sentinel surveillance

Influenza (2000–2015)

All influenza seasons reviewed, except 2009, began in November, peaked in late January to mid-March and finished in May. Sentinel sites reported 18 508 470 cases, averaging 243.5 annual cases per sentinel site (see **Table 2**). There were 9905 (2013–2014 season) and 12 705 (2014–2015 season) hospitalized cases with laboratory evidence of infection. No human infection with avian influenza A(H5N1), A(H5N6), A(H7N9) or A(H9N2) has been reported in Japan.

Seasonal influenza vaccinations for those aged >64 years or 60–64 years with certain chronic diseases or immunocompromised conditions are in the routine schedule. For anyone else, vaccinations are voluntary.

Varicella (2005–2016)

A peak of 88.1 varicella cases per sentinel site (n = 265 453) was reported in 2006. The ratio decreased to 67.1 (n = 202 732) in 2009, increased to 76.2 (n = 238 645) in 2011 and decreased to 24.7 (n = 77 614) in 2015. Early in the reviewed period, cases peaked in November–June, but later they did not. Children <5 years old represented 77% of cases in 2005–2011 and 54% in 2015. In total, 2 018 171 cases were reported from sentinel sites for 2005–2016 (65.5 cases per site per year). There were 521 hospitalized cases (clinically diagnosed or with laboratory evidence of infection) reported in Japan from mid-September 2014 through March 2016 (0.27 per 100 000 person-years).

Since October 2014, the routine vaccination schedule has included two varicella vaccination doses for children between 1 and 2 years old. The vaccine is available on a voluntary basis for those aged ≥2 years.

Mumps (2000–2015)

Mumps cases in Japan peaked in 2001 (84.4 cases per sentinel site), 2006 (66.6 cases per site) and 2010 (59.3 per site) without seasonality. No prefecture consistently reported high numbers of cases. Cases aged 2–5 years accounted for 57% (n = 1 048 851) and males for 54% (n = 1 051 903) of cases. In total, 1 963 679 cases were reported from sentinel sites from 2000 to 2015 (40.1 per sentinel site per year).

A monovalent mumps vaccination replaced the measles, mumps and rubella (MMR) vaccine in 1993 and is available on a voluntary basis for those aged at least 1 year.

Pertussis (2000–2015)

The number of reported pertussis cases per sentinel site fluctuated during the reviewed period: 1.28 (n = 3804) in 2000, 0.44 (n = 1358) in 2005, 2.24 (n = 6753) in 2008, 0.53 (n = 1662) in 2013 and 0.85 (n = 2675) in 2015. We did not observe seasonality. In 2001, 27% (n = 471) of the cases were 6–11 months old and 3% (n = 49) were aged ≥20 years. By 2010, those aged ≥20 years were 48% (n = 2607) and those 6–11 months were 4% (n = 205) of cases. For the 2000–2015 period, 48 783 pertussis cases were reported from sentinel sites (0.996 per sentinel site per year).

Four doses of DTaP-IPV are included in the routine schedule between ages 3 months and 7½ years.

DISCUSSION

Most VPDs in Japan present low risk for the majority of travellers attending the 2019 Rugby World Cup and 2020 Tokyo Summer Olympic and Paralympic Games. Occurrence has either declined or maintained a low level. Rubella, mumps, influenza, measles and IMD, however, present more complicated pictures. Hepatitis A and JE may pose higher risk for some travellers as discussed below.

Due to the epidemiology of rubella, mumps and influenza in Japan, these diseases should be prioritized for pre-travel advice. Rubella surged in 2013, likely related to undervaccination among adult males. A rubella antibody seroprevalence study in Japan in 2016 suggested that males 35–54 years old had less immunity than women for that age group; the gap narrowed to <10 percentage points for those aged 20–34 and ≥55.[10] The vaccine was introduced in 1977 for 11–12-year old girls and was expanded in 1995 to boys 11–12-year-old and both sexes 12–89 months old.[11]

For mumps, 4–5 year peak cycles are also likely related to undervaccination. Recent mumps vaccination

Table 2. **Comparison of case and case-per-site totals and characteristics of reported selected sentinel based VPDs, Japan, 2000–2015**

Disease (period reviewed)	Total cases	Cases per site (yearly range)	Range of *n* sites per year	Year-to-year trend	High season	Case reporting	Vaccination
Influenza (2000–2015)	18 508 470	243.5 (56.4–643.3)	4477–4924	Peaks every 2–3 years	Nov–May; peak: Jan–Mar	Clinical or rapid-kit detection of influenza A or B	Voluntary; routine for some*
Varicella (2006–2015)	2 018 171	65.5 (24.7–88.1)	3012–3146	Overall decrease	Nov–June early on then none	Clinical	Routine
Mumps (2000–2015)	1 936 679	40.1 (13.1–84.4)	2978–3146	Peaks every 4 years	None	Clinical	Voluntary
Pertussis (2000–2015)	48 783	1.0 (0.44–2.24)	2978–3146	Fluctuating	None	Clinical	Routine

* Those aged >65 and those 60–65 with certain chronic diseases or immunocompromised conditions.

coverage in Japan has been 30–40%.[12] Vaccinations against mumps were voluntary until 1989 when MMR became routine; due to concerns with mumps component-related aseptic meningitis, MMR was replaced with a voluntary monovalent mumps vaccination in 1993. Mumps outbreaks with up to 214 cases have been reported at MGs in Europe.[13,14]

For influenza, seasons typically occur outside of when MGs are scheduled to occur in Japan. Nevertheless, travellers from the southern hemisphere leaving during its influenza season could import the virus and transmit it to northern hemisphere attendees who have not yet been vaccinated. To prevent mumps, rubella and influenza, advice should include ensuring up-to-date (or for influenza early) vaccinations, practising proper hygiene and recognizing and reporting signs and symptoms of these diseases.

Although case numbers have been low, measles and IMD outbreaks with international transmission suggest these diseases should also be considered during pre-travel consultations. The endemic measles strain (D5) was last detected in Japan in 2010, and WHO verified elimination in 2015.[15] In 2016, however, measles outbreaks occurred in Japan. All were linked to importation, including an outbreak at an international airport. Most cases were undervaccinated.[16] For IMD, authors have noted Japan's low incidence compared to other developed countries.[17] A 2015 outbreak with six IMD cases was detected after an international youth event in Japan with more than 33 000 participants from 162 countries. All cases were from Europe, one of which did not attend the event.[18] These events show how importation can cause outbreaks even when domestic incidence is low; pre-travel advice should include ensuring up-to-date vaccinations, frequent handwashing and avoiding contact with items that contain others' saliva or respiratory droplets as much as possible.

Travel advisers should also consider individual traveller behaviours and itineraries. Hepatitis A transmission in Japan has primarily been linked to food, particularly shellfish and seafood.[19] This information was obtained through self-reporting, which can be biased by social desirability. In 2017, outbreaks of hepatitis A among men who have sex with men were reported in both Europe and the Americas.[20] Individuals who engage in activities that put them at risk for hepatitis A should be advised on preventive measures like vaccination, safe-sex practices, handwashing and food selection. Travellers intending to visit western Japan, especially non-urban areas, should consider JE vaccination and mosquito-bite prevention.

Though not reviewed, rotavirus disease tends to increase from February to May, outside the scheduled MG periods, and tuberculosis has been decreasing since 1999 with 14.4 new cases per 100 000 person-years in 2015.[21,22]

The selection of diseases for this work was largely based on expert opinion and discussion among leaders within the Infectious Diseases Surveillance Center (IDSC) at NIID. We could have unintentionally left out diseases that might affect travellers visiting the upcoming MGs. Most passive disease surveillance systems may be limited by incomplete reporting, lack of representativeness or failure to identify outbreaks.[23] NESID may also suffer

these limitations. Additionally, it lacks catchment population data for sentinel surveillance, limiting the ability to estimate sentinel disease incidences. Nonetheless, NESID comprises the most standardized, robust national data available. We believe comparisons across time and place are valid and sufficient for our purposes. In most cases, we attempted to review 10 years of data. For some diseases the introduction or change of reporting requirements prevented that. Readers should conclude with caution when considering diseases with very short reviewed periods.

Few outbreaks associated with sports-based MGs have been reported in literature. Most were reported from the United States of America[24,25,26] with one from the United Kingdom of Great Britain and Northern Ireland,[27] limiting generalization. Their findings nevertheless imply important considerations: outbreak risk at sports-based MGs is low but not null; outbreaks occur among athletes and nonathletes, associated and unassociated persons and populations of high and low vaccination coverage; importation can spark an outbreak even in low-incidence countries; and, as noted in one article,[25] the difficulties of conducting surveillance on international visitors could mean misunderstanding the size or nature of an outbreak or missing an outbreak entirely. Ministries of health, organizations, health-care providers and travellers should ensure up-to-date vaccinations of travellers before they attend MGs, and they should also promote and support travellers carrying updated vaccination records to assist the home country with any potential case or outbreak investigations.

As we have outlined, up-to-date vaccinations with additional preventive measures should be included in pre-travel advice for visitors to the 2019 Rugby World Cup and 2020 Tokyo Summer Olympic and Paralympic Games, specifically for mumps, measles, rubella, influenza and IMD for all travellers and for hepatitis A and JE for travellers at higher risk. When providing advice, health professionals should also inform travellers about the role they could play in transmitting or preventing the transmission of disease to MG attendees from across the world.

Conflicts of interest

None.

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