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Human infections with avian influenza A(H7N9) virus in China: preliminary assessments of the age and sex distribution

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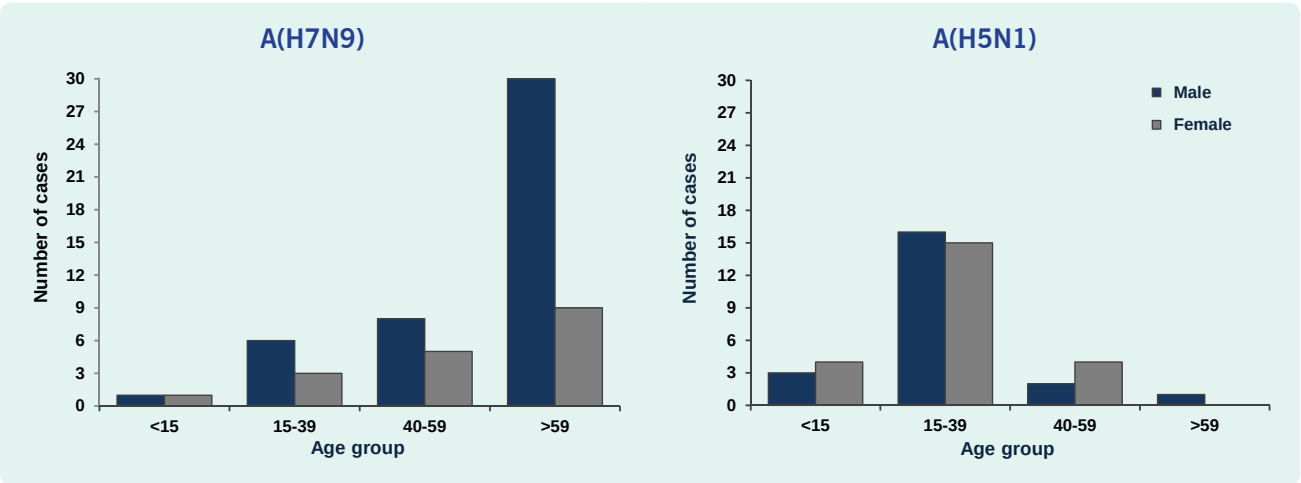
Since 31 March 2013, the government of China has been notifying the World Health Organization (WHO) of human infections with the avian influenza A(H7N9) virus,[1] as mandated by the International Health Regulations (2005).[2] While human infections with other subgroups of H7 influenza viruses (e.g. H7N2, H7N3, and H7N7) have previously been reported,[3] the current event in China is of historical significance as it is the first time that A(H7N9) viruses have been detected among humans and the first time that a low pathogenic avian influenza virus is being associated with human fatalities.[4] In this rapidly evolving situation, both detailed epidemiologic and clinical data from reported cases are limited—making assessments challenging—however, some key questions have arisen from the available data. Age and sex data, as one of the first and most readily available data, may be an important proxy for gender-specific behaviours/conditions and an entry point for response.[5,6] Here, we describe the age and sex distribution of the human cases of avian influenza A(H7N9) to better inform risk assessments and potential next steps.

Between 31 March and 16 April 2013, there were 63 reported cases of avian influenza A/H7N9. The median age was 64 years (range 4-87), and 45 cases (71%) were male. Notably, 39 of the 63 cases (62%) were ≥ 60 years of age. When stratified by age and sex, elderly men were the most affected demographic group (Figure 1). This is different to the Chinese population which has a large proportion of young and middle-aged adults and a greater number of women among the elderly.7 Although the case fatality rate (CFR) in all males at 23% (10/45) was similar to females at 22% (4/18), when restricted to elderly cases ≥ 60 years of age, the CFR in males is 20% (6/30) compared to no deaths in females (0/9). The case distribution of current avian influenza A/H7N9 cases is also different to reported avian influenza

Figure 1. **Age group and sex distribution of reported human infections with avian influenza A(H7N9) and A(H5N1) viruses, China, as of 16 April 2013**



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A(H5N1) cases in China (N=45), where the majority were young working age adults (median: 26 years; range 2-62), with no difference in gender (**Figure 1**).[8] Hence, the question naturally arises – why are we seeing the current age and sex distribution, and what key questions can we ask to allow public health practitioners respond in an efficient and effective manner?

Three main reasons may be considered for the current case distribution: (1) differential exposure between males and females due to gender-associated practices and norms; (2) biological differences between males and females in the clinical course post exposure/infection; and (3) differential healthcare-seeking/access behaviour between men and women, i.e. surveillance/detection bias.

Determining whether the current distribution is due to differential exposures is difficult to assess. If the same is true with many other field investigations of acute outbreaks due to the lack of detailed case-based exposure information. Despite this, information among current cases point to poultry-related exposures, such as live bird markets (LBMs) as a potential risk factor.[9] LBMs have been the primary site where avian influenza A(H7N9) virus has been detected in poultry and environmental samples in the affected areas,[9] although age- and sex-specific LBM visit patterns are unknown. Elderly Chinese men are well-known to be hobbyists of "walking" ornamental pet songbirds and take frequent and extended walks with their caged birds, congregating together in parks.[10] As the source and mode of infection remain unknown, control and prevention efforts are difficult. A better understanding of the social norms and behaviours among elderly Chinese men in affected areas may better guide us in the investigation (e.g. by identifying hypotheses for case-control studies).

Biological characteristics particular to elderly men may also be a possible explanation for the observed age and sex distribution. A defining feature of seasonal influenza is its severe morbidity and mortality among the elderly, due to higher biological susceptibility to severe outcomes from influenza infection among this age group.[11,12] While poultry exposure appears to be a common risk factor in the current event, the age distribution among reported cases also raises the question why so few young adults (i.e. those of working age exposured to poultry as vendors/LBM workers/breeders/transporters) have been reported. This not only suggests greater exposure among elderly men but also a possible greater biological susceptibility to more severe outcomes. Among the elderly, the number of cases and the CFR is higher among men relative to women (although this may be a function of dose response due to greater or more frequent exposure). While serologic investigations among close contacts and other subpopulations in the area will assist with our understanding regarding the clinical spectrum of this infection, information regarding smoking, underlying medical conditions and other risk factors among the current case series would help to elucidate some of these issues.

Healthcare-seeking behaviour and access also need to be considered as an explanatory factor. If elderly men are more likely to access healthcare, be detected or reported, surveillance bias may occur such that the distribution of the reported cases does not reflect the underlying distribution of disease occurrence in the population. However, given the high severity among the majority of the reported cases to date, the current high awareness level in both the public and the healthcare community and the nation-wide implementation of enhanced influenza-like illness and severe acute respiratory illness surveillance activities, such an artefact where elderly men are being overly selected seems unlikely.

At this time, it is clear that there are more questions than answers. Still, based on the basic age and sex distribution, we identify several critical questions and options to guide the ongoing investigation:

- What are the societal norms and common social practices among elderly men in the affected provinces? Qualitative approaches and involvement of anthropologists/sociologists specializing in the sociology of health of the Chinese population may be beneficial.

- What is the age and sex distribution of severe acute respiratory illnesses and key risk factors for respiratory illness (e.g. smoking) in the underlying population in the affected provinces? While detailed case-based clinical information is pending, data from the general population may be helpful for initial assessments.

- What is the age and sex distribution of healthcare utilization in the Chinese population in the affected

provinces? Ruling out any possible selection bias will be an important initial step in understanding both the clinical and epidemiologic spectrum of infection.

In these situations, it is easy to dismiss preliminary epidemiologic assessments as being too low in numbers or with too few variables of interest. Clearly, there is a need for further case-based information, such as zoonotic exposures and underlying medical conditions. However, for public health workers engaged in rapid response to acute events, it is essential to operate as observational scientists and assess available information to help formulate next steps. Following age and sex distributions closely over time may detect important changes in the epidemiology of this virus and with better understanding, high-risk populations, targeted interventions (e.g. gender-specific risk communication messages), prevention and control measures (e.g. vaccination) and treatment options (e.g. antivirals) may be identified. While this brief and rapid communication cannot offer answers, we hope that public health practitioners involved in such response–at various capacities around the world–may consider these key concerns and questions to help counter against not only the current virus but other emerging infectious threats.

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Avian influenza A(H7N9) and the closure of live bird markets

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On 31 March 2013, the National Health and Family Planning Commission, China notified the World Health Organization of three cases of human infection with avian influenza A(H7N9) from Shanghai and Anhui.[1] By 8 May, 131 cases, including 26 deaths, had been notified from 11 provinces/municipalities.[1,2] The majority (81%) of reported cases were from Shanghai municipality and Zhejiang and Jiangsu provinces. Available data indicate that more than three quarters of cases (59/77, 76%) had recent exposure to animals. Among these, 58% (34/59) had direct contact with chickens and 64% (38/59) visited a live bird market (LBM).[3] Provincial and national authorities in China have collected more than 80 000 samples from LBMs, poultry slaughter houses, poultry farms, wild bird habitats, pig slaughter houses and their environments. As of 7 May, 50 samples were positive for avian influenza A(H7N9): 39 samples from poultry from LBMs in Anhui, Jiangsu, Jiangxi, Guangdong, Shanghai and Zhejiang provinces (26 chickens, three ducks, four pigeons, six unknown) and 11 environmental samples from LBMs in Shanghai, Henan and Shandong provinces.[4] None of the samples from poultry farms or pigs were positive.[5]

Data on the background rate of exposure to LBMs among the general population in the affected areas are not available. However, the high proportion of human cases with exposure to poultry, as well as the finding of positive samples from poultry and the environment in LBMs, suggests exposure from LBMs, either through poultry contact or certain practices or behaviours in the LBM, as the most likely source of human infections for the majority of reported cases.

LBMs play a crucial role in the maintenance, amplification and dissemination of avian influenza viruses and hence are considered high risk locations for potential zoonotic transmission of influenza viruses to humans.[6–8] Control measures in LBMs and along the market chain such as temporary or permanent closure of markets, market rest days, species segregation or bans on sale of certain species of poultry and wild birds, regular cleaning and disinfecting of markets and by-products disposal, proper drainage and poultry transport cage washing facilities have been found to be effective for reducing the spread of H5N1 viruses.[9,10] Market rest days have been found to reduce significantly the rate of isolation of low pathogen avian influenza viruses in retail markets.[6]

Following the detection of avian influenza A(H7N9) virus infection in poultry in LBMs in Shanghai on 4 and 5 April 2013, authorities initiated a series of public health measures including: closure of all three LBMs and sale spots on 6 April; culling of all live birds in wholesale markets; safely disposing of culled birds, excreta, polluted feed and water; and disinfection of the materials, transportation and tools in contact with live birds and the market environment.[11] The last case from Shanghai had its onset on 13 April, and since then no new cases have been reported from this municipality (**Figure 1**). In Zhejiang province, cases were reported from five cities; the majority (42/46, 91%) were from

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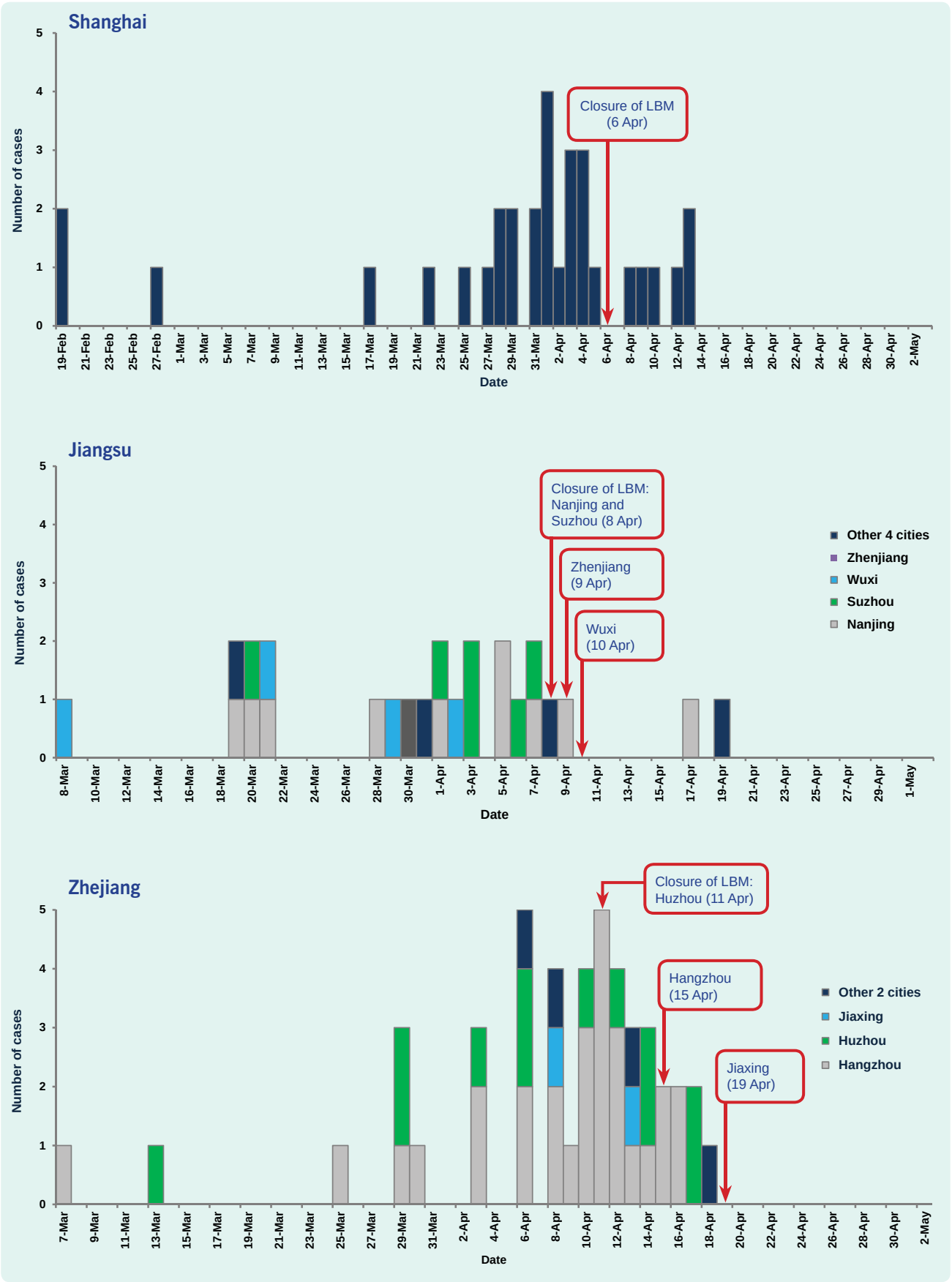
Figure 1. **Distribution of human cases of influenza A (H7N9) by date of onset in Shanghai, Zhejiang and Jiangsu**



Note: Information about the onset date of three cases from Shanghai and one case from Jiangsu was not available.

LBM – live bird market

Hangzhou, Huzhou and Jiaxing cities. LBMs in these cities were closed on 11, 15 and 19 April, respectively. In Jiangsu province, LBMs in four (Nanjing, Suzhou, Wuxi and Zhenjiang cities) of the eight cities that reported human cases of avian influenza A(H7N9) were closed. These four cities accounted for 21 of the 26 (81%) cases reported from this province. Similar to Shanghai, there has been a decline in the number of cases reported from Jiangsu and Zhejiang after the closure of LBMs, with the last case reported from the areas that implemented market closures on 17 April (**Figure 1**).

Available data do not support a hypothesis of sustained human-to-human transmission.[1] The median incubation period for avian influenza A(H7N9) was estimated to be six days (range: one–10 days).[3] Absence of new cases from Shanghai since the closure of LBMs suggests that the market-related control measures reduced further human infections and thereby supports the hypothesis that exposure to LBMs was the main source of infection among the Shanghai cases. The decline in the number of cases in Zhejiang and Jiangsu provinces also supports this hypothesis. However, surveillance data in the coming days will show if these control measures at LBMs were effective in the other provinces. Urban/rural location was a modifying factor for the risk of avian influenza A(H5N1) in China as urban cases were associated with LBM exposure while rural cases have been associated with backyard poultry.[12] Given the urban location of most of the cases of avian influenza A(H7N9) in China,[3] an association with LBMs is consistent.

At present, the animal reservoir and specific mode of transmission of the virus to humans are still being investigated. Although we do not currently know if the exposure history of cases differs significantly from the general population or if the observed decline in reported cases from some areas may be due to exposure or behaviour changes unrelated to LBMs such as diminished sale or consumption of poultry, taken together the data do suggest that closure of LBMs has reduced human infections in the areas where the closures were implemented. Additional studies are needed to ascertain if specific behaviours of people visiting and/or working in LBMs are exposing them to higher risk. These studies would enable targeted preventative messaging with greater public health impact and may provide further clues about the relatively high proportion of cases among older males.[3,13]

The potential benefits of public health measures need to be carefully balanced against their potentially significant societal and economic costs.[14] Whether the temporary closure of LBMs should be continued and expanded to reduce the transmission and protect public health needs to be decided by the local and national authorities based on local context. Such a decision should consider the potential negative impact on those working in the poultry trade,[6] pricing of the poultry and the potential for unintended consequences such as the spread of infected animals through the movement of the poultry and the displacement of poultry trading to other areas.

Conflict of interest

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The threat of chikungunya in Oceania

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The Oceania region, which includes Australia, New Zealand, Papua New Guinea and the islands of the tropical Pacific Ocean, has historically been free from chikungunya. However, the 2011 outbreak in New Caledonia and the ongoing outbreak in Papua New Guinea have highlighted the risk to other communities in Oceania where there are competent mosquito vectors and permissive social factors and environmental conditions. In this article we discuss the threat to this region that is posed by the recent evolution of the E1:A226V mutant strains of chikungunya virus (CHIKV).

Chikungunya is a mosquito-borne disease caused by infection with CHIKV, an alphavirus from the Togaviridae family. The clinical characteristics of chikungunya include acute onset of fever which may last up to two weeks and painful, potentially debilitating, polyarthritis in adults which may last for up to a year following infection. Chikungunya was first recognized in Africa in the 1950s, principally, as polyarthritis in adults.[1] Other symptoms, reported during the large outbreak on Réunion Island in 2005–2006, included maculopapular rash on the trunk and limbs, headache, nausea, vomiting, diarrhoea and fatigue.[2]

There are three distinct genotypes of CHIKV: (1) Asian, (2) Eastern/Central/Southern African (ECSA), and (3) Western African. The ECSA genotype has been the dominant strain throughout Asia and the islands and countries in the Indian Ocean over the last decade. This genotype gained dominance in 2004 and 2005 when it was introduced from Kenya into the Indian Ocean islands of Comoros, Réunion, Seychelles, Mauritius and Mayotte where it was associated with an outbreak involving hundreds of thousands of reported cases.[3] On the island of Réunion, it was estimated that more than 30% of the 770 000 inhabitants were infected by CHIKV.[2] In 2005, an epidemic of chikungunya began in India which resulted in more than 1.39 million suspected cases by 2011.[4] The ECSA genotype of CHIKV also spread to other Asian countries including Sri Lanka, Malaysia, Singapore, Thailand, Indonesia, China and Myanmar.[3,5]

Previous outbreaks of CHIKV infection have been associated with the mosquito vector *Aedes aegypti*, which is also the vector of yellow fever and dengue viruses. However, *Aedes albopictus* has been the principal mosquito vector during many of the recent outbreaks of chikungunya associated with ECSA strains.[6] Analysis of CHIKV from the explosive outbreaks in Réunion and India revealed that the ECSA strains had acquired a point mutation resulting in a change from alanine to valine at position 226 in the E1 glycoprotein which enhanced the transmissibility of CHIKV in *Aedes albopictus*.[7] Subsequent studies demonstrated that amino acid changes in the E2 glycoprotein had a strong modulating effect on the E1:A226V change.[8]

Until the outbreak of chikungunya in New Caledonia from February to June 2011, which was caused by Asian-lineage CHIKV rather than the E1:A226V ESCA lineage,[9] Oceania had been free from chikungunya. During this outbreak, only 33 cases were detected, attributed to the onset of the cold season and the comprehensive control measures implemented after the diagnosis of the first cases.

In June 2012, an outbreak of fever and arthritis was detected in Vanimo, Papua New Guinea. Subsequent investigations showed that the outbreak was caused by an ECSA strain of CHIKV which harboured the E1:A226V mutation. During the Vanimo outbreak more than 1500 suspected cases of chikungunya were reported through passive surveillance.[10] The vector in this outbreak was suspected to be *Aedes albopictus* due to the high density of this mosquito species in the area.

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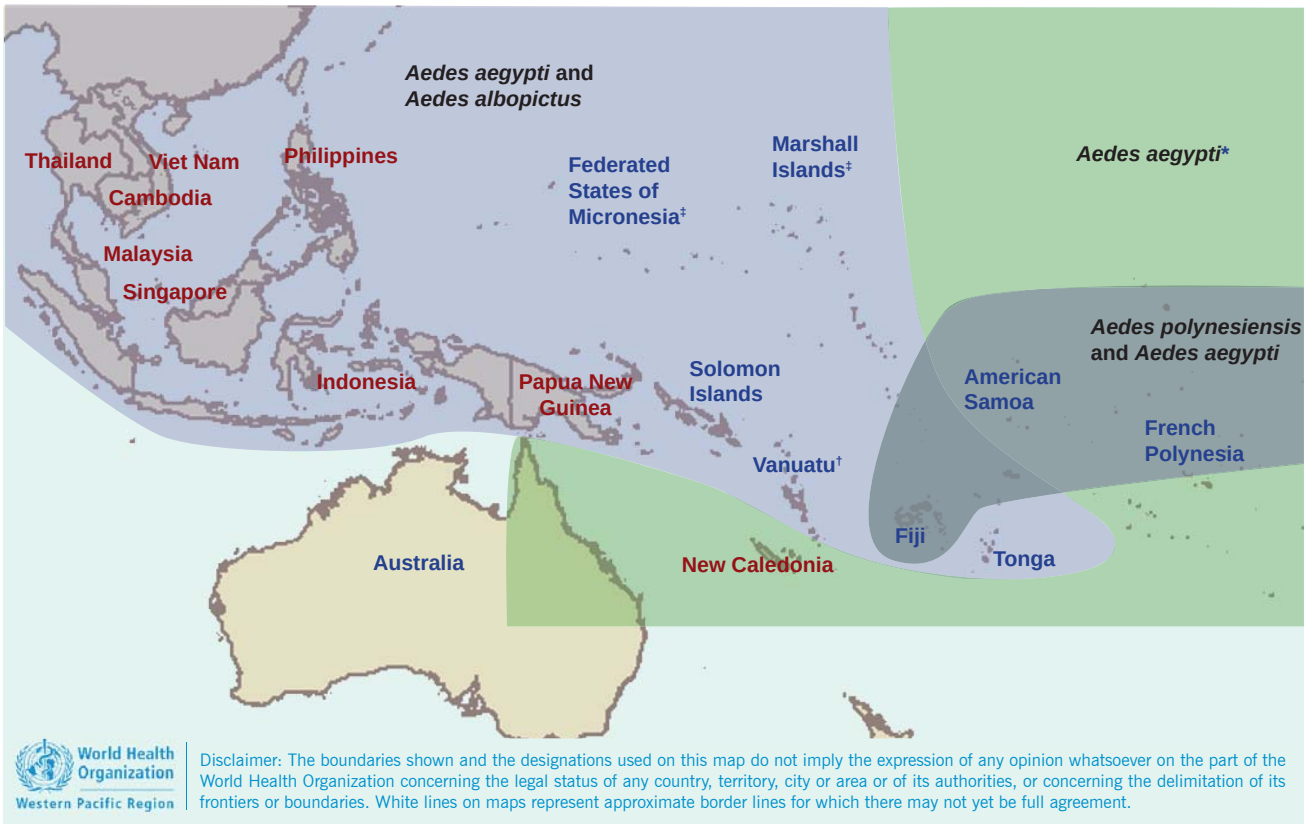
Figure 1. **Recent outbreaks of chikungunya in Oceania and the distribution of *Aedes* vectors**



Note: Countries in red had previous chikungunya outbreaks.

* *Aedes aegypti* is found throughout the region except in Futuna and some isolated islands.

† The presence of *Aedes albopictus* has not been officially confirmed in Vanuatu; however, its presence is strongly suspected.

‡ *Aedes albopictus* has not been detected in the Marshall Islands or the Federated States of Micronesia; however, its presence is suspected due to the proximity of islands such as Guam and Palau where the vector has been confirmed.

Following this outbreak, chikungunya cases were confirmed by real-time reverse-transcriptase polymerase chain reaction from eight provinces of Papua New Guinea, with another three provinces having suspected outbreaks. Interestingly, the outbreak extended to the Highlands Region of Papua New Guinea, which is the first confirmed arboviral outbreak recorded in this region of the country. Although no entomologic surveys have been conducted in the Highlands Region for many years, it has been shown that *Aedes* mosquitoes are present in abundant numbers. This may have important implications as more than 50% of the Papua New Guinea population live in the Highlands Region.

In Oceania, a considerable number of endemic mosquitoes belonging to the genus Stegomyia and the "Scutellaris group," such as *Aedes polynesiensis* in French Polynesia, are recognized as vectors of CHIKV.[11,12] More importantly, the principal vectors of chikungunya, *Aedes aegypti* and *Aedes albopictus*, are both prevalent throughout the region. *Aedes aegypti* is present in all countries in the Pacific except for New Zealand, Futuna and some small isolated islands.[13] *Aedes albopictus* invaded Oceania in the 1960s[14] and now can be found throughout Papua New Guinea, the Torres Strait region of Australia, Fiji, Solomon Islands, Tonga and probably Vanuatu,[13,15] thus rendering the human populations of these islands vulnerable to introduction of the epidemic ECSA strains of CHIKV. The explosive outbreak of chikungunya in the Indian Ocean islands and the speed with which the related alphavirus, Ross River virus, swept through the Pacific in 1979 and 1980,[16] is a reminder of the potential impact CHIKV could have in Oceania (**Figure 1**).

Social, economic and environmental factors all play an important role in the introduction and sustained transmission of arboviral diseases like chikungunya. In developing countries such as Papua New Guinea and many other Pacific island communities, poor living conditions and the abundance of natural and artificial

mosquito breeding sites can result in the rapid spread of arboviral epidemics. The climatic conditions of Oceania (temperature, humidity) favour year-round mosquito breeding and are unlikely to interrupt the transmission cycle of CHIKV. It is doubtful that any Pacific island community has the human or financial resources to mount a vector control effort that would *prevent* an outbreak of chikungunya. However, efficient surveillance, targeted vector control (including active community participation for breeding sites elimination) and education in mosquito avoidance measures may provide a cost effective reduction in the burden of disease in the event of an outbreak. A coordinated regional strategy to prevent and respond to vectorborne disease outbreaks in Oceania is urgently needed to mitigate future outbreaks of arboviral diseases such as chikungunya and dengue.

Conflicts of interest

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The tuberculosis profile of the Philippines, 2003–2011: advancing DOTS and beyond

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The Philippines is one of the highest tuberculosis (TB) burden countries in the world with nationwide coverage of directly observed treatment, short-course (DOTS) achieved in 2003. This study reports on the National TB Control Programme (NTP) surveillance data for the period 2003 to 2011. During this period, the number of TB symptomatics examined increased by 82% with 94% completing the required three diagnostic sputum microscopy examinations. Of the 1 379 390 cases diagnosed and given TB treatment, 98.9% were pulmonary TB cases. Of these, 54.9% were new smear-positive cases, 39.3% new smear-negative cases and 4.7% were cases previously treated. From 2008 to 2011, 50 030 TB cases were reported by non-NTP providers. Annual treatment success rates were over 85% with an average of 90%; the annual cure rates had an eight-year average of 82.1%. These surveillance data represent NTP priorities – the large proportion of smear-positive cases reflected the country's priority to treat highly infectious cases to cut the chain of transmission. The performance trend suggests that the Philippines is likely to achieve Millennium Development Goals and Stop TB targets before 2015.

The Philippines is an archipelago of more than 7107 islands with an area of 300 000 km^2 in south-eastern Asia. The country is divided into 17 administrative regions with 81 provinces, 136 cities including 16 highly urbanized centres, 1495 municipalities and 42 008 barangays.[1] The population of the Philippines was 92.3 million in 2010 with 33.4% aged between zero and 14 years, 62.3% in the working age group of 15–64 years, and 4.3% being 65 years and older.[2] Poverty incidence in the population was 26.5% in 2009.[3]

Tuberculosis (TB) is the sixth leading cause of morbidity and mortality in the Philippines; the country is ninth out of the 22 highest TB-burden countries in the world and has one of the highest burdens of multidrug-resistant TB. Directly observed treatment, short-course (DOTS)[4] strategy for TB control commenced in 1997 and nationwide coverage was achieved in 2003.[5] The prevalence of TB in 2007 was 2.0 per 1000 for smear-positive TB and 4.7 per 1000 for culture-positive TB. Compared with 1997, there was a 28% and 38% decline in prevalence for smear-positive and culture-positive TB, respectively.[6]

The National TB Control Programme (NTP) is managed by a central team at the National Center for Disease Prevention and Control of the Department of Health.[4] This team develops policies and plans and provides technical guidance to regional and provincial/city-level NTP management teams, overseeing the implementation of the programme at the municipal and *barangay* levels based on NTP policies and standards.

Under NTP, TB control services are provided mainly through public primary health care facilities (also called DOTS facilities) operated by local government units in a devolved set-up. There are additional DOTS facilities within the NTP's network of service providers that either refer diagnosed TB patients for treatment or directly provide TB treatment services using DOTS strategy. These include private outpatient clinics; public and private primary, secondary and tertiary care hospitals; workplaces; clinics under faith-based organizations and community-based nongovernmental organizations (NGOs); and public institutions such as military facilities, jails and prisons. The NTP has also established public–public and public–private partnerships for TB control consisting of public non-NTP providers such as public hospitals, public medical colleges, prisons/detention centres and military facilities; private DOT providers include private physicians, private hospitals, private clinics, private workplaces and NGOs. Nationwide expansion of TB testing in children has been part of NTP

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since 2004,[7] while the programmatic management of drug-resistant TB was mainstreamed into NTP starting in 2008.[8]

The NTP surveillance system is based on the standardized recording and reporting system used in all DOTS facilities under the NTP network of providers. Reports from rural health units, health centres and other DOTS providers include data for laboratory, case finding and case holding activities. These are reported quarterly and annually to the provincial or city health offices on paper-based, standardized forms. The provincial or city health offices then consolidate these paper-based reports and convert them into an electronic format (in tabular form using Microsoft Excel or Word). These are then forwarded to the respective regional health offices for consolidation and further analysis. The regional electronic-based reports are then forwarded to the central NTP team at the Department of Health.

Modernization of the TB registry was initiated in 2005 with the launching of the electronic TB registry in two regions (National Capital Region and CHD III Central Luzon). However, the initiative was discontinued in 2010 and was replaced by the Integrated TB Information System in 2011. This system is being implemented in phases and is currently used in selected facilities in four of the country's 17 regions including South Luzon, National Capital Region, Central Luzon and Western Visayas.

The objective of this report is to provide a national summary of TB cases reported to the NTP surveillance system from 2003 to 2011.

METHODOLOGY

Data submitted to the central NTP team for the nine-year period 2003 to 2011 were consolidated and summarized. Descriptive statistics were used to analyse the data. Treatment outcome data are for 2003 to 2010 only; 2011 data are not yet complete and not included in the report.

As case finding and treatment outcome data for drug-resistant TB are not fully integrated into the system, they are not included in this report. Data for pulmonary TB (PTB) cases previously treated were disaggregated by case classification starting only in 2008 and are only reported for 2008 to 2011.

RESULTS

TB cases

From 2003 to 2011, a total of 4 638 939 TB symptomatics were examined with sputum smear microscopy (**Figure 1**). On average, 94% of TB symptomatics completed the required three diagnostic sputum microscopy examinations each year. Compared to 2003, the number of TB symptomatics examined increased by 82% in 2011.

From these, a total of 1 379 390 cases of TB all forms were diagnosed and given TB treatment from 2003 to 2011. PTB comprised 98.9% of all TB cases notified; extra-pulmonary TB (EPTB) made up the remaining 1.1%. The nine-year average proportions of PTB cases are disaggregated as follows: new smear-positive, 54.9%; new smear-negative, 39.3%; and cases previously treated, 4.7% (**Figure 2**). Compared to 2003, the number of new smear-positive PTB cases increased by 34% in 2011; new smear-negative PTB cases increased by 70%.

Non-NTP providers

From 2008 to 2011, a total of 50 030 TB cases were reported by non-NTP providers – 7.4% of total cases reported to NTP in this time (**Table 1**). Most of these were from the private sector (38 565, 77.1%); 11 465 were from public partners (22.9% from 2010 to 2011 only).

New smear-positive PTB cases

The case notification rate (CNR) for new smear-positive PTB cases increased from 2003 to 2011 (**Figure 3**). The lowest CNR was in 2003 (86 per 100 000) and the highest was in 2006 (100 per 100 000). During the nine-year period, 63% of new smear-positive cases were aged 25 to 54 years, with 20% in the 25–34 years age group, 22% in the 35–44 years age group and 21% in the 45–54 years age group (**Figure 4**). The average male-to-female ratio for the period was 2.3.

Cases previously treated

The number of PTB cases previously treated increased from 2008 to 2011 (**Table 2**). On average, relatively large proportions of PTB cases previously treated were

Figure 1. **Number of TB symptomatics examined and proportion that had three diagnostic sputum microscopy examinations by year, the Philippines, 2003 to 2011**

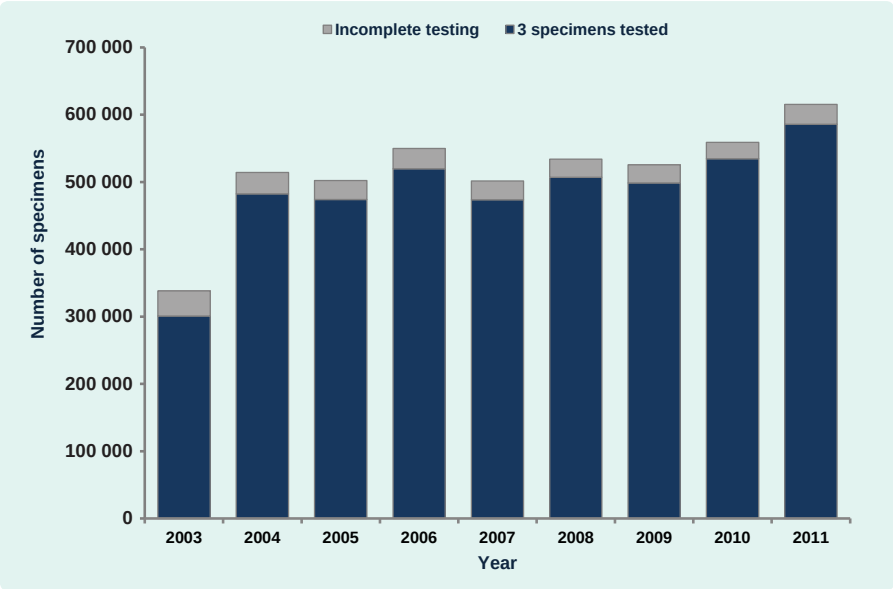
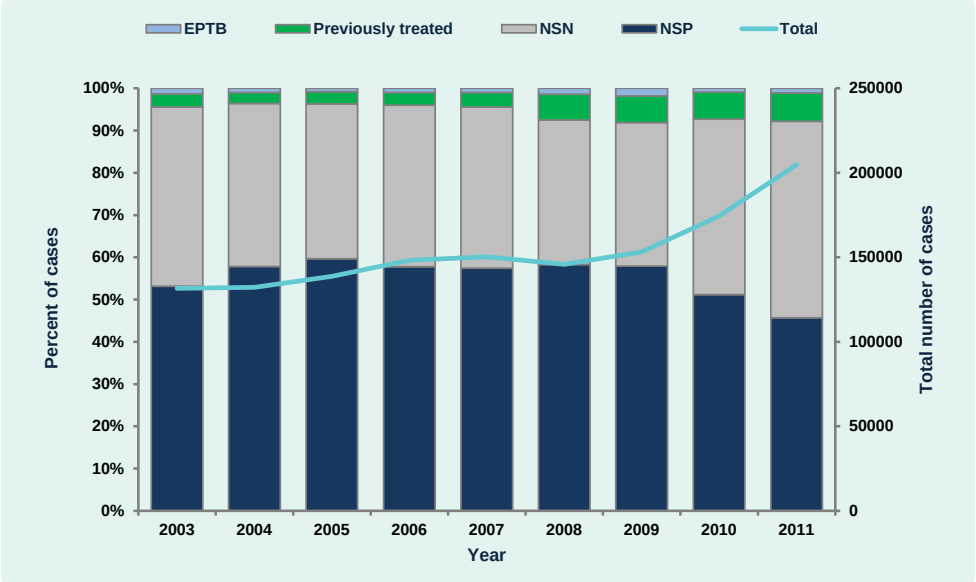


Figure 2. **Total number of TB cases and the proportion by case classification, the Philippines, 2003 to 2011**



EPTB – extrapulmonary TB; NSN – new smear-negative TB; NSP – new smear-positive TB

from relapses (27%) or other smear-negative cases (50%).

Treatment outcomes

Treatment outcomes for successive yearly cohorts of new smear-positive cases from 2003 to 2010 showed treatment success rates of over 85% with an average of 90% (**Table 3**). The average annual cure rate for eight years was 82.1%. The eight-year annual average for the other treatment outcomes were: treatment completed at 7.9%, death at 2.3%, treatment failure at 1%, defaulted from treatment at 4.4%, and transferred out at 2.4%.

DISCUSSION

Changes observed in the TB surveillance data in the Philippines from 2003 to 2011 reflected NTP priorities. The increase in the number of reported TB cases can be attributed to various NTP initiatives to improve access

Figure 3. **Case notification rate of new smear-positive cases by year, the Philippines, 2003 to 2011**

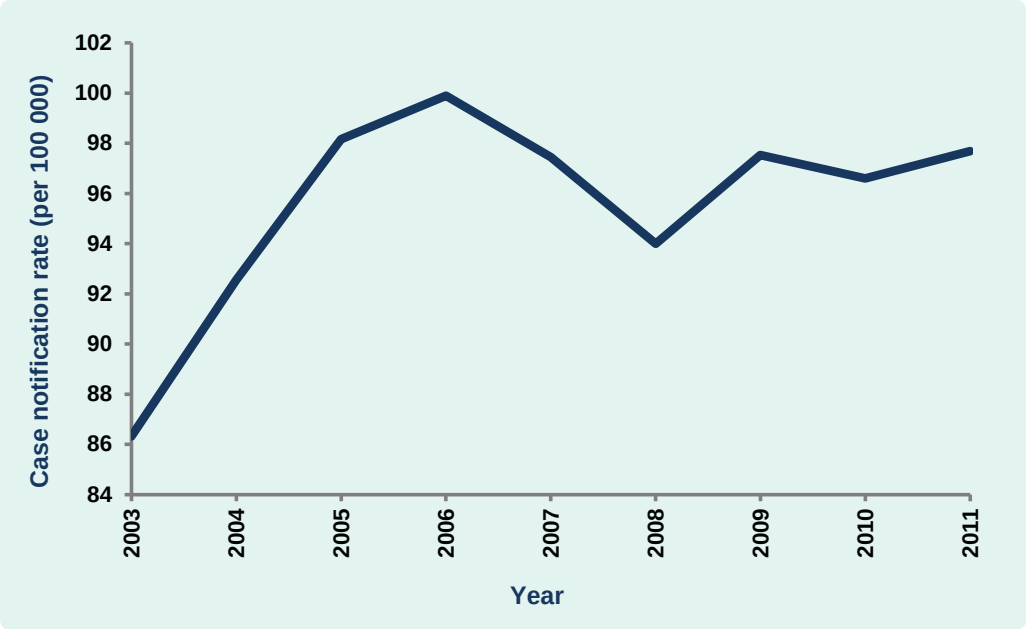


Figure 4. **Proportion of all new smear-positive cases by age group, the Philippines, 2003 to 2011**

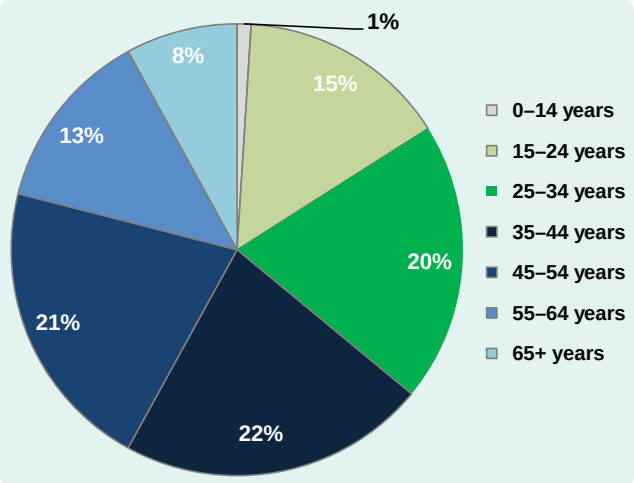


Table 1. **Number of TB cases reported by non-NTP public and private health providers, the Philippines, 2008 to 2011**

Year	Private providers	Non-NTP public providers	Total
2008	6 914	–	6 914
2009	4 866	–	4 866
2010	12 081	2 138	14 219
2011	14 704	9 327	24 031
Total	**38 565**	**11 465**	**50 030**

NTP – National TB Control Programme

to diagnostic and treatment services especially for the vulnerable sectors. Examples of these initiatives include the expansion of laboratory services and establishing partnerships with public and private health providers. The number of cases contributed by the non-NTP public and private partners also increased from 2008 to 2011; in 2011, these partnerships contributed 11.7% of the total number of cases notified.

More than half the cases per year were new smear-positive cases (apart from 2011 at 46%). This reflects NTP's high priority for the detection and treatment of highly infectious TB cases to cut the chain of transmission. The increase in the number of new smear-negative cases in 2010 and 2011 reflects a change in programme priorities to detect all forms of TB following the new WHO recommendations issued at that time.[9] It also explains the decrease in the proportion of new smear-positive cases in 2011. The increasing trend in the number of cases previously treated from 2008 may be due to the heightened efforts to detect drug-resistant TB cases among these cases. Also in 2008 the management of drug-resistant TB cases was mainstreamed into NTP.

The global target for treatment success rate is 85%,[10] this has been exceeded in the Philippines with an

Table 2. **Number and proportion of pulmonary tuberculosis cases previously treated by case classification and year, the Philippines, 2008 to 2011**

Year	Relapses		Returns after default		Treatment failure		Other (smear-positive)		Other (smear-negative)		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
2008	2 577	29	720	8	522	6	864	10	4 183	47	8 866	100
2009	2 973	31	804	8	585	6	947	10	4 266	45	9 575	100
2010	3 075	28	914	8	566	5	1 135	10	5 451	49	11 141	100
2011	3 217	23	900	7	466	3	1 205	9	7 957	58	13 745	100
Total	**11 842**	**27**	**3338**	**8**	**2139**	**5**	**4 151**	**10**	**21 857**	**50**	**43 327**	**100**

Table 3. **Proportion of new smear-positive cases by treatment outcome and year, the Philippines, 2003 to 2010**

Year	Treatment outcome indicators (%)						
	Cure	Treatment completed	Success	Death	Failure	Defaulted	Transferred out
2003	80.5	7.9	88.4	3.0	1.0	5.0	3.0
2004	81.0	7.8	88.8	2.4	1.0	5.0	2.6
2005	82.4	7.4	89.8	2.5	1.0	4.3	2.4
2006	82.2	8.2	90.4	2.4	1.0	3.9	2.4
2007	79.9	9.6	89.5	2.0	1.1	4.4	2.5
2008	82.0	8.4	90.4	2.0	1.1	4.4	2.5
2009	84.1	6.9	91.0	2.0	1.0	4.0	2.0
2010	84.8	6.7	91.5	2.1	0.9	3.8	2.0
Average	**82.1**	**7.9**	**90.0**	**2.3**	**1.0**	**4.4**	**2.4**

eight-year average of 90%. However, the country's target of 85% for annual cure rates[11] was met only in 2010. The low cure rates in previous years were mainly due to the high number of patients who completed treatment without laboratory confirmation of cure (i.e. treatment completed). The average rate of cases defaulting from treatment for the eight-year study period was 4.4%, contributing to the low cure rate and therefore treatment success rates. Moreover, these defaulters may become the future drug-resistant cases.

The death rate of notified TB cases, while low, still contributed to the overall unfavourable treatment outcome as did those cases that transferred out as their outcome is unknown. However, the sustained high treatment success rate reflects ongoing efforts to improve case holding through various NTP strategies such as the administration of DOT in workplaces, homes and other acceptable venues in the community other than the health facility using community volunteers as treatment partners.

In this study, EPTB comprised only 1% of cases, compared to the 15% to 20% reported from other countries.[12,13] The low case detection for EPTB in the Philippines may be due to the limited capability of primary care facilities to diagnose these cases or because EPTB cases are diagnosed in hospitals that are not part of NTP. Only 7% of public and 4% of private hospitals report to NTP. However, the higher number of EPTB cases reported from 2008 onwards may reflect the inclusion of more private and non-NTP public providers to NTP. This limitation to the surveillance system is being addressed by increasing the number of NTP-engaged hospitals and improving capacities to confirm EPTB diagnosis.

The proportion of children aged zero to 14 years notified to NTP was 1% for the whole study period,

and although there was an increase over this time, its proportion relative to other TB cases did not exceed 2% from 2003 to 2011. It has been estimated that the 0–14 age group should comprise around 15% of cases in low-income countries,[14] suggesting that cases in children are either not being diagnosed or if being diagnosed they are not being reported to NTP.

There are some limitations in using NTP surveillance system data to report on TB in the Philippines. Cases diagnosed and treated in health facilities outside the NTP network of providers, including private clinics and hospitals, are not included, therefore the surveillance system is underreporting the total number cases of TB in the Philippines. The submission of case reports are still paper-based, particularly at the peripheral level, which contributes to delays and errors in reporting. Not all regional health units have the capacity to consolidate their data in an electronic format because of gaps in infrastructure and equipment.

CONCLUSION

The Philippines has achieved improvements in case detection and exceeded the target for treatment success despite numerous challenges, particularly in making services accessible in difficult geographic and socioeconomic settings. The country aims to further improve access to diagnostic and treatment services, especially for highly vulnerable groups, while sustaining high cure and treatment success rates particularly among smear-positive PTB cases. Efforts will be directed at improving diagnostic capabilities in DOTS facilities and hospitals, addressing barriers to follow-up examinations for patients under treatment as well as the factors that promote treatment default and improving the referral system to reduce transfer-outs. Factors that contribute to TB mortality such as diagnostic and treatment delay and co-morbidities need to be addressed as well. Finally, the TB information system will be strengthened to improve its usefulness for surveillance, planning and decision-making. With the current trend of NTP performance, it is predicted that the country will achieve Millennium Development Goals and Stop TB partnership targets before 2015.[10]

Conflicts of interest

None declared.

Funding

None.

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Assessment of gender distribution in dengue surveillance data, the Lao People's Democratic Republic

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Objective: Adolescent and young adult males account for a large proportion of dengue cases reported through national surveillance systems in the Western Pacific Region. To preliminarily assess the validity of these observed distributions, a field investigation was conducted in the Lao People's Democratic Republic's Savannakhet Province in November 2011.

Methods: Mixed quantitative and qualitative methods were used. Dengue surveillance data from Savannakhet Province, and aggregate hospital admission data from the Savannakhet Provincial Hospital for outpatients and inpatients were analysed by age and sex. Unstructured informal interviews were conducted with local health care workers, primary and secondary school officials and villagers.

Results: An excess of males was found among reported dengue cases in Savannakhet Province in the 15–49 year age group. Females in the same age group, however, were found to access health care more than their male counterparts. Qualitative assessments attributed this distribution to young females being more health-conscious and having greater health care-seeking behaviour.

Discussion: The excess of male dengue cases in the surveillance data appeared to be associated with a truly higher risk of dengue rather than greater health care access or health care-seeking behaviour by young men. This investigation indicated the importance of assessing the reported surveillance data within the context of health care utilization behaviour of the population under surveillance.

In tropical and subtropical Asia Pacific countries, dengue is responsible for considerable public health burden.[1,2] The mosquito-borne infection can cause severe illness and death and is considered a national priority emerging infectious disease among dengue-endemic countries in the World Health Organization (WHO) Western Pacific Region.

Dengue data reported through national surveillance systems have indicated that adolescent and young adult males are found to be consistently at high risk of dengue.[3–5] These patterns become apparent when the data are stratified by both age and gender. Studies from the Western Pacific Region have reported that gender differentials in the reported dengue surveillance data may be due to: (1) differentials between the genders in exposure-associated behaviours/activities[5] (e.g. working age males exposed to outdoor environments during the day when dengue virus-infected *Aedes aegypti* mosquitoes are active); (2) biological differences between the sexes (e.g. male–female differences in disease severity once infected);[6,7] and (3) differential health care access/seeking behaviour between men and women[6,8] (e.g. working age males may have better access to health care than their female counterparts or working age females may seek health care less often than their male counterparts).

Males would be the high risk group if the observed male excess in dengue cases was due to differential exposure or to sex differentials in the biological response to infection. However, since the reported case numbers were based on patients captured from health care sites, they may not reflect the true gender distribution of disease risk in the population.[3,9,10] Health care utilization, if differential by gender, would bias the gender distribution in the surveillance data.

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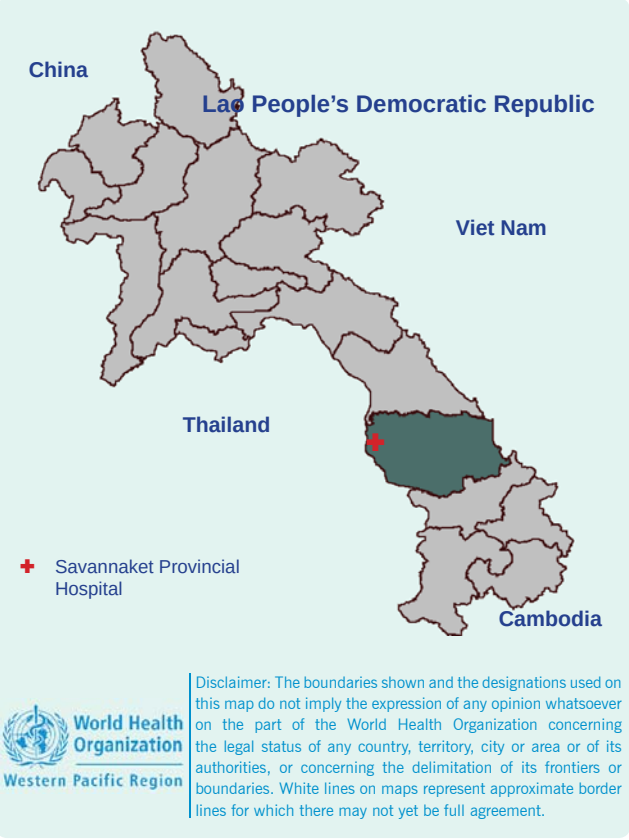
To investigate potential surveillance bias and to assess the validity of the observed dengue distribution, an investigation was conducted in the Lao People's Democratic Republic, a dengue-endemic country in the Region that experienced a dengue epidemic in 2010. The Lao People's Democratic Republic had an estimated population of 6.2 million in 2010[11] and is one of the least populous and least developed countries of South-eastern Asia.[12] Indicator-based surveillance is in place for monitoring dengue with weekly reporting of clinically suspected cases presenting at health care facilities; dengue outbreaks are also reported from communities and health facilities through event-based surveillance. This study was conducted in Savannakhet Province, the most populous of the Lao People's Democratic Republic provinces with a population of 824 552 persons of which 51% are female (**Figure 1**).[11] We describe both quantitative and qualitative assessments from the dengue surveillance system and from information on health care access and health care-seeking behaviour.

Figure 1. **Location of study site, Savannakhet Province, the Lao People's Democratic Republic**



METHODS

Periurban Savannakhet Province was selected as the province for this assessment for the following reasons: (1) sample size, as the most populous province of the Lao People's Democratic Republic; (2) the existence of a well-functioning provincial health office with access to a reliable surveillance system; and (3) accessibility, transportation and logistical factors. Aggregate dengue surveillance data stratified by age and sex for both the Lao People's Democratic Republic and Savannakhet Province were collected from the National Centre for Laboratory and Epidemiology, Ministry of Health and Savannakhet Provincial Health Office. To calculate notification rates, the latest population data were obtained from the Lao People's Democratic Republic's 2005 census.[11] Savannakhet provincial-level census data disaggregated by age and sex were not available.

Inpatient and outpatient data from 2010 and 2011 for the top 10 most admitted conditions were collected from Savannakhet Provincial Hospital and stratified by age and sex to assess the gender distribution of health care access. The hospital is a major health care facility for the province, serving all 15 districts and capturing the majority of the reportable diseases and conditions for surveillance purposes. Crude gender comparisons among age groups were made by indicating those age groups that had 20% or more patients for one gender relative to the other (with at least 10 patients per age and sex category) for each condition. Statistical analyses were done using Stata 11.0 and Microsoft Excel.

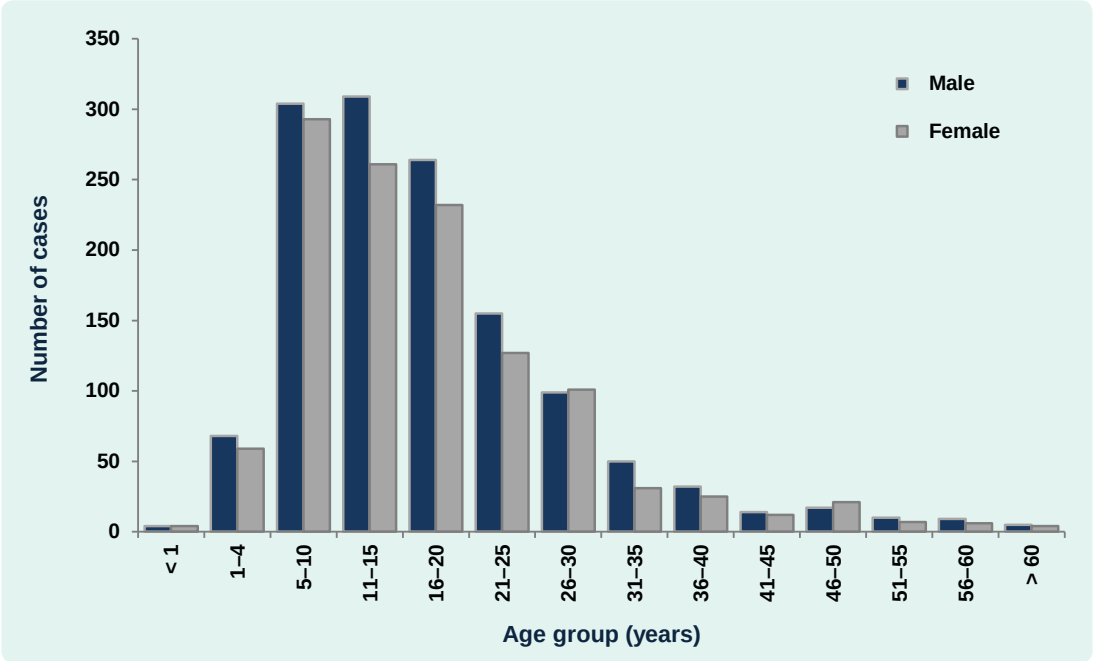
Informal, unstructured key informant interviews were conducted among health care workers (Savannakhet Provincial Hospital staff, Savannakhet Provincial Epidemiology Unit staff, Othomphone District Health Office staff, Othomphone District Hospital staff and Phin Tai Health Centre staff) and local community members (Ban Na village health volunteer, Ban Na Lao People's Democratic Republic Women's Union Leader, Ban Na Primary school and Secondary School board and teachers). Othomphone District Hospital covers five health centres in Othomphone District. Phin Tai Health Center serves five local villages in Othomphone District with a mean of approximately 15 patients visiting per day. Interviews consisted of both one-on-one and group discussions. Content analysis of the interviews was conducted with tagging of key concepts. Key questions focused on why specific age and gender groups visited health care facilities more than others.

Table 1. **Number of reported dengue cases, underlying population and notification rate by sex and age group, the Lao People's Democratic Republic, 2010 (n = 21 119)**

Age group (years)	Males			Females		
	Cases	Population	Notification rate (per 1000)	Cases	Population	Notification rate (per 1000)
< 5	622	351 559	1.8	624	349 356	1.8
5–15*	4 049	770 922	5.3	3 176	745 442	4.3
16–40*	6 329	1 129 864	4.7	4 625	1 152 083	3.4
> 40*	1 000	548 035	0.8	694	574 061	0.5
Total*	**12 000**	**2 800 380**	**4.3**	**9 119**	**2 820 942**	**3.2**

* $P < 0.05$ comparing notification rate between males and females, chi-squared test.

Figure 2. **Number of reported dengue cases by sex and age group, Savannakhet Province, the Lao People's Democratic Republic, 2010 (n = 2523)**



RESULTS

In 2010, the Lao People's Democratic Republic had 22 912 reported dengue cases and 46 deaths, an estimated national annual notification rate of four dengue cases per 1000 persons. This was a significant increase relative to the previous year (7810 cases; chi-squared test, $P < 0.01$) and the previous two years (2008: 4328 cases; 2007: 5896 cases). Age and sex data were available for 21 119 of 22 912 cases (92%). Except for those aged less than five years, males were found to have significantly higher notification rates of dengue than their female counterparts, and the risk difference was greatest among those 16–40 years of age (**Table 1**).

Savannakhet Province reported a similarly high annual dengue notification rate of three cases per 1000 persons in 2010 with 2523 reported cases. The age and sex distribution was similar to that of the overall national pattern with an excess of male cases particularly among those aged 11 to 25 years (**Figure 2**).

At the Savannakhet Provincial Hospital, similar to the overall provincial and national distributions, an excess of male dengue patients was reported in 2010 and 2011 among 15–49 year olds (**Tables 2** and **3**). In contrast to 2010, there were only 145 dengue patients reported among inpatients in 2011, and stratification by age and sex resulted in small numbers.

Table 2. **Ten most common diseases for *outpatients* by age and sex from Savannakhet Provincial Hospital, Savannakhet Province, the Lao People's Democratic Republic, 2010 and 2011***

Diseases	Sex	Age group (years)				
		< 1	1–4	5–14	15–49	> 49
2010						
Influenza-like illness	M	190	644	502	501	84
	F	89	428	382	483	83
Sore throat	M	115	647	572	103	13
	F	85	413	421	118	11
Gastroenteritis	M	0	2	18	592	217
	F	0	3	15	772	250
Dengue	M	5	86	344	511	39
	F	2	64	278	449	64
Pneumonia	M	16	81	45	356	114
	F	4	47	25	426	100
Tuberculosis	M	0	1	2	307	289
	F	0	3	6	354	248
Tonsilitis	M	6	41	106	267	33
	F	8	31	93	376	41
Bronchitis	M	50	56	54	174	93
	F	31	70	31	193	91
Acute watery diarrhoea	M	65	129	62	99	30
	F	31	71	47	107	43
Hypertension	M	0	0	0	57	235
	F	0	0	0	44	263
2011						
Influenza-like illness	M	121	919	357	338	54
	F	61	441	192	472	56
Sore throat	M	92	837	372	101	18
	F	37	399	207	148	15
Gastroenteritis	M	0	3	25	561	222
	F	0	0	13	882	238
Pneumonia	M	7	65	36	419	112
	F	3	33	25	560	120
Tonsilitis	M	3	42	81	415	45
	F	1	25	61	586	35
Bronchitis	M	23	86	61	170	128
	F	10	41	21	258	103
Hypertension	M	0	0	0	54	444
	F	0	0	0	61	316
Tuberculosis	M	0	1	20	234	200
	F	0	4	9	204	110
Otitis media	M	0	11	22	168	58
	F	0	5	16	268	45
Acute watery diarrhoea	M	14	108	41	95	49
	F	11	56	27	94	40

* cells indicate 20% or more females than males, and cells indicate 20% or more males than females (with at least 10 cases per age and sex category).

For 2010 and 2011, the majority of both inpatient and outpatient visits to the provincial hospital were for diseases or conditions with an infectious etiology (**Tables 2** and **3**). Among outpatients, there was an excess of males among those 14 years or younger and an excess of females among those 15–49 years of age (**Table 2**). In 2010, 63% of the 6517 patients younger than 15 years were male, relative to 47% of the 6289 patients in the 15–49 year age group ($P < 0.01$, chi-squared test); similarly, in 2011, 66% of the 5045 patients less than 15 years old were male, relative to 42% of the 6088 patients in the 15–49 year age group ($P < 0.01$, chi-squared test). Among inpatients, those 14 years or younger were

Table 3. **Ten most common diseases for *inpatients* by age and sex from Savannakhet Provincial Hospital, Savannakhet Province, the Lao People's Democratic Republic, 2010 and 2011***

Diseases	Sex	Age group (years)				
		< 1	1–4	5–14	15–49	> 49
2010						
Dengue	M	8	53	425	572	17
	F	5	51	419	443	20
Acute watery diarrhoea	M	76	98	22	42	14
	F	35	92	12	49	38
Pneumonia	M	29	130	38	40	38
	F	20	84	29	17	33
Sore throat	M	24	74	111	34	6
	F	20	59	86	37	4
Bronchitis	M	112	76	25	5	5
	F	67	52	10	5	7
Gastroenteritis	M	0	8	16	73	27
	F	0	4	20	68	51
Hypertension	M	0	0	0	25	53
	F	0	2	1	24	72
Typhoid	M	0	8	47	34	4
	F	0	1	30	21	14
Tuberculosis	M	0	0	0	41	48
	F	0	0	0	26	32
Malaria	M	2	4	18	75	9
	F	1	2	11	23	2
2011						
Acute watery diarrhoea	M	69	100	15	68	29
	F	34	78	14	52	44
Pneumonia	M	27	118	24	44	61
	F	19	67	20	38	69
Bronchitis	M	109	85	13	8	17
	F	57	45	19	7	12
Gastroenteritis	M	1	5	15	82	32
	F	0	7	19	103	48
Sore throat	M	17	48	39	31	3
	F	12	50	28	33	4
Hypertension	M	0	0	0	17	69
	F	0	0	0	21	98
Diabetes	M	0	0	1	15	45
	F	0	0	1	28	83
Tuberculosis	M	0	0	2	48	55
	F	0	0	3	29	28
Dengue	M	0	1	11	52	7
	F	1	2	15	52	4
Malaria	M	0	2	4	72	7
	F	0	1	5	7	4

* cells indicate 20% or more females than males, and cells indicate 20% or more males than females (with at least 10 cases per age and sex category).

similarly more likely to be male, but there was no longer an excess of females among those 15–49 years of age (**Table 3**). In 2010, 56% of 2517 patients less than 15 years old were male, compared to 57% of 1654 patients in the 15–49 year age group ($P = 0.53$, chi-squared test); in 2011, 59% of 1203 patients less than 15 years old were male, relative to 54% of 807 patients in the 15–49 year age group ($P = 0.03$, chi-squared test). Of those 15–49 years of age, the proportion of males among outpatients (47% in 2010 and 42% in 2011) as against the inpatients (57% in 2010 and 54% in 2011) was significantly different ($P < 0.01$ for both years).

Interviews among health care workers indicated that clinicians see more female than male outpatients, particularly for milder conditions. Health care staff indicated that many young women of childbearing age were very health conscious and actively sought health care to ensure the best for their newborn. The Phin Tai Health Centre had large posters and banners promoting maternal health care and clinic visits for young women. Interviews conducted at the local Ban Na village with village health volunteers and the Lao Women's Union director found that there has been active promotion for maternal and child health, and women's health had been increasingly emphasized as a priority. It was noted that young adult males prefer pharmacies for self treatment rather than making hospital visits, and some men prefer to send their wives (rather than visiting a clinician themselves) to health care facilities to obtain professional advice and medicines. There was no indication that the excess of male paediatric patients was attributable to better education and thus better access to health care. At the local Ban Na Primary School, 168 of the 286 pupils were female (59%). While 141 of the 346 pupils were female (41%) at the Ban Na Secondary School, the school board members and teachers stated that sick adolescents, whether they are students or not, all go to the same health care facilities as there is no health clinic or special health care privileges through secondary school enrolment. Key informant interviews among local health care providers reported gender differences in exposure-associated behaviours and activities (e.g. playing outdoors, swimming in lakes and being more adventurous).

DISCUSSION

Similar to other dengue-endemic countries in the Western Pacific Region (e.g. Cambodia, the Philippines and Singapore),[3–5] adolescent and adult males had significantly higher dengue notification rates than their female counterparts in the Lao People's Democratic Republic overall and in Savannakhet Province. In the Western Pacific Region, gender is a concern given the historical gender norms and its possible association with health care access.[10] Such concerns raise questions regarding the sex distribution observed in the surveillance data that are not only a reflection of who is getting ill but also who is accessing health care. This investigation highlighted the importance of assessing the surveillance data within the context of health care utilization of the population under surveillance.

This study found that the excess of adolescent and young adult male dengue cases in the surveillance data appears to be associated with a truly higher risk of disease. This male excess was observed despite the backdrop of higher health care-seeking behaviour among their female counterparts. There were more females aged 15–49 years seen as outpatients at the provincial hospital for the top 10 diseases/conditions. This may be due to a truly higher risk of illness among women; however, the opposite pattern was observed among inpatients: a larger number of females aged 15–49 years were admitted for only two of the 10 diseases/conditions in 2010 and for four in 2011.

Qualitative information supported these findings. Key informant interviews indicated that women of childbearing age are highly health conscious and readily seek health care up to around 35 years of age, as they reportedly want to be healthy during their childbearing years to give birth to healthy children. It was also noted that young adult males prefer self treatment. A recent study found that men of the Lao People's Democratic Republic are significantly more likely to smoke than women, but the proportion of men who sought treatment for respiratory illness was the same between the genders. Men were more likely to answer that they did not think they were sick enough when asked about reasons for not seeking treatment.[13] Such gender-specific health care-seeking behaviours may explain the excess of females among outpatients but not for more severe inpatients. The presence of a Lao Women's Union leader who championed maternal health and various posters and banners promoting maternal health care and clinic visits for young women were indicative of the current status of health care provision and accessibility in the area. Women's health and family planning campaigns, funded by development agencies, have been actively reaching out to Lao women in recent years.[14]

An excess of male patients for most diseases and conditions was observed among young children. Unlike adolescents and young adults, such excess of young male patients was observed for both outpatients and inpatients with no indication that boys were preferentially being brought to health care. Interviews indicated potential gender differentials in exposure-associated behaviours and activities. In addition, once becoming infected (and assuming all other things being equal), there may be biological differences between

the sexes such that males may have a more severe outcome to disease relative to their female counterparts. There has been a growing recognition that biological differences between males and females based on genetic, immunological and hormonal factors may determine the susceptibility to disease and clinical outcomes,[9,15–18] including for dengue infection.[6,7] Females may mount a more vigorous immune response to infection than males.[19]

Although a greater proportion of outpatients were women and a greater proportion of inpatients were men, there is a concern that women may have not been able to be treated as inpatients due to financial or other reasons. However, such gender bias in health care and treatment opportunities would be expected to result in higher female mortality in the community, which was not observed. Life expectancy for males increased from 50 to 59 years from 1995 to 2005, and the same period saw an increase from 52 to 63 years among females.[11] While age-stratified sex population data were not available for Savannakhet Province, 51% of the population were female.

There are several limitations in this study. There was no detailed case-based information available for this investigation. Data were obtained from existing, recorded aggregate summaries, and such information as severity of illness or time from onset to hospital visit was unavailable. Such data would have provided an indication of gender differentials in health care-seeking behaviour and the severity of the condition at the time of health care access. In addition, the number of dengue cases recorded in the provincial hospital was greater than that reported to the national surveillance system of the whole province, possibly because hospital records were based on unverified clinic records (and not strict case definitions). However, such discrepancy is unlikely to be differential by gender, and the sex and age distributions were similar between that reported by the hospital, province and the country. Also, as gender norms, health care-seeking behaviour and access can vary not only between countries but within countries (especially in the Lao People's Democratic Republic among different ethnic groups and urban versus rural subpopulations),[10,14,20] these findings should not be generalized.

Despite these limitations, the health care access data and the behavioural information show that it is unlikely that the excess of male dengue cases among adolescents and young adults can be explained through higher health care accessibility by young men in Savannakhet Province. It is unlikely that for dengue alone – and not for other diseases or conditions – young men would seek health care more than their female counterparts. If anything, when considering the underlying gender-specific health care-seeking behaviour, the number of dengue cases among young men may be underreported. While the specific reasons why this demographic group appears to be at higher risk (i.e. due to exposure and/or biological factors) cannot be determined by this study, the presumed higher risk of dengue for young men agrees with previous findings from other countries in the Region that differ from the Lao People's Democratic Republic in ethnicity, religion, culture and development stage,[3] such that the observed distributions may have a common risk factor associated with male sex and/or gender-specific behaviours. Adopting a more gender-sensitive approach and taking health care access information into consideration will assist public health practitioners in interpreting the reported surveillance data.

Conflicts of interest

None declared.

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None.

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Oseltamivir resistance among influenza viruses: surveillance in northern Viet Nam, 2009–2012

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Introduction: Antiviral resistance has been reported in seasonal influenza A viruses and avian influenza A(H5N1) viruses in Viet Nam, raising concerns about the efficacy of treatment.

Methods: We analysed specimens from two sources during the period 2009–2012: influenza-positive samples from influenza-like illness patients at sentinel clinics in northern Viet Nam and isolates from patients with confirmed A(H5N1) infections. Pyrosequencing was used to detect mutations: H275Y [for A(H1N1) and A(H5N1)], E119V [for A(H3N2)] and I117V [for A(H5N1)]. A neuraminidase inhibition assay was used to determine the Inhibitory Concentration 50 (IC_{50}) values for all influenza A and B isolates.

Results: There were 341 influenza A positive samples identified; influenza A(H1N1)pdm09 was identified most frequently (n = 215). In 2009, oseltamivir resistance was observed in 100% (19 of 19) of seasonal A(H1N1) isolates and 1.4% (3/215) of A(H1N1)pdm09 isolates. This H275Y mutation was not found in influenza subtypes A(H5N1) or A(H3N2) isolates.

Discussion: In Viet Nam, seasonal and A(H5N1) influenza vaccines are not currently available; thus, effective treatment is required. The presence of oseltamivir-resistant viruses is therefore a concern. Active surveillance for oseltamivir resistance among influenza viruses circulating in Viet Nam should be continued.

Influenza infection causes annual epidemics throughout the world. There are two common types of influenza viruses that cause human infection – influenza A and influenza B. Influenza A viruses caused several influenza pandemics in the 20th century, and a pandemic caused by the influenza A(H1N1)pdm09 virus occurred in 2009.[1] National influenza surveillance was initiated in Viet Nam in 2006, and the data collected so far have shown that influenza viruses circulate year-round with similar peaks and subtypes observed across all surveillance regions.[2] Between 2003 and 2012, 123 human cases of A(H5N1) infection were confirmed from 40 of the 63 provinces in Viet Nam, with 81 cases (66%) from northern Viet Nam.[3] Although influenza vaccines that protect against A(H1N1)pdm09 or influenza A(H5N1) are being developed in Viet Nam, they are currently only available through private market purchase.

The neuraminidase inhibitors oseltamivir and zanamivir are the primary antiviral agents recommended for the treatment of influenza infections,[4,5] yet antiviral resistance to influenza A viruses is increasingly being reported.[6,7] Oseltamivir is currently recommended as the first-line option by the Viet Nam Ministry of Health for treating suspected infections of A(H5N1) and A(H1N1) pdm09. The emergence of oseltamivir resistance of clinical isolates of influenza A virus has been associated with substitution at residue V116, I117, E119, Q136, K150, D151, D199, I223, H275 and N295 in the neuraminidase active site.[8] For influenza B there have been two main substitutions: residues R152 and D198.[8,9] In Viet Nam, oseltamivir-resistant strains harboring mutations at positions I117V, H275Y and N295S were reported for A(H5N1) in 2005,[6] A(H1N1) in 2007[10] and A(H1N1)pdm09 in 2009.[7,11] The limitations of other antiviral drugs, as well as the risk of oseltamivir resistance, have raised concerns about the efficacy of oseltamivir for influenza infection treatment. We report here on a pilot study for the establishment of a routine antiviral resistance surveillance programme in northern Viet Nam.

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MATERIALS AND METHODS

As an initial step in establishing a surveillance programme for antiviral resistance in northern Viet Nam, genetic analysis was conducted for both clinical specimens and isolates collected through sentinel sites and isolates of influenza A(H5N1). Neuraminidase activity was measured using a phenotypic method for viral isolates of influenza A and B. Pyrosequencing assays were then applied to detect the common mutations related to reducing susceptibility or resistance of influenza A viruses to oseltamivir – I117V, E119V and H275Y. Data from the National Influenza Surveillance System in Viet Nam were also analysed for the period 2009–2012.

Source of samples

Throat swabs were collected as part of the sentinel surveillance system for influenza-like illness in northern Viet Nam between 2009 and 2012 and were screened using standard methodology (conventional reverse transcriptase polymerase chain reaction, RT–PCR) at the National Influenza Center of the National Institute of Hygiene and Epidemiology in Hanoi.[2] Influenza isolates were then cultured from throat swabs positive for influenza A and B.[2,6] In addition, isolates from throat swabs, pharyngeal swabs or tracheal swabs collected from A(H5N1)-infected patients admitted to intensive care units of general hospitals in northern Viet Nam between 2009 and 2012 were obtained.

Madin-Darby canine kidney (MDCK) cells, obtained from the American Type Culture Collection, were used to culture viruses. Swabs positive for influenza A(H5N1) by RT–PCR were inoculated biosafety level III culture facilities. Viruses were harvested and stored at −80 °C for further analysis. All influenza isolates with a minimum of eight haemagglutination units by haemagglutination inhibition assay were selected for neuraminidase inhibition assay.[6,8,10,11]

Pyrosequencing assay

Pyrosequencing assays were used to further characterize all RT–PCR influenza-positive samples (n = 341) and influenza isolates (n = 67). Viral RNA was extracted directly from clinical specimens or from supernatants of isolates propagated in MDCK cells by using a viral RNA extraction kit (Qiagen, USA) according to the manufacturer's instructions. RT–PCR amplification was conducted using the Qiagen PyroMark PCR kit with specific primer sets for A(H1N1)pdm09, seasonal A(H1N1), A(H3N2) and A(H5N1).[12,13] Three sets of RT–PCR primers were used to generate corresponding amplicons of the neuraminidase gene segment covering the sequences encoding the target residues 117, 119 and 275 according to procedures described previously.[14]

The pyrosequencing reactions and data analysis were performed using a PyroMark Q24 ID Platform (Qiagen, USA). Briefly, biotinylated PCR products were washed through a series of buffers, and single-stranded DNA was generated and used as a template for hybridization to residue-specific sequencing primers, which were used at a concentration of 100 μM.[11,15]

Neuraminidase inhibition (NAI) assay

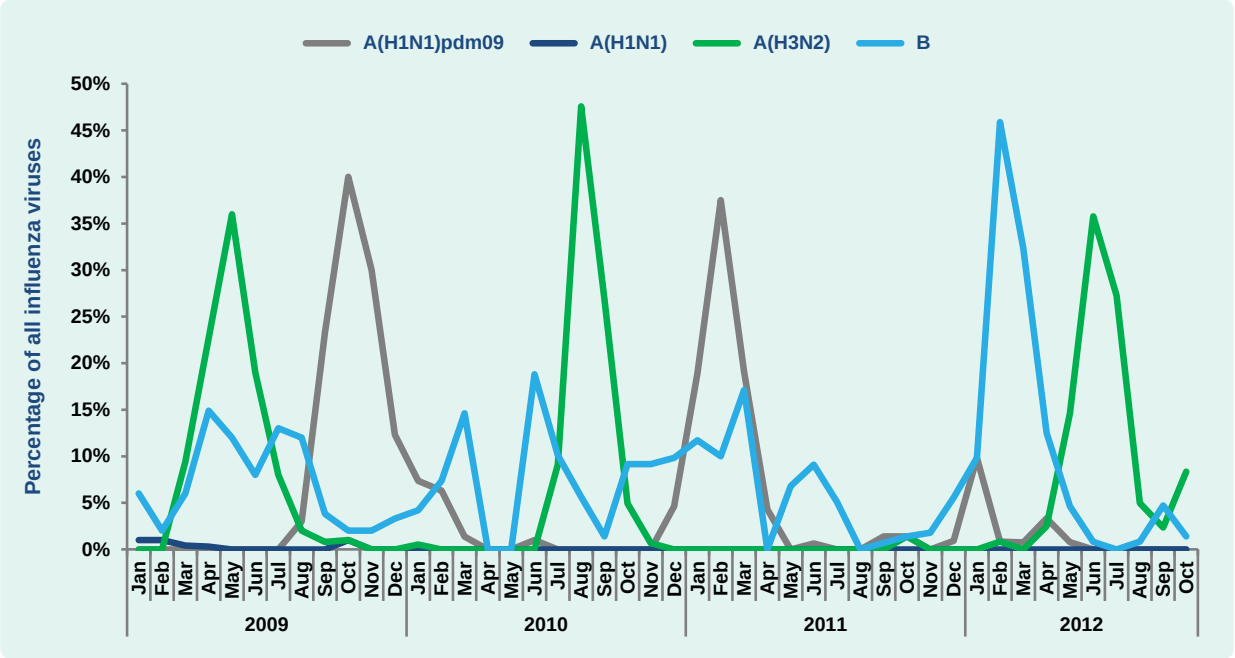
Oseltamivir carboxylate (GS4071) and its active form (GS4104) were provided by Roche Laboratories, Inc, Basel, Switzerland. The reference influenza viruses were provided by the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia. Influenza A(H5N1) isolates were inactivated by 1% formalin for 24 hours before the NAI assay. The NAI assay was performed according to procedures described previously.[8]

RESULTS

During the period 2009–2012, there was year-round circulation of seasonal influenza viruses with frequent co-circulation of influenza A and influenza B (**Figure 1**). A total of 341 influenza A positive samples were identified by RT–PCR (**Table 1**). Of these, influenza A(H1N1)pdm09 was identified most frequently (n = 215) throughout the whole study period; 100 were A(H3N2) and seven were A(H5N1). Seasonal A(H1N1) was isolated only in 2009 (n = 19).

Oseltamivir resistance, as determined by detection of H275Y in the neuraminidase gene, was observed in 100% (19 of 19) of seasonal A(H1N1) isolates in 2009 and was identified in 1.4% (3/215) of A(H1N1)pdm09 isolates collected in 2009. This H275Y mutation was not found in influenza subtypes A(H5N1) or A(H3N2) isolates. I117V was not observed in any of the isolates of subtypes A(H1N1), A(H5N1) or A(H1N1)pdm09; I119V also was not found in any A(H3N2) isolates (**Table 1**).

Figure 1. **Percentage of influenza viruses by subtype, northern Viet Nam, 2009 to 2012**



There were 67 isolates that underwent NAI assay; six seasonal A(H1N1), 14 A(H3N2), seven A(H5N1), 27 A(H1N1)pdm09 and 13 influenza B. All of the seasonal A(H1N1) isolates (n = 6) had Inhibitory Concentration 50 (IC_{50}) values that ranged from 541.61 to 703.48 nM higher than the reference virus (A/Mississippi/3/2001, oseltamivir-resistant) and reached 1000-fold higher than the reference wild-type virus (A/Mississippi/3/2001, oseltamivir-sensitive). Among the 27 viruses of A(H1N1)pdm09, IC_{50} values ranged from 118.59 to 127.91 nM and reached 250-fold higher than the reference wild type virus. The IC_{50} values obtained from non-mutant viruses [A(H1N1)pdm09, A(H3N2), A(H5N1) or influenza B] had median IC_{50} ranging from 1.07 nM [A(H1N1)pdm09] to 8.56 nM [A(H5N1)] and 24.79 nM (B), i.e. sensitive to oseltamivir (**Table 2**).

Table 1. **Influenza A subtypes and resistance mutations identified by year, northern Viet Nam, 2009 to 2010**

Influenza A subtypes	Year			
	2009	2010	2011	2012
A(H1N1)	19	0	0	0
I117V	0	0	0	0
H275Y	19	0	0	0
A(H3N2)	4	57	0	39
E119V	0	0	0	0
A(H1N1)pdm09	132	25	46	12
I117V	0	0	0	0
H275Y	2	0	1	0
A(H5N1)	4	3	0	0
Total	**159**	**85**	**46**	**51**

DISCUSSION

Our study of oseltamivir-resistant influenza viruses in northern Viet Nam shows that seasonal A(H1N1) isolates circulating in 2009 were oseltamivir-resistant by virtue of having the H275Y mutation and IC_{50} values indicative of resistance. This finding is consistent with reports from Japan, the United States of America and Europe of high rates of resistance (100%) during the 2008 to 2009 season.[12,13,15] WHO also reported the spread of resistant A(H1N1) strains worldwide during that time.

The A(H1N1)pdm09 virus was first detected in June 2009 in Viet Nam and was the predominant virus during the 2009 and 2011 influenza seasons. However, in this study, the oseltamivir-resistent mutation (H275Y) was identified in only two specimens in 2009 and one in 2011, a rate of 1.5% in 2009. A separate cluster of seven cases of oseltamivir-resistant A(H1N1)pdm09 was also reported from Viet Nam in July 2009.[5] The rate from this study is consistent with that collected through the WHO Global Influenza Surveillance and Response System of 1.7% frequency of resistance of A(H1N1)pdm09 in the first two years of the pandemic

Table 2. **The IC_{50} of oseltamivir carboxylate of non-mutant and mutant influenza viruses (H275Y) by subtype, northern Viet Nam, 2009 to 2012**

Influenza subtype	Virus	IC_{50} (nM)	IC_{50} median (nM)	Interpretation
A(H1N1) (*n* = 6)				
Mutant	A/Viet Nam/32036/2009	703.48	571.96	Highly reduced inhibition
	A/Viet Nam/ELI197/2009	582.81		
	A/Viet Nam/Q271/2009	455.80		
	A/Viet Nam/31808/2009	541.61		
	A/Viet Nam/34381/2009	583.30		
	A/Viet Nam/N116/2009	564.74		
A(H1N1)pdm09 (*n* = 27)				
Non-mutant	24 virus strains	-	1.07	-
Mutant	A/Viet Nam/33419/2009	125.99	124.16	Highly reduced inhibition
	A/Viet Nam/36530/2011	127.91		
	A/Viet Nam/DN42/2009	118.59		
A/H3N2 (*n* = 14)				
Non-mutant	14 virus strains	-	0.19	-
A(H5N1) (*n* = 7)				
Non-mutant	7 virus strains	-	8.56	-
Influenza B				
-	13 virus strains	-	24.79	-

IC_{50} – Inhibitory Concentration 50

(2009–2010).[16,17] Similar data reported elsewhere ranged from 0.5% in the United States of America to 0.8% in the United Kingdom and 1.1% in the Asia-Pacific.[12,14,18–20]

In our study, A(H5N1), A(H3N2) and B viruses were determined to be oseltamivir-sensitive by genotypic and phenotypic testing. These results are reassuring for future treatment of A(H5N1) infections in Viet Nam with oseltamivir, as the A(H5N1) influenza vaccine is not available. However, an oseltamivir-resistant A(H5N1) virus was reported in human isolates in 2005, and the emergence of mutations associated with reducing susceptibility (I117V) to oseltamivir was also determined among A(H5N1) isolates from both human and poultry in 2009–2010. Thus, continuing oseltamivir-resistance surveillance is critical for public health as oseltamivir is the most widely used antiviral medication for H5N1 infection.[16]

This study is subject to several limitations. The main limitation is the sample size of both biological and viral isolates, as we experienced difficulty in growing influenza A(H3N2) and A(H1N1)pdm09 and the quality of samples caused a reduced number of viral isolates to be tested. Also, it should be noted that phenotypic data (and sequencing) can only indicate that a virus is resistant: a direct relationship between IC_{50} values and actual clinical resistance is yet to be proven. Our data represent northern Viet Nam only and might not provide an accurate picture of the prevalence of oseltamivir-resistant viruses in the whole country. The data collected from the national influenza surveillance system did not report periodic antiviral use, and therefore it is difficult to assume that any resistance found in our study was due to transmitted resistance. Active surveillance in the future should be expanded to include data on oseltamivir use in hospitals and private clinics.

In conclusion, phenotypic and sequencing data indicated that oseltamivir resistance was present in seasonal A(H1N1) and A(H1N1)pdm09 subtypes in Viet Nam during the period 2009–2012. An increase of antiviral-resistant influenza viruses might occur in Viet Nam in the future. Enhancing active surveillance by

expanding this pilot study to different regions, monitoring the use of oseltamivir, analysing more specimens and reviewing more epidemiological information is recommended for Viet Nam.

Conflicts of interest

None of declared.

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An increase in neural tube defect notifications, South Australia, 2009–2010

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Introduction: In South Australia, reporting of live births, stillbirths of at least 20 weeks or 400g birth weight, termination of pregnancies and congenital anomalies is mandated. We describe the investigation of an increase in notifications of neural tube defects (NTDs) in South Australia in 2009 and 2010 using data from several surveillance systems.

Methods: NTD trend data from 1966 to 2010 were reviewed. Comparisons of pregnancies affected by an NTD in 2009 and 2010 were made with pregnancies affected by an NTD in the period 2003–2008 and with all pregnancies in 2009 and 2010. Statistical analysis was undertaken using Poisson regression, chi-squared or Fisher's exact tests.

Results: The prevalence of NTD-affected pregnancies was 1.95 per 1000 births (39 cases) in 2010 and 1.91 per 1000 births in 2009 (38 cases), the highest annual rates since 1991. Case series comparisons indicated women with NTD-affected pregnancies in 2009 and 2010 were less likely to be Caucasian compared with women who had NTD-affected pregnancies in the period 2003–2008. Women born in the Middle East and African region (n = 7) were significantly more likely to have NTD-affected pregnancies in the years 2009 and 2010 (relative risk: 3.03; 95% confidence interval: 1.39–6.62) compared with women born in the Oceania region.

Discussion: The increased notifications of NTDs can only be partially explained by the increase in numbers of women from the Middle East and African region, with no other contributory causes revealed. This analysis highlighted areas where prevention efforts should be strengthened and surveillance data improved.

The neural tube usually closes by day 28 of prenatal life, and incomplete or incorrect closure results in malformations called neural tube defects (NTDs).[1,2] There is a spectrum of severity of NTDs from anencephaly, which is incompatible with life beyond the neonatal period, to spina bifida occulta, which may be asymptomatic.[1]

Globally there are wide variations in birth prevalence of NTDs related to geography,[3,4] race and ethnicity[2,3] and socioeconomic status.[3,5–9] The majority of NTDs are non-syndromal with various maternal risk factors associated with increased likelihood of development of NTDs in offspring including: folate deficiency in the periconceptional period,[10,11] low maternal vitamin B12,[10,12,13] a previous NTD-affected pregnancy,[3,4,14] diabetes mellitus,[11] drug exposure during pregnancy,[14–16] overweight and obesity,[3,17–19] genetic alterations in folate-related genes,[2–4] exposure to environmental pollutants[20,21] and early pregnancy maternal hyperthermia.[3,11,20,22]

Periconceptional folic acid supplementation has been shown to decrease the risk of NTDs.[23,24] Folic acid supplementation one month prior and three months post conception is recommended to reduce the risk of an NTD-affected pregnancy.[4,25–27] In Australia, voluntary fortification of selected foods with folic acid was permitted from 1995, with fortification of non-organic, bread-making flour mandated from September 2009.[7]

In South Australia, reporting of all births, induced termination of pregnancy (ITOP) procedures and congenital abnormalities to the Pregnancy Outcome Unit (POU) of the South Australian Department for Health and Ageing is mandated,[28] and form the Birth Defects Register surveillance system.

An increase in the number of notifications of NTDs was observed in South Australia in 2009 and 2010,[28,29] with 39 and 38 NTD-affected pregnancies reported, respectively, as compared with between 21 and 25 notifications annually in the period 2003 to 2008.

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To help determine whether this increase represented a true increase, data from 1966 were reviewed. To discover possible underlying reasons for this increase and identify intervention targets, an investigation was undertaken comparing NTD-affected pregnancy notifications in 2009 and 2010 with notifications in the period 2003–2008 and with all pregnancy outcomes in the years 2009 and 2010.

METHODS

Data sources

NTD trend data from 1966 to 2010 were accessed from the Birth Defects Register surveillance database. Information on NTD-affected pregnancies (excluding spina bifida occulta) was obtained from three sources:

- The Abortion Statistics Collection is based on the Doctors Certificate and Notice Schedule (ITOP procedure form). Notifiers must include "grounds for termination of pregnancy," with "suspected medical condition of fetus" specified.
- The Perinatal Statistics Collection, using the Supplementary Birth Record completed by hospital and home-birth midwives, records the outcome of all live births, stillbirths of at least 20 weeks duration or 400g birth weight and includes a question regarding congenital abnormalities apparent in the baby.
- The Birth Defects Register includes reports of an NTD within first year of life from the Congenital Abnormality Form, which is completed by the notifying medical officer, midwife or South Australian Birth Defects Register staff.

Although reporting of births, ITOP procedures and congenital abnormalities is legally required, information is not always complete. To ensure the accuracy and maximize the completeness of the database of NTD notifications for the period 2003–2010, the data items were verified against the following:

1. the Open Architecture Clinical Information System, which contains electronic records of hospital discharge summaries, laboratory investigations and radiology undertaken in the public system;
2. the Integrated South Australian Activity Collection, a database of all hospitalizations in South Australia, to determine indigenous status and country of birth;
3. maternal and/or child case notes; and
4. treating doctor of the woman.

The POU is not permitted to contact the mother.

Analyses

To determine whether there was a systematic difference in the characteristics of women with NTD notifications in the years 2009 and 2010, the following comparisons were undertaken:

1. a case series comparison of NTD notifications from 2009 and 2010 with those from the period 2003–2008; and
2. a cohort comparison of NTD notifications in 2009 and 2010 with all South Australian pregnancy outcomes (excluding NTD cases) in 2009 and 2010.

Comparisons included demographics (age, race, country of birth, location of residence), previous pregnancies (parity, gravidity and number of previous terminations, live births and stillbirths), medical history (assisted reproductive therapies [ART], diabetes mellitus and epilepsy), smoking status and body mass index (BMI). Country of birth was grouped using the Standard Australian Classification of Countries.[30] Data on folate use were only available for women with NTD-affected pregnancies; therefore, comparisons were limited to the case series. The relative risk for women in regard to BMI was not calculated due to the considerable number of cases where these data could not be ascertained.

As South Australia experienced an extreme heat wave in early 2009,[31] meteorological effects were also analysed for the case series comparison. Maximum daily ambient temperature for 14 weather stations across South Australia was accessed from the Australian Government Bureau of Meteorology web site.[32]

Each woman with an NTD-affected pregnancy was assigned to the nearest weather station; women from metropolitan Adelaide were assigned to Kent Town weather station (in central Adelaide). The estimated date of conception was calculated from the date of the last menstrual period, if known, or from the estimated date of confinement. The number of days with a recorded maximum temperature of 35 °C or more from the date of conception until day 28 was calculated and compared for women with NTD-affected pregnancies in the periods 2009–2010 and 2003–2008.

Statistical analysis was undertaken using STATA 12. The level of significance was set at 5%. NTD prevalence trend was analysed with Poisson regression. Other analyses were undertaken using chi-squared tests with Fisher's exact test used where expected counts were less than five. Missing data were excluded from analyses.

Ethical approval was granted by the South Australian Health Ethics Committee and the Aboriginal Health Council of South Australia.

RESULTS

Prevalence of NTDs

The prevalence of NTDs was relatively stable between 1966 and 1990 and declined significantly thereafter (Poisson regression 1966 to 2010, $P < 0.001$). Secular trend data from 1990 incorporating the number of notifications in 2009 and 2010 continued to trend downward but at a reduced rate (from 2.8% decline during the period 1990–2008 to 1.8% decline between 1990 and 2010). The annual rate of NTD-affected pregnancies per 1000 births was 1.91 in 2009 and 1.95 in 2010, which were the highest rates since 1991 (2.03 per 1000 births). The birth prevalence (births and ITOP procedures) of anencephaly, spina bifida, encephalocoele and all NTDs show considerable yearly variation. Spina bifida and anencephaly are the most common types of NTDs (**Figure 1**).

NTD-affected pregnancies in 2009 and 2010 compared with NTD-affected pregnancies in 2003–2008

Women with NTD-affected pregnancies in 2009 and 2010 as compared with women with NTD-affected pregnancies in the period 2003–2008 were similar in regard to age, marital status, plurality, gravidity and Indigenous status. The majority of women were Caucasian; however, there were significantly fewer Caucasian women with NTD-affected pregnancies in 2009 and 2010 compared with the period 2003–2008 ($P = 0.01$). Region of birth was significantly different between cases in the two time periods ($P = 0.01$). Regional analysis indicated that women with NTD-affected pregnancies in 2009 and 2010 were more likely to have been born in the Middle East and African region ($P = 0.04$). Analysis by presence of epilepsy or diabetes mellitus was unremarkable. Analysis by ART use and BMI was hampered by a considerable number of cases where these data could not be ascertained (**Table 1**).

Thirty-six women (46.8%) with NTD-affected pregnancies in 2009 and 2010 did not experience any hot days with maximum reported ambient temperature of 35 °C or above in early pregnancy compared with 70 (51.5%) women with NTD-affected pregnancies in 2003–2008. There was no significant difference in the number of hot days (no hot days compared with at least one hot day) in early pregnancy for women with NTD-affected pregnancies in 2009 and 2010 as compared with the period 2003–2008.

Fewer women with NTD-affected pregnancies in the 2009–2010 period were reported as having taken no folate compared with the 2003–2008 period (six [7.8%] compared with 19 [14.0%]); however data regarding folate use were not available for 18 (23.4%) and 51 (37.5%) women, respectively (**Table 2**).

NTD-affected pregnancies in 2009 and 2010 compared with all pregnancies in 2009 and 2010

Women with NTD-affected pregnancies were significantly more likely to be born in the Middle East and African region (relative risk [RR]: 3.03; 95% confidence interval [CI]: 1.39–6.62) compared with all pregnancies in 2009 and 2010 (excluding NTD births). Among the seven Asian-born women with NTD-affected pregnancies, four came from India (57%). Women with NTD-affected pregnancies in 2009 and 2010 were also more likely to report using ART than women with births in 2009 and 2010 (RR 4.89, 95% CI: 1.97–12.14, $P = 0.0002$) (**Table 3**).

Women with NTD-affected pregnancies in 2009 and 2010 were less likely to be married or in a de facto

Table 1. Characteristics of women with neural tube defect-affected pregnancies (births and termination procedures), South Australia, 2003–2008 and 2009–2010

Characteristics	2003–2008		2009–2010		*p*-value
	n	%	*n*	%	
Age					
< 30 years	64	47.1	38	49.4	*P* = 0.75
≥ 30 years	72	52.9	39	50.6	
Marital status					
Married/de facto	114	83.8	62	80.5	
Other	20	14.7	15	19.5	*P* = 0.39
Unknown	2	1.5	0	0.0	
Plurality					
Singleton	131	96.3	76	98.7	*P* = 0.66
Multiple	4	2.9	1	1.3	
Race					
Caucasian	121	89.0	61	79.2	
Not Caucasian	11	8.1	16	20.8	*P* = 0.01
Unknown	4	2.9	0	0.0	
Region of birth					
Oceania	114	83.8	60	77.9	
Europe, Americas and former USSR	11	8.1	1	1.3	
Middle East and Africa	3	2.2	7	9.1	*P* = 0.01
Asia	7	5.1	7	9.1	
Unknown	1	0.7	2	2.6	
Indigenous status					
Aboriginal and/or Torres Strait Islander	2	1.5	3	3.9	
Not Aboriginal or Torres Strait Islander	131	96.3	74	96.1	*P* = 0.36
Unknown	3	2.2	0	0.0	
Gravidity					
Primigravida	41	30.1	26	33.8	*P* = 0.59
Multigravida	95	69.9	51	66.2	
Parity					
Primipara	60	44.1	36	46.8	*P* = 0.71
Multipara	76	55.9	41	53.2	
Assisted reproductive therapy use					
Yes	10	7.4	5	6.5	
No	84	61.8	61	79.2	N/A†
Unknown	42	30.9	11	14.3	
Body mass index					
Underweight or normal weight (< 25 kg/m^2)	14	10.3	14	18.2	
Overweight or obese (≥ 25 kg/m^2)	19	14.0	30	39.0	N/A†
Unknown	103	75.7	33	42.9	
Residence*					
Metropolitan	100	75.8	52	71.2	*P* = 0.48
Not metropolitan	32	24.2	21	28.8	

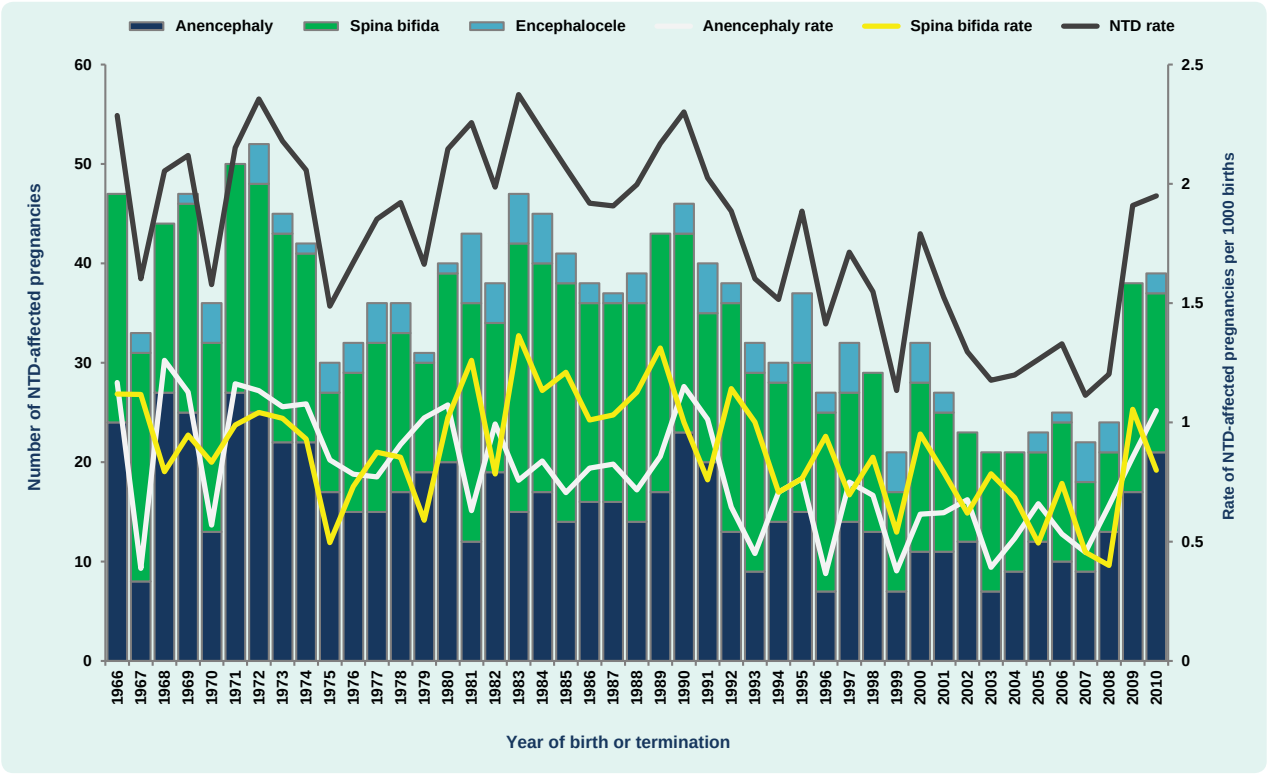
Note: Pearson chi-squared test, or Fisher's exact test where expected frequencies are small.

USSR – Union of Soviet Socialist Republics; N/A – not applicable.

* Cases in interstate residents (n = 8) not shown.

† Calculation not undertaken due to large numbers of unknowns.

Figure 1. **Birth prevalence (births and termination procedures) of neural tube defects, spina bifida, anencephaly and encephalocele, South Australia, 1966 to 2010**



NTD – neural tube defect

Note: The South Australian folate promotion campaign ran from October 1994 to August 1995.

Table 2. **Folate consumption of women with neural tube defect-affected pregnancies (births and termination procedures), South Australia, 2003–2008 and 2009–2010**

Folate consumption		Year of delivery or termination				Total	
		2003 to 2008		2009 to 2010			
		n	%	*n*	%	*n*	%
Periconceptional folate	Before and early pregnancy	35	25.7	21	27.3	56	26.3
	Early pregnancy only	16	11.8	11	14.3	27	12.7
	Unknown timing	15	11.0	21	27.3	36	16.9
No folate		19	14.0	6	7.8	25	11.7
Unknown folate		51	37.5	18	23.4	69	32.4
Total		136	100.0	77	100.0	213	100.0

relationship compared with other women giving birth in these years (21% compared with 60%). Otherwise, women with NTD-affected pregnancies were similar to women with births in 2009 and 2010 in regard to age, plurality, Indigenous status, Caucasian ethnicity, gravidity, parity and metropolitan residence (**Table 3**). Analysis by presence of epilepsy or diabetes mellitus was unremarkable.

DISCUSSION

This study aimed to investigate an observed increase in the number of NTD-affected pregnancies notified in 2009 and 2010 in South Australia using routinely collected surveillance data. No explanation was found that could fully account for the increase in NTD notifications; however, factors that were likely contributory were

Table 3. **Characteristics of women with neural tube defect-affected pregnancies (births and termination procedures) and all births, South Australia, 2009 and 2010**

Characteristics	NTD		Births‡		Risk per 1000	Relative risk§ (95% CI)	
	n	%	n	%			
Age							
< 30 years	38	49.4	19 302	48.4	1.97	1.04	(0.66–1.62)
≥ 30 years	39	50.6	20 567	51.6	1.90		
Marital status							
Married/de facto	62	80.5	35 448	88.9	1.75	0.52	(0.29–0.91)
Other	15	19.5	4420	11.1	3.39		
Unknown	0	0.0	1	0.0			
Plurality							
Singleton	76	98.7	38 617	96.9	1.97	2.46	(0.34–17.68)
Multiple	1	1.3	1252	3.1	0.80		
Race							
Caucasian	61	79.2	33 451	83.9	1.82	0.73	(0.42–1.27)
Not Caucasian	16	20.8	6418	16.1	2.49		
Region of birth							
Oceania	60	77.9	32 471	81.4	1.85	1.00	
Asia	7	9.1	3795	9.5	1.84	1.00	(0.46–2.18)
Middle East and Africa	7	9.1	1245	3.1	5.60	3.03	(1.39–6.62)
Other	2	2.6	1	0.0			
Unknown	1	1.3	2357	5.9			
Indigenous status							
Aboriginal and/or Torres Strait Islander	3	3.9	1245	3.1	2.41	1.26	(0.40–3.98)
Not Aboriginal or Torres Strait Islander	74	96.1	38 624	96.9	1.92		
Gravidity							
Primigravida	26	33.8	12 153	30.5	2.14	1.16	(0.73–1.86)
Multigravida	51	66.2	27 716	69.5	1.84		
Parity							
Primipara	36	46.8	16 781	42.1	2.15	1.21	(0.77–1.89)
Multipara	41	53.2	23 088	57.9	1.78		
Assisted reproductive therapy use							
Yes	5	6.5	653	1.6	7.66	4.89	(1.97–12.14)
No	61	79.2	39 216	98.4	1.56		
Unknown	11	14.3	0	0.0			
Body mass index							
Underweight/normal (<25kg/m2)	14	18.2	14 838	37.2			N/A†
Overweight or obese (≥25kg/m2)	30	39.0	15 373	38.6			
Unknown	33	42.9	9658	24.2			N/A†
Residence*							
Metropolitan	52	71.2	29 657	74.9	1.75	0.83	(0.50–1.38)
Not metropolitan	21	28.8	9959	25.1	2.10		

NTD – neural tube defect; CI – confidence interval; N/A – not applicable

* Excludes interstate residents (n = 4 cases; n = 253 comparison births)

† Calculations not undertaken due to large number of missing data

‡ Excludes 34 NTD notifications from 2009 to 2010

§ Unknowns excluded for calculation of relative risk

found. Women with NTD-affected pregnancies in 2009 and 2010 were less likely to be Caucasian as compared with women with NTD-affected pregnancies in the period 2003–2008. Women born in the Middle East and African region were more likely than women born in the Oceania region to have NTD-affected pregnancies in 2009 and 2010.

An elevated number of notifications can be due to a change in detection methods, a change in notification practices or a real increase in disease. Given the severe nature of most NTDs, the majority will be diagnosed either prenatally or within the first year of life;[1] therefore, it is unlikely that a change in detection methods could account for the increase in NTD notifications. Since 1998, the South Australian Births Defects Register has been screening childhood admission data for missing notifications; hence, it is unlikely that a change in notification practices could account for the increase in notifications. It is likely that the increase in NTD notifications reflected a real increase in the number of NTD-affected pregnancies and warranted further investigation.

Women with NTD-affected pregnancies in 2009 and 2010 in this study were less likely to be Caucasian and more likely to have been born in the Middle East and African region compared with women who had NTD-affected pregnancies in the period 2003–2008. Women born in the Middle East and African region were also significantly more likely to have NTD-affected pregnancies in the years 2009–2010 compared with women born in the Oceania region. Periconceptional folic acid is a key modifiable risk factor in NTD prevention, and several studies have noted reduced intake of folic acid supplementation in pregnant ethnic minority women compared with women of the ethnic majority.[33,34] Poor language proficiency is also likely a barrier to adequate folic acid supplementation.[34] Closer inspection of folate use among the Middle East and African-born women and Asian-born women with NTD-affected pregnancies in 2009 and 2010 did not reveal a consistent pattern of reduced folate consumption during pregnancy.

Of the women with NTD-affected pregnancies in 2009 and 2010, 69% reported taking folate (8% reported not taking folate during pregnancy; 23% had missing data). Recent data from the South Australian Monitoring and Surveillance System indicated that in 2010, 92.6% (95% CI: 88.4%–95.6%) of women currently pregnant or pregnant within the past three years reported taking folic acid supplementation in pregnancy.[35] Although these proportions are not directly comparable, there is evidence of the continued need for education of women regarding the importance of periconceptional folic acid.

Three women had two NTD-affected pregnancies within the 2003–2010 period. Women who have had one NTD-affected pregnancy have a 2%–3% chance of a subsequent NTD-affected pregnancy.[14] It would be expected that women who are multiparous would more likely be exposed to health promotion messages regarding folate during previous pregnancies and thus have a greater awareness of the need for periconceptional folic acid.[34] However, in our study, there was no significant difference between gravidity or parity and risk of an NTD-affected pregnancy. This is in keeping with a previously reported link between inadequate folate consumption and multiparity.[33] It is important that women of childbearing age at increased risk of NTD such as women with a previous NTD-affected pregnancy or family history of NTD are advised to take 5mg of folic acid supplementation daily orally as opposed to the 0.5 mg recommended for women not at increased risk.[25–27] This may represent opportunities missed by health services to inform pregnant women of the importance of periconceptional folic acid use in future pregnancies.

Inadequate vitamin B12 may also be associated with an increased risk of NTD.[10,12,13,36] Vitamin B12 deficiency is likely to be a public health issue in both developed and developing countries worldwide; however, there is a lack of population-based prevalence studies.[37] In a South Australian-based study of recently arrived refugees, no women of childbearing age (15–44 years) from Middle Eastern and Southern and central Asian countries were folate deficient (serum folate < 7 nmol/L), although approximately 26.1% were vitamin B12 deficient (serum vitamin B12 < 150 pmol/L) (Dr Jillian Benson, Senior Medical Officer, Migrant Health Service, Adelaide, personal communication, 24 July 2012). There have been no trials of vitamin B12 supplementation in pregnancy; hence, it is currently unknown whether vitamin B12 supplementation is of benefit in NTD prevention.[36] It may be that vitamin B12 supplementation in addition to folic acid supplementation is required to minimize the risk of NTD in this community.

Married or de facto married women were significantly less likely to have had NTD-affected pregnancies in 2009–2010 compared with other women giving birth. However, this observation is more likely to reflect the characteristics of the Abortion Statistics Collection data set rather than risk factors for NTD. Case series comparison indicated the cases in the periods 2003–2008 and 2009–2010 were similar with respect to marital status.

More women with NTD-affected pregnancies in 2009 and 2010 reported using ART than all other women with births in 2009 and 2010. However, there is likely differential misclassification of exposure due to incomplete ascertainment of ART usage in birth data compared with NTD notifications because of measurement bias, especially recall bias. In the South Australia 2009 to 2010 birth data, ART was reported in 1.6% births, whereas the Australian Institute of Health and Welfare estimated that 4.0% of births had used ART in Australia.[38,39] Therefore, it is likely that there has been incomplete ascertainment of pregnancies where ART has occurred in the 2009 to 2010 birth data. Moreover, women who undergo ART may be different in other ways that affect NTD risk apart from the requirement for ART. A recent study using South Australian data found no significant difference in risk of neurological congenial anomalies in pregnancies resulting from ART compared with all pregnancies.[40]

Maternal hyperthermia in early pregnancy is associated with an increased risk of an NTD-affected pregnancy.[3,11,20,22] South Australia experienced an extreme heat wave in early 2009,[31] therefore, meteorological effects were analysed as a possible reason for increased numbers of women with NTD-affected pregnancies in 2009 and 2010. However, no significant difference was found. Improving methodologies to determine the association of meteorological effects on congenital anomalies is important as Australia is likely to experience more extreme weather conditions, including heat waves, in association with climate change.[31]

This study, as it was based on surveillance and other routinely collected data, has several limitations. Data were obtained from three separate sources, each with a different focus and thus different variables. Missing data was also an issue, particularly for BMI, ART and folate status, making interpretation of these comparisons difficult. Folate consumption was only routinely collected for women with NTD-affected pregnancies with data frequently missing. Clinicians reported they were reluctant to question women with NTD-affected pregnancies, particularly those requesting ITOP, regarding their periconceptional folate intake given the sensitivity of the situation. As POU is not legally permitted to contact the women, this analysis had to rely on reported data.

Additionally, measurement bias was likely as notifications of pregnancies with no reported complications are subject to less scrutiny than pregnancies with reported congenital anomalies. Women with NTD-affected pregnancies, compared to women without complications, may be more likely to recall medical procedures (e.g. ART). Exclusion of women with previous NTDs from the analyses did not result in any significant difference from the results reported. As this study was based on an observed population, it involved small numbers, and therefore, multivariable analysis to control for potential confounders was not feasible.

This study has several strengths. It reported a whole-of-state collection of pregnancies with a NTD including both ITOP procedures and births. There was likely almost complete capture of NTD-affected pregnancies (excluding early miscarriages) due to mandatory reporting and routine screening for missed notifications. Inclusion of ITOP in analysis of NTD epidemiology is essential as in South Australia 84% of pregnancies with an NTD during the period 2003–2010 resulted in ITOP. This study was based on routinely collected data which enabled comparison of NTD-affected pregnancies in 2009 and 2010 with all births in 2009 and 2010 and NTD-affected pregnancies in the period 2003–2008 for a large number of demographic factors and risk factors. Additionally, trend data on NTD birth prevalence were available for more than 40 years.

In conclusion, a small but significant increase in the numbers of women born in the Middle East and African region partially contributed to the observed increase in notifications of NTD-affected pregnancies in South Australia in 2009 and 2010. However, this cannot fully explain the observed increase in NTD notifications, and it is likely that these two years of increased notifications represent a chance event rather than signalling the beginning of an epidemiological shift. This study highlighted the need for surveillance systems of congenital anomalies to be able to respond

to such increases. It also drew attention to the need to improve universal health promotion messages regarding periconceptional folic acid supplementation in pregnancy and to further investigate other potentially contributory nutritional deficiencies such as vitamin B12, particularly among women born in the Middle East and Africa.

Conflicts of interest

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Three cases of neonatal tetanus in Papua New Guinea lead to development of national action plan for maternal and neonatal tetanus elimination

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Maternal or neonatal tetanus causes deaths primarily in Asia and Africa and is usually the result of poor hygiene during delivery. In 2011, three neonatal tetanus cases were investigated in Papua New Guinea, and all three cases were delivered at home by untrained assistants. The babies were normal at birth but subsequently developed spasms. A neonatal tetanus case must be viewed as a sentinel event indicating a failure of public health services including immunization, antenatal care and delivery care. The confirmation of these cases led to the drafting of the Papua New Guinea National Action Plan for Maternal and Neonatal Tetanus Elimination. This included three rounds of a tetanus toxoid supplementary immunization campaign targeting women of childbearing age (WBCA) and strengthening of other clean delivery practices. The first immunization round was conducted in April and May 2012, targeting 1.6 million WBCA and achieved coverage of 77%. The government of Papua New Guinea should ensure detailed investigation of all neonatal tetanus cases reported in the health information system and perform sub-provincial analysis of tetanus toxoid coverage following completion of all three immunization rounds. Efforts also should be made to strengthen clean delivery practices to help eliminate maternal and neonatal tetanus in Papua New Guinea.

Tetanus causes around 300 000 deaths worldwide each year predominantly in low-income and middle-income countries, and deaths from maternal or neonatal tetanus are concentrated mostly in Asia and Africa.[1] Neonatal tetanus (NNT) is primarily caused by lack of hygiene during delivery, and it usually occurs when the umbilical cord is contaminated while being cut or dressed with non-sterile instruments. Symptoms, in the form of spasms, usually begin three days after birth. Without any specific treatment, more than 95% of infants with NNT die; even with treatment 10%–90% die depending on the intensity of the supportive care.[2] Evidence suggests that infants surviving NNT suffer from brain damage, which often manifests as neurological abnormality and developmental impairment.[3] Cases of NNT are common in rural and disadvantaged settings where babies are born at home and die without registration of either event. Thus, the true burden is always unknown.[1]

Around 1500 suspected cases of NNT have been reported from Papua New Guinea to the World Health Organization (WHO) since 1992, an average of 75 per year.[4] Cases are reported to the National Health Information System based on clinical diagnosis only per the WHO-recommended standards for surveillance of selected vaccine-preventable diseases.[5] These reported cases are not systematically investigated, impeding the ability of national and provincial managers in effective decision-making. In 2010, there were 50 suspected cases of NNT reported in Papua New Guinea through syndromic surveillance by health workers.[4] In 2012, Papua New Guinea was classified as one of the 31 countries that had not yet achieved maternal and neonatal tetatus (MNT) elimination.[6]

In Papua New Guinea, vaccination for tetanus has been provided since 2008 as part of the combined diphtheria pertussis-tetanus-Hepatitis B and -

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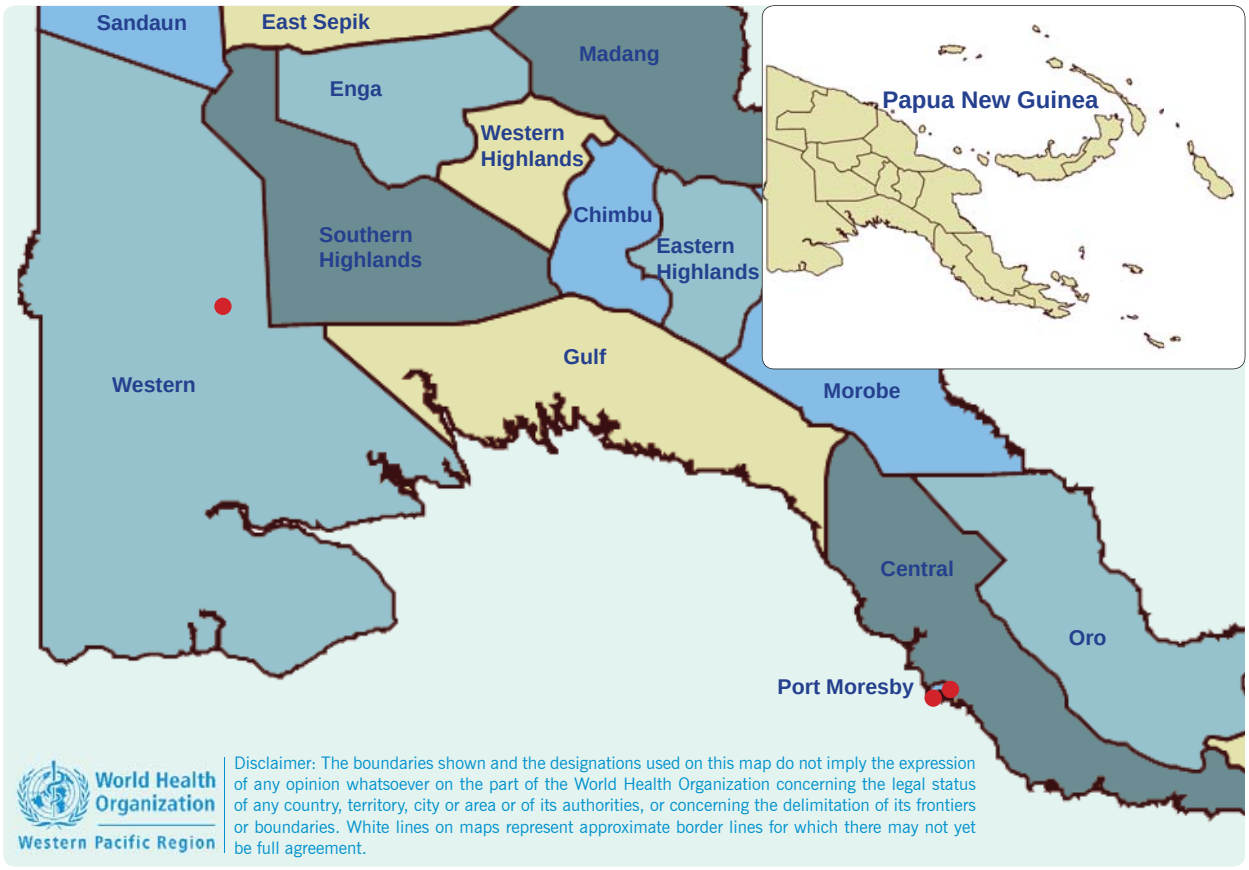
Figure 1. **Map of the location of neonatal tetanus cases, Papua New Guinea, 2011**



Haemophillus influenzae B (pentavalent) vaccine. However, accessibility to vaccination programmes is inequitable across Papua New Guinea; provinces such as Western, Eastern Highlands and West Sepik have health services that are not accessible to at least 40% of their population.[7] Also, the number of maternal health staff decreased by 25% from 1987 to 2000.[7] In 2011, 61% of children less than one year of age in Papua New Guinea received three doses of pentavalent vaccine, and 51% of pregnant women received tetanus toxoid (TT) vaccine.[8] According to WHO and the United Nations International Children's Fund, the proportion of births that could be considered protected against tetanus[6] was around 61% in Papua New Guinea in 2011. Both the TT and pentavalent vaccine coverage in Papua New Guinea varies widely between and within the provinces.

We discuss three cases of NNT that were reported and subsequently investigated in 2011 and the development of national policy of MNT elimination in Papua New Guinea.

The cases

In 2011, two cases of NNT were reported from the paediatric unit of Port Moresby General Hospital (PMGH) and one case of NNT was reported from Rumginae Rural Hospital (RRH) in Western Province of Papua New Guinea. The two PMGH cases resided in Goilala district, Central Province and the Rumginae case in Middle Fly district, Western Province (**Figure 1**). Middle Fly is characterized by forests, swamps, rivers and coast, and access is predominantly by dugout canoes, outboard powered dinghies and aircraft due to the vastly scattered villages being separated by large bodies of water.[9] The average household size of Middle Fly district is 6.8; 89% of the population are reside in traditional dwellings, and 87% of the population are engaged in agriculture as the principal economic activity.[10] The Goilala district is a remote district characterized by very rugged topography with more than 70% comprised of deeply dissected valleys and mountains.[11] There is no road access to the Goilala district from provincial headquarters in Port Moresby, and the communities are usually serviced

Table 1. **Characteristics of mother and births for the three neonatal tetanus cases, Papua New Guinea, 2011**

Characteristic	Case 1	Case 2	Case 3
District of origin	Goilala	Goilala	Middle fly
Age of mother	16 years old	29 years old	23 years old
First pregnancy	No	No	No
Antenatal care of mother in present/past pregnancy	No/No	No/Yes	No/No
Tetanus Toxoid received by mother in present/past pregnancy	No/No	No/Yes	Unknown/Unknown
Delivery conditions	Floor at home	Floor at home	Floor at home
Birth attendants	Untrained relative	Untrained attendant	Untrained attendant
Cord-cutting practices	Old razor blade	Bush knife	Bush knife
Cord-tying practice	Strings from used rope	Strings from rice bag	Strings from grass skirt
Onset of symptoms	Day 5	Day 7	Day 12
Died	No	No	Yes

by light aircraft landing on treacherous mountain top airstrips.[11] TT vaccine coverage for women of childbearing age (WCBA) in Goilala and Middle Fly districts were low at 9% and 12%, respectively, in 2011.

All three cases (two males and a female) were delivered at home on the floor, and the births were attended by untrained assistants (**Table 1**). The umbilical cord was cut in two of these cases with a bush knife, while in the other an old razor blade was used. The umbilical cords in these three cases were tied with strings from a rope, a rice bag and a grass skirt. All three babies were reportedly normal at birth and had normal crying and sucking for the first two days of life. All three babies started having difficulty in sucking after two days, and they developed symptoms of convulsions and spasms at an average of eight days after birth. The youngest of the multi-gravidae mothers was 16 and the eldest 29 years. Only one of the mothers received any antenatal care or TT vaccination in her past pregnancies, while none of these mothers received any antenatal care or TT vaccination in the current pregnancy. The two cases that were admitted to PMGH survived, while the case at RRH died three days after admission to the hospital; there was no fatality among the mothers. Follow-up of the cases discharged from PMGH was not possible due to the geo-topography of their residential location; hence, no comment can be made on the final clinical outcome in regards to neurological and developmental status of these cases after discharge.

The policy

The confirmation and detailed investigation of these three cases by hospital physicians in 2011, along with the reported suspected cases of NNT by the health workers through the syndromic surveillance system, led to the drafting of the National Action Plan for Elimination of Maternal and Neonatal Tetanus in Papua New Guinea.[12] The action plan targeted WCBA (15–45 years) for three rounds of nationwide supplementary immunization activities with TT. This is in line with the WHO position paper on tetanus.[13] A "high-risk approach" to control NNT in countries where the elimination target (<1 case per 1000 live births at the district level) has not yet been reached. This high-risk approach should be targeted towards all WCBA and immunization doses must be delivered using a campaign-style immunization programme of three doses of TT with an interval of at least four weeks between doses one and two and of at least six months between doses two and three. Strengthening other measures to prevent MNT in the country, including clean delivery, training of midwives and community health workers ,and improvement in ante-natal care services, were also highlighted in the national elimination plan.

The first immunization round targeted 1.6 million WBCA and was conducted in April and May 2012. Around 1.3 million (77%) women were reached with the TT vaccine during the first round.[14] This supplementary

immunization campaign was administered using multiple approaches at fixed site (maternal and child health clinics at health centres, school vaccination sessions, markets and congregation site sessions), day mobile and overnight patrol outreach sessions. The second immunization round was conducted in October through December 2012; final coverage results are pending.

DISCUSSION

These three NNT cases in Papua New Guinea must be viewed as sentinel events indicating a triple failure of public health in routine immunization, antenatal care and clean delivery/cord care services. Unsafe cord practices were evident in all three cases. As reported in Papua New Guinea as early as 1991, unsafe birth practices, including cutting the cord with sharpened sea shells, fresh bamboo knifes, metal blades or knifes, were common practices.[15] Strengthening clean delivery practices is one component of the National Action Plan that aims to decrease the incidence of such unsafe practices. Following the introduction of a programme promoting clean delivery practices and the replacement of cow dung for postnatal umbilical cord care with clean water or milk in Kenya and Tanzania, there was significant reduction in annual NNT incidence. After introduction of the programme in 1981, NNT rates fell sharply, and by 1988 annual death rates had dropped to 0.75 per 1000 births in the intervention areas compared with 82 per 1000 in control areas. These changes were both culturally acceptable and safer alternatives.[16]

Although cases of NNT have been reported every year in the National Health Information System, it was the reporting and confirmation of the these three NNT cases by physicians at PMGH and RRH that led to the formulation of the National Action Plan for Elimination of Maternal and Neonatal Tetanus in Papua New Guinea. In order to achieve the elimination of MNT in Papua New Guinea, the other components of the National Action Plan need to be implemented, including the third and final immunization round, the strengthening of clean delivery practices and NNT surveillance. More detailed investigations of NNT cases reported in the health information system as well as sub-provincial analyses following completion of all three immunization rounds should be conducted.

Conflicts of interest

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Avian influenza A(H7N9): information-sharing through government web sites in the Western Pacific Region

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Under the International Health Regulations (2005),[1] the Chinese Government reported three human cases of avian influenza A(H7N9) virus on 31 March 2013 to the World Health Organization (WHO). Previous public health events have shown that early detection, rapid response and sharing of information can reduce the impact of emerging and re-emerging diseases.[2] Risk communication is critical in providing accurate, direct and relevant information as the event unfolds, especially when the disease is of public health importance and/or there is high public anxiety.[3,4] Communication between government authorities and the public is especially important during these health events, particularly during outbreaks.[5] The Internet is one important tool used to present information to the public; globally, one in three people have access to the Internet[6] and Internet search engines, such as Google and Yahoo, have become a frequently used means to obtain information.[7,8]

To assess the web-based risk communication response in the WHO Western Pacific Region for the A(H7N9) event in China, we collated public health-related information on A(H7N9) from the countries and areas of the Region for the period 30 April to 2 May 2013. A systematic search of government web sites for each of the 37 countries and areas in the WHO Western Pacific Region was conducted using Google. The search terms used were Ministries of Health, Ministries of Agriculture, Ministries of Foreign Affairs and National Centers for Disease Control. If this strategy did not identify a web site for a country or area, the cabinet or whole-of-government web site was sourced. Once a government web site was identified, and if it had a search facility, the keyword "H7N9" was used to identify information provided for the A(H7N9) event. If the web site did not have a search facility, press releases or other available information on that site were reviewed for mention of A(H7N9). Pages in languages other than English were assessed by WHO staff from these countries. The information on A(H7N9) from these web sites was categorized according to topics on the WHO A(H7N9) internet pages: general information, epidemiological updates, prevention, advice to travellers, vaccination, clinical guidance and links to WHO web sites.[9–12] Prevention information was further categorized into four groups: hand hygiene, respiratory hygiene, food preparation and contact with poultry.

We were able to find government web sites for 32 of the 37 countries and areas (four of which were whole-of-government web sites only) using our search strategies. Of these, 13 countries and areas had dedicated and functioning A(H7N9)-related pages on 22 government agency web sites: Australia, China, Guam, Hong Kong (China), Japan, Macao (China), Malaysia, Mongolia, New Zealand, Palau, the Philippines, Republic of Korea and Singapore. Six countries and areas had dedicated web sites managed by government agencies: Australia, Hong Kong (China), Japan, Mongolia, New Zealand and two in Singapore.

Seventeen agencies from 12 countries and areas provided information regarding the official notification of the A(H7N9) incident, the actions taken and links to further detailed information on their web sites. Epidemiological updates of reported cases with A(H7N9), along with information such as numbers of cases identified, sex, age or occupation was provided by

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Table 1. **Avian influenza A(H7N9) information provided on web sites by countries and areas, Western Pacific Region, 30 April to 2 May 2013**

Countries and areas	Agency	Number of pages in English	Number of pages in own language(s)	General information	Epidemiological information	Prevention	Hand hygiene	Respiratory hygiene	Food preparation	Contact with poultry	Advice to travellers	Vaccination	Clinical guidance	WHO link
Australia	MOH	12		✓	✓	✓	✓		✓		✓		✓	✓
China	NHFPC	-	217	✓	✓	✓	✓	✓	✓			✓		
	MOA	3												
Guam	MOH	2		✓		✓	✓	✓	✓					
Hong Kong (China)	DOH	128		✓	✓	✓	✓	✓		✓	✓		✓	✓
	DOA	1		✓										
Japan	MOH	1	38	✓		✓	✓	✓	✓	✓	✓	✓		✓
	MOA	-	16											
Macao (China)	DOH	-	10	✓		✓	✓	✓	✓		✓		✓	
	DOA	-	63	✓		✓	✓	✓	✓		✓		✓	
Malaysia	MOH	33	13	✓	✓	✓	✓					✓		
	MOFA	61	1	✓	✓									
Mongolia	MOH	-	7	✓	✓	✓	✓		✓	✓	✓		✓	✓
	MOFA	-	1	✓	✓									
New Zealand	MOH	2		✓	✓	✓	✓		✓		✓			✓
Palau	MOH	3												✓
The Philippines	DOH	2		✓									✓	
Republic of Korea	MOH	-	1	✓										
Singapore	MOH	2		✓	✓	✓	✓	✓			✓			
	MOA	1		✓	✓	✓		✓	✓					
Total		**251**	**367**	**17**	**10**	**12**	**11**	**8**	**9**	**3**	**8**	**3**	**6**	**6**

D/MOA – Department/Ministry of Agriculture; MOFA – Ministry of Foreign Affairs; D/MOH – Department/Ministry of Health; NHFPC – National Health and Family Planning Commission

10 agencies from seven countries and areas (**Table 1**). The Singapore Government also uploaded case reports on their Consular web site aimed at foreign residents and incoming travellers.

Twelve agencies from 10 countries and areas provided information on prevention for A(H7N9). The most common prevention recommendations were for frequent hand washing (with two agencies also specifying that the concentration of alcohol in the hand cleanser should be more than 60%), respiratory hygiene such as covering the mouth when sneezing or coughing and food preparation recommendations including avoidance of raw or undercooked meat and eggs (**Table 1**). None of the web sites mentioned the importance of separating uncooked food from cooked food and kitchen utensils.

Eight agencies from seven countries and areas advised travellers returning from affected areas to monitor their health and seek medical attention if certain symptoms developed; a smaller number suggested that travellers avoid live/wet bird markets in affected countries. Two countries and areas referred to WHO advice that screening at points of entry or travel restrictions are not necessary (**Table 1**).

Clinical guidance information specific to A(H7N9) was provided by six agencies from five countries and areas (**Table 1**) that included advice on case management for general practitioners and clinicians, the criteria set for requesting laboratory tests from suspected cases, standard laboratory test procedures and contact information of local and national test centres.

Links to the WHO A(H7N9) resource web sites, including pages on clinical management,[13] technical guidance specific to virology and laboratory,[13] "Frequently Asked Questions,"[9] "Background and summary of human infection with influenza A(H7N9) virus,"[11] "Global Alert and Response"[16] and its subsection "Disease Outbreak News"[16] were provied on the web sites of six countries and areas.

Although we have provided a snapshot of the information being disseminated though the Internet for the A(H7N9) response, there are some limitations to our analysis. First, the search method used was not exhaustive, thus some relevant web sites and pages may have been missed. Also, the web sites that were accessed may have been updated since our assessment. To obtain updated information provided by these agencies, direct access to their web sites is strongly recommended.

The Internet is only one mechanism for risk communication, and not all people have equal access to the Internet. Some countries and areas may not have the capacity to build and maintain a web site or upload information in a timely manner for emerging events. Others may not want to duplicate efforts and instead rely on existing web sites. Nevertheless, the internet has become a commonly-used way of sharing information with the public that can be disseminated worldwide. The Internet is an inexpensive risk communication tool compared to traditional means such as printing pamphlets or posters or radio and television.

Our assessment, one month after the first cases were reported, revealed that 13 of 37 WHO Western Pacific Region countries and areas were providing information to the public through their government web sites, consisting mostly of information on the epidemiology of the event in China, prevention methods for avian influenza, clinical management and links to WHO web sites. We recommend that the countries that have not yet done so consider following the example of others in the Region in providing information about A(H7N9) (or links to other web sites with this information) on their web sites.

Conflicts of interest

None declared

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Epidemiologic update on the dengue situation in the Western Pacific Region, 2011

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Dengue is an emerging vectorborne infectious disease that is a major public health concern in the Asia and the Pacific. Official dengue surveillance data for 2011 provided by ministries of health were summarized as part of routine activities of the World Health Organization Regional Office for the Western Pacific. Based on officially reported surveillance data, dengue continued to show sustained activity in the Western Pacific Region. In 2011, Member States reported a total of 244 855 cases of which 839 died for a case fatality rate of 0.34%. More than 1000 cases were reported each from Cambodia, the Federated States of Micronesia, the Lao People's Democratic Republic, Malaysia, the Philippines, the Marshall Islands, Singapore and Viet Nam. Cambodia, the Federated States of Micronesia and the Marshall Islands reported higher activity relative to 2010. There continues to be great variability among the dengue-endemic countries and areas in the Region in the number of cases and serotype distribution. The continued high notification rate and complex dengue epidemiology in the Region highlight the need for information-sharing on a routine and timely basis.

Dengue, an emerging arboviral infection, continues to cause a substantial public health burden in the Asia and the Pacific. Thanks to continuous, and increasingly more reliable and systematic, dengue surveillance systems in many dengue-endemic countries in the Western Pacific Region, dengue has shown not only its high burden but also its complex epidemiology of seasonality, multiyear oscillations and varying age, gender and serotype distributions over time.[1–4] Substantial economic costs have also been associated with the disease at the household and overall economy levels,[5,6] highlighting the continued need to respond to this threat. The reported number of dengue cases have increased over the past decade; since 2007, more than 200 000 cases have been consistently reported in the Region annually.

In 2010, there were 353 907 dengue cases and 1073 dengue deaths reported from 24 of 37 countries and areas in the Western Pacific Region.[7] Countries that reported more than 1000 cases were Australia, Cambodia, the Lao People's Democratic Republic, Malaysia, the Philippines, Singapore and Viet Nam. Cambodia, the Lao People's Democratic Republic, Malaysia, the Philippines, Singapore and Viet Nam contributed 1070 of the reported 1073 deaths. Continuous and systematic dengue surveillance is variable and limited among the Pacific island countries and areas; however, dengue cases continued to be reported. In 2010, there were fewer dengue notifications relative to 2009; relatively high notification rates were reported from American Samoa (77/100 000 population), French Polynesia (92/100 000 population) and Vanuatu (78/100 000 population). Dengue surveillance is not conducted in Papua New Guinea but circulation of the virus there is well known given the importation of cases into Australia.[8]

Based on officially reported national surveillance data, the World Health Organization (WHO) Regional Office for the Western Pacific communicates the latest annual regional dengue situation.

METHODS

This report provides a descriptive summary of dengue cases reported in 2011 from indicator-based surveillance systems from countries and areas in the Western Pacific Region.

Further data are provided from Australia, Cambodia, the Lao People's Democratic Republic,

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Table 1. **Dengue case definitions, laboratory sampling and testing methods used for surveillance in Cambodia, the Lao People's Democratic Republic, Malaysia, the Philippines, Singapore, Viet Nam and Australia, 2011**

Country	Case definition		Laboratory sampling and testing method
	Clinical criteria*	Laboratory confirmation	
Cambodia	2009 dengue case classification†	No	5 sentinel sites send maximum of 5 samples per week for testing, focusing primarily on children. Confirmation is based on enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) and/or virus isolation.
Lao People's Democratic Republic	2009 dengue case classification†	No	A proportion of dengue cases, such as ad hoc outbreak specimens, are tested by ELISA.
Malaysia	Acute onset of high fever ≥ 2–5 days with ≥ 2 of following: headache, retro-orbital pain, myalgia, arthralgia, rash and mild haemorrhagic manifestation	No	A proportion of dengue cases are tested: detection of dengue IgM/IgG from serum; ≥ 4-fold rise in IgG/IgM antibody titres to dengue virus antigen(s) in paired serum samples; isolation of dengue virus; detection of viral sequences by PCR.
Philippines	Acute onset of fever 2–7 days with ≥ 2 of following: headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, leucopenia	No	A proportion of dengue cases, such as ad hoc outbreak and cluster specimens, are tested by serology (IgM), and a limited number by PCR.
Singapore	Acute onset of fever lasting 2–7 days with ≥ 2 of following: headache, backache, myalgia, rash, retro-orbital pain, bleeding, leucopenia	Required	All clinically diagnosed cases are laboratory tested and only those positive by serology (IgM) or PCR/NS-1 are registered.
Viet Nam	2009 dengue case classification†	No	A proportion of dengue cases are tested through serology and a limited number by virus isolation.
Australia	Fever, headache, arthralgia, myalgia, rash, nausea and vomiting	Required	All clinically diagnosed cases are laboratory tested and only those confirmed by the following method are registered: isolation/detection of dengue virus OR IgG seroconversion or significant increase in antibody level or ≥ 4-fold rise in titre to dengue virus OR detection of dengue virus-specific IgM in cerebrospinal fluid OR detection of dengue virus-specific IgM in serum

* Only the minimum criteria required for fulfilling a clinical dengue case definition are included here; additional signs and symptoms required for more severe forms (e.g. dengue haemorrhagic fever, dengue shock syndrome) are not listed here

† A probable dengue case is defined as any case with fever and two or more of the following: nausea, vomiting; rash; aches and pains; positive tourniquet test; leucopenia; any warning sign. A case with warning signs are defined as a clinically diagnosed case with any of the following warning signs: abdominal pain or tenderness; persistent vomiting; clinical fluid accumulation; mucosal bleed; lethargy, restlessness; liver enlargement >2cm; increase in hematocrit concurrent with rapid decrease in platelet count. Severe dengue is defined as severe plasma leakage leading to any of the following: shock; fluid accumulation with respiratory distress OR severe bleeding as evaluated by clinician OR severe organ involvement of liver (aspartate amino transferase or alanine amino transferase ≥1000), central nervous system (impaired consciousness) or heart and other organs.

Malaysia, the Philippines, Singapore and Viet Nam; their dengue surveillance systems, case definitions, laboratory sampling methodologies and serotype data are described (**Table 1**). A brief summary of the dengue outbreaks in the Federated States of Micronesia and the Marshall Islands is included.

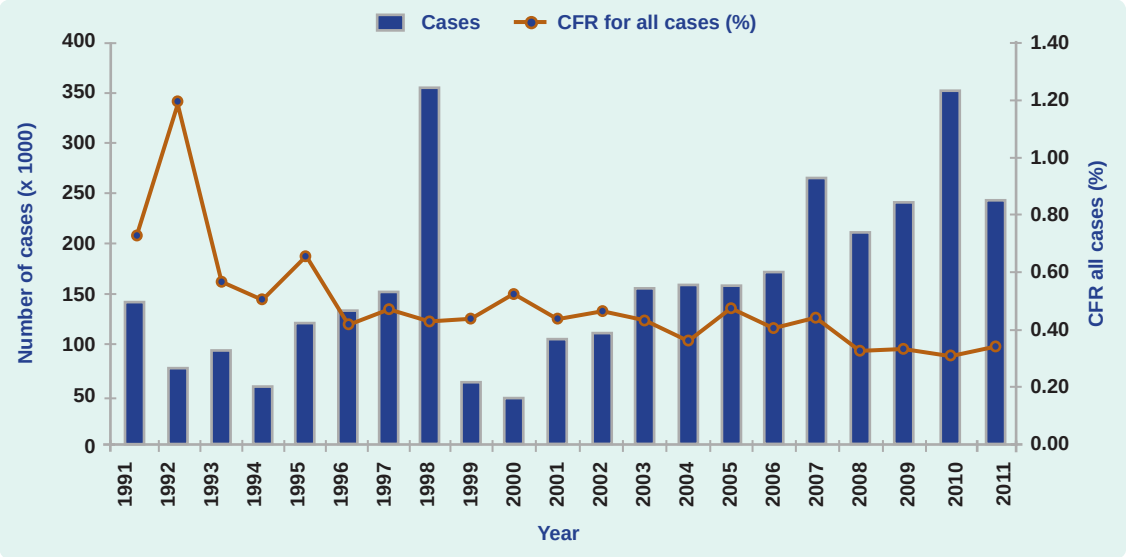
RESULTS

Dengue Situation in the Western Pacific Region

In 2011, Western Pacific Member States reported a total of 244 880 cases of which 839 died for a case fatality rate (CFR) of 0.34% (**Figure 1**). In the Asia subregion, both the notification rate and the absolute number of reported dengue cases were highest in the Philippines (**Table 2**). Although reporting was not complete for the Pacific subregion, more than 1000 cases were reported from the Marshall Islands and the Federated States of Micronesia in late 2011 (**Table 2**). In New Zealand, 42 cases were reported in 2011 with 41 of these travelling overseas during the incubation period of the disease; seven of these cases (17%) were reported from Thailand, Indonesia and Malaysia.

Among dengue-endemic countries with routine dengue surveillance and reporting systems (and

Figure 1. **Number of reported dengue cases and case fatality rates in the Western Pacific Region, 1991 to 2011**



* Source: World Health Organization Western Pacific Regional Office.

Note: Dengue surveillance and reporting systems vary by country.

Table 2. **Cases of dengue, including imported cases, and dengue-attributed deaths in the Western Pacific Region, for 2011**[*]

Countries/territories[†]	Cases	Notification (per 100 000)	Deaths	Case fatality rate (%)	Population (per 1000)
Asia subregion					
Brunei Darussalam	25	6.16	0	0	406
Cambodia	15 980	119.29	73	0.46	13 396
China	124	0.01	0	0	1 370 537
Hong Kong (China)	30	0.42	0	0	7 068
Japan	104	0.08	0	0	128 056
Republic of Korea	72	0.15	0	0	48 875
Lao People's Democratic Republic	3 905	63.72	7	0.18	6 128
Macao (China)	3	0.54	0	0	552
Malaysia	19 884	70.38	36	0.18	28 251
Mongolia	0	0.00	0	0	2 780
Philippines	125 975	134.00	654	0.52	94 013
Singapore	5 330	102.82	6	0.11	5 184
Viet Nam	69 680	81.00	61	0.09	86 025
Total for subregion	**241 112**	**13.46**	**837**	**0.35**	**1 791 271**
Pacific subregion					
Australia	820	3.67	0	0	22 342
Cook Islands	0	0.00	0	0	23
Fiji	245	28.69	0	0	854
French Polynesia	12	4.46	0	0	269
Marshall Islands	1 257	2327.78	0	0	54
Federated States of Micronesia	1 024	994.17	2	0.20	103
New Caledonia	1	0.41	0	0	246
New Zealand	42	1.01	0	0	4 143
Palau	334	1590.48	0	0	21
Vanuatu	33	14.10	0	0	234
Total for subregion	**3 768**	**13.32**	**2**	**0.05**	**28 289**
TOTAL	**244 880**	**13.46**	**839**	**0.34**	**1 819 560**

Source: World Health Organization Regional Office for the Western Pacific

* Dengue surveillance and reporting systems vary by country.

† The following countries and areas did not report dengue data: American Samoa, Guam, Kiribati, Nauru, Niue, the Commonwealth of the Northern Mariana Islands, Papua New Guinea, Pitcairn Islands, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, and Wallis and Futuna.

Table 3. **Reported number of dengue cases, deaths, and case fatality rates (CFRs) from Cambodia, the Lao People's Democratic Republic, Malaysia, Philippines, Singapore, Viet Nam and Australia, 2007 to 2011***

Country	2007			2008			2009			2010			2011		
	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)
Cambodia	39 851	407	1.02	9 542	65	0.68	11 699	38	0.32	12 500	38	0.30	15 980	73	0.46
Lao People's Democratic Republic	4 943	4	0.08	4 149	21	0.51	7 214	12	0.17	22 929	46	0.20	3 905	7	0.18
Malaysia	48 846	98	0.20	49 335	112	0.23	41 486	88	0.21	46 171	134	0.29	19 884	36	0.18
Philippines	55 639	533	0.96	39 620	373	0.94	57 819	548	0.95	135 355	793	0.59	125 975	654	0.52
Singapore	8 826	24	0.27	7 031	10	0.14	4 497	8	0.18	5 363	6	0.11	5 330	6	0.11
Viet Nam	104 393	88	0.08	96 451	97	0.10	105 370	87	0.08	128 831	55	0.04	69 680	61	0.09
Australia	316	0	0	56	0	0	1 401	0	0	1 171	0	0	820	0	0
Total	**262 814**	**1154**	**0.44**	**206 692**	**678**	**0.33**	**229 486**	**781**	**0.34**	**352 321**	**1070**	**0.30**	**241 574**	**837**	**0.35**

Source: World Health Organization Regional Office for the Western Pacific

* Dengue surveillance and reporting systems vary by country.

Australia where the dengue vectors *Aedes aegypti* and *Aedes albopictus* are present and cases occur in North Queensland and the Torres Strait Islands), there has been sustained occurrence of dengue cases over the past five years (**Table 3**). Except for Cambodia, the number of reported cases in 2011 was less than that of 2010 for these countries.

Asia subregion

Cambodia

Under the National Dengue Control Programme, all government health facilities report all clinically suspected dengue cases, and other sites also report passively. In 2011, Cambodia incorporated the 2009 dengue case classification system (**Table 1)** and reported 15 980 cases (73 fatal) with a peak in week 29 (n = 854 cases) in July (**Figure 2**). Males made up a higher proportion of the reported adolescent and adult cases relative to females. Among 422 laboratory-tested cases from five sentinel hospitals, 245 (58%) were confirmed by enzyme linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) or virus isolation. While all four serotypes circulated, the predominant serotype based on PCR and/or virus isolation (n = 194) was DEN-1 (150 [77%] DEN-1, 36 [19%] DEN-2, 4 [2%] DEN-3 and 4 [2%] DEN-4).

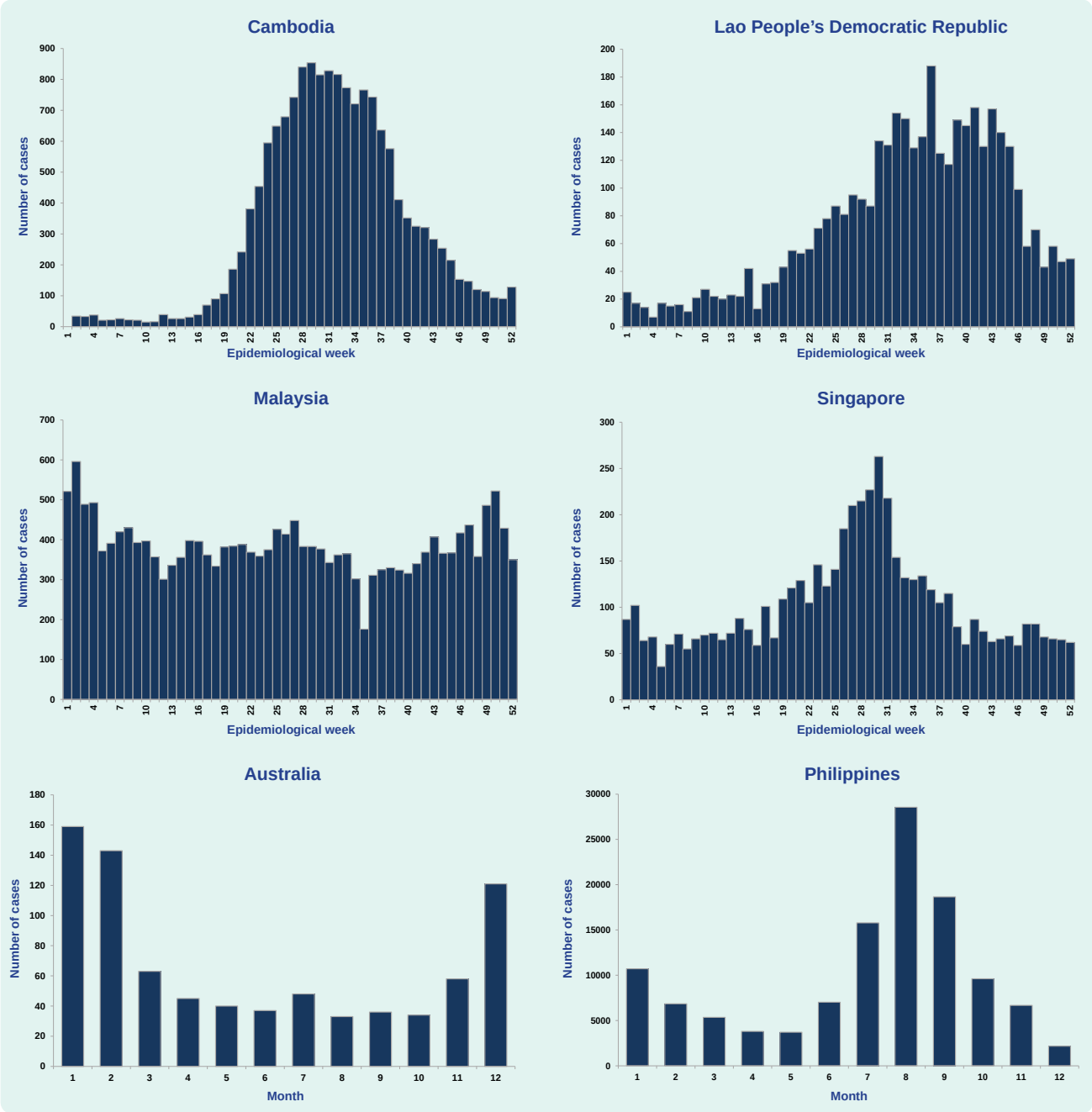
The Lao People's Democratic Republic

Under the National Surveillance System for Selected Notifiable Diseases (the Lao People's Democratic Republic Early Warning and Response Network), the 2009 dengue case classification system was incorporated in 2011 (**Table 1**), and all cases fulfilling the clinical criteria are reported. In 2011, the Lao People's Democratic Republic reported 3905 cases (seven fatal), with a peak in week 36 (n = 188 cases) in September (**Figure 2**). Among 111 laboratory-tested cases, 49 (44%) were laboratory confirmed by ELISA. IgM-positive specimens for which the time between date of onset and date of collection is less than five days and IgG negative were selected for serotyping; among eight serotyped cases, the predominant serotype was DEN-1 (6 DEN-1, 1 DEN-2 and 1 DEN-3).

Malaysia

Under the National Notifiable Infectious Diseases system, all clinically suspected dengue cases, including dengue haemorrhagic fever and dengue shock syndrome, are reported (**Table 1**). In 2011, Malaysia reported 19 884 cases (36 fatal). The highest number of cases (n = 596) was reported during week two in January; the weekly number of cases was overall low and stable throughout the year (**Figure 2**). Among 8105 laboratory-tested cases, 7301 (90%)

Figure 2. **Reported number of dengue cases by calendar week (Cambodia, the Lao People's Democratic Republic, Malaysia and Singapore) or month (Australia and the Philippines), 2011**



were confirmed by serology (IgG/IgM) or antigen detection (NS-1). Among the 235 serotyped cases, all four serotypes circulated (74 [32%] DEN-1, 60 [25%] DEN-3, 57 [24%] DEN-2 and 44 [19%] DEN-4).

The Philippines

Under the Philippines Integrated Disease Surveillance and Response, all clinically suspected and probable dengue cases are reported by the Department of Health's National Epidemiology Center (NEC) (**Table 1**). NEC is in the transition period for adopting new case definitions based on the 2009 dengue classification. In 2011, the Philippines reported 125 975 cases (654 fatal) with a peak in the month of August (n = 28 549) (**Figure 2**). Adolescent and adult males made up a higher proportion of the reported cases relative to females. Among 190 laboratory-tested cases, 190 (100%) were confirmed by serology (IgM) and a limited number by PCR. Among the 88 serotyped cases, the predominant serotypes were DEN-1 and DEN-3 (39 [44%] DEN-1, 38 [43%] DEN-3 and 11 [13%] DEN-2).

Singapore

Under the Infectious Diseases Management and Outbreak System, dengue cases are reported as dengue fever or dengue haemorrhagic fever cases. Laboratory testing occurs for all clinically suspected or probable cases, and only cases that are laboratory confirmed (by serology (IgM) or PCR/NS-1) are registered as dengue cases (**Table 1**). In 2011, Singapore reported 5330 cases (six fatal) with a peak in week 30 (n = 263 cases) in July (**Figure 2**). Adolescents and adult males made up a higher proportion of the reported cases relative to females. A proportion of the confirmed cases are serotyped; among the 712 serotyped cases, the predominant serotype was DEN-2 (549 [77%] DEN-2; 75 [10%] DEN-1, 61 [9%] DEN-3 and 27 [4%] DEN-4).

Viet Nam

Under the National Notifiable Disease Surveillance system, the 2009 dengue case classification system was incorporated in 2011, and all cases fulfilling the clinical criteria are reported (**Table 1**). In 2011, Viet Nam reported 69 680 dengue cases (61 fatal). Laboratory testing occurs for a proportion of clinically suspected dengue cases (7% by serology and 3% by virus isolation). Among 7249 laboratory-tested cases, 3262 (45%) were confirmed by serology or virus isolation. Among the 674 serotyped cases, the predominant serotype was DEN-1 (284 [42%] DEN-1, 217 [32%] DEN-2, 118 [18%] DEN-4 and 55 [8%] DEN-3).

Pacific subregion

Australia

Under the National Notifiable Diseases Surveillance System, all clinically suspected dengue cases that are laboratory-confirmed are reported (**Table 1**). In 2011, Australia reported 820 cases (zero fatal; personal communication, Phil Wright, Office of Health Protection, Australian Commonwealth Department of Health and Ageing) with a peak in the month of January (n = 158 cases) (**Figure 2**). The predominant serotype detected in North Queensland, among 69 locally acquired dengue cases, was DEN-2 (47 [68%] DEN-2, 13 [19%] DEN-4 and 9 [13%] DEN-1); 34 of 67 (51%) with gender information were male. Among 27 imported cases in North Queensland, nine were DEN-1, eight were DEN-3, seven were DEN-2, one was DEN-4 and two were unspecified; 17 of 27 (63%) were male (personal communication, Gregor Divine, Tropical Regional Services, Health Services and Clinical Innovation Division, Queensland Health).

The Federated States of Micronesia and the Marshall Islands

More than 2000 cases were reported from the Federated States of Micronesia and the Marshall Islands (**Table 1**). In Yap, a state of the Federated States of Micronesia, an outbreak started in September 2011 with more than 1000 clinically suspected cases (two deaths) reported by the end of the 2011 calendar year; the predominant serotype was DEN-2. The outbreak in the Marshall Islands started in October 2011 with more than 1000 clinically suspected cases (zero deaths) reported by the end of the 2011 calendar year; the predominant serotype was DEN-4.

DISCUSSION

In 2011, dengue continued to show high levels in the Western Pacific Region. While overall occurrence was lower than that of the previous year in the Asia subregion, Cambodia reported a considerably higher number of cases and CFR relative to 2010. In Cambodia, the Lao People's Democratic Republic, the Philippines and Singapore, peaks in dengue activity followed historic seasonal trends, occurring shortly after the onset of the rainy season from July to September, similar to that observed in 2010. In the Pacific subregion, the Federated States of Micronesia and the Marshall Islands experienced unusually large dengue outbreaks with more than 1000 cases each.

The dengue levels in the Region, which are variable by country, season, year and serotype, highlight the need for continuous surveillance and information-sharing. Rapid information-sharing at the local level for vector control and case-based response are essential to interrupt transmission. Routine and timely information-sharing at the regional level helps to improve the countries' awareness and understanding of the dengue situation in neighbouring countries or those with close trade/travel links (e.g. in the isolated Pacific island countries and areas, dengue activity has been associated with introductions from Asia).[9] Thus, sharing of regional information can feed into better-informed assessments

and responses by each country such as timely enhanced awareness activities. Since routine biweekly reporting of the regional dengue situation was initiated in late 2010,[10] information has also been regularly disseminated through wider public health surveillance networks, such as ProMED.[11] Regional surveillance data showing continued high level dengue levels led to the launch the Association of Southeast Asian Nations Dengue Day in June 2011 aimed at improving advocacy and community participation. The WHO Regional Office for the Western Pacific has been working on sharing additional surveillance data such as serotype and gender information that can further improve assessment activities; monitoring these data may inform of important changes in dengue epidemiology (e.g. who/where to target, herd immunity/susceptibility).[4,12] For instance, young adult males in several dengue-endemic countries in the Region continued to have a higher reported number of cases relative to their female counterparts.

These surveillance data have important limitations both in interpreting the actual burden of dengue (e.g. underreporting of mild cases) and trends over time (e.g. changes in disease awareness, reporting behaviour and surveillance systems). Australia and Singapore report laboratory-confirmed cases only, and dengue surveillance in Cambodia, the Lao People's Democratic Republic, Malaysia, the Philippines and Viet Nam is based on clinically suspected cases; therefore, the true number of incident dengue cases may be under- or over-reported. The proportion of true dengue cases among clinically suspected cases may differ across seasons due to differential physician awareness and reporting behaviour (e.g. during low versus dengue high season).

There have been notable changes in the surveillance systems in recent years. The new dengue case classification scheme was incorporated by Cambodia, the Lao People's Democratic Republic and Viet Nam in 2011; the Philippines surveillance system has been transitioning from a sentinel to an all-case reporting system since 2008. As dengue surveillance across countries differs, any comparison between countries should be interpreted with caution. CFRs are affected not only by clinical management but also by the reporting behaviours of clinicians, case definitions, follow-up and verification procedures. Sampling schemes for laboratory confirmation differ across countries and may not be systematic, limiting the interpretability of the reported serotype distribution. Due to late/incomplete reporting, these data are provisional and some countries will have final figures that are different from those reported here.

While acknowledging these limitations, as dengue epidemiology continues to evolve in the Region, at times unpredictably, there will continue to be a need for region-wide sharing of dengue data on a routine, timely basis. A dengue vaccine may become a reality in the near future, and there is even more reason to have continuous, reliable and systematic dengue surveillance to assist in evaluation of the vaccine once it is launched. Enhancement or implementation of dengue surveillance can act as an entry point for countries where surveillance capacities are limited for endemic infectious diseases, and such activities are in line with WHO Regional Office for the Western Pacific's Asia Pacific Strategy for Emerging Diseases framework to strengthen national capacities for surveillance and response. Even in countries where dengue is not currently endemic (e.g. Japan), the ever-increasing importation of cases signifies the importance of monitoring and sharing dengue information across the Region.[13] While dengue continues to burden our Region, we hope that regional surveillance and information-sharing can contribute to countering the threat.

Conflicts of interest

None declared.

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None.

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Western Pacific Surveillance and Response Instructions to Authors

ABOUT WPSAR

The aims of WPSAR are:

1. to provide an open access journal to publish articles on the surveillance of and response to public health events and emergencies in the WHO Western Pacific Region and in areas with relevance to the Western Pacific Region; and
2. to build capacity in communicating epidemiological and operational research within the WHO Western Pacific Region.

Our objectives are:

1. to provide a platform for people working in surveillance and response in the Western Pacific Region to share their scientific and operational findings;
2. to publish a broad range of articles not limited to conventional research articles:
   - to disseminate short reports on outbreak investigations;
   - to publish analyses of surveillance data on communicable diseases;
   - to encourage the publication of evaluations of new and existing surveillance systems;
   - to promote the use of risk assessment for public health by facilitating risk assessment articles;
   - to support preparedness and response to public health events and emergencies through the dissemination of lessons learnt from such events; and
3. to build capacity in communicating epidemiological and operational findings in the Western Pacific Region through pre-submission assistance.

Scope

WPSAR covers all activities related to the surveillance of and response to public health events and emergencies, with a focus on topics that are relevant to the Western Pacific Region. Public health events may be acute or ongoing and can fall under any of the following areas: communicable diseases, natural disasters, food safety, bioterrorism, and chemical and radiological events. Other events and topics may also be considered. Response activities include those for acute events, e.g. responding to natural disasters, or for response to cases or epidemics of disease.

Why publish in WPSAR?

WPSAR is not limited to conventional research. It publishes a broad range of articles, including short outbreak investigation reports, lessons from the field, analyses of surveillance data, evaluations of surveillance systems and risk assessments for public health events. There are limited opportunities to publish these types of articles in other journals. We also accept the more traditional original research, perspectives and case reports/case series articles.

WPSAR is an open access journal, meaning it is free of charge for both readers and authors. It is also a continuous publication, which means articles are published as soon as they have completed the review and editing process.

WPSAR accepts all articles that fit the scope of the journal and that meet the minimum publication standards. We are especially interested in field epidemiology and operational research.

WPSAR also aims to build capacity in scientific writing and encourages submissions from authors with little or no experience in publishing in peer-reviewed journals. The Coordinating Editor often works with new authors on their submissions to ensure that articles fit the scope of WPSAR and meet the minimum standards for publication.

INSTRUCTIONS TO AUTHORS FOR ARTICLE WRITING AND SUBMISSION

WPSAR follows the guidelines of the *Uniform Requirements for Articles Submitted to Biomedical Journals by the International Committee for Medical Journal Editors* (ICMJE).

Formatting guidelines

Please submit your article in a Microsoft® Office Word file or a compatible file in English. Double-spaced, 12-point Arial font should be used to format your article. Please remove all automatic formatting including automatic numbering and referencing before submitting.

The format of the article will depend on the article type. Please see below for specific instructions per article type.

Outbreak Investigation Report

A short article describing a field or outbreak investigation including how it was detected, investigated and controlled. Rapid risk assessments undertaken during these investigations are also encouraged. These articles may be considered for rapid publication.

- Structured article with an abstract of ≤ 250 words and sections for introduction, methods, results and discussion
- Structured abstract with sections for objective, methods, results and discussion
- Word limit: ≤ 1500 words
- ≤ 15 references
- ≤ 2 figures/graphs/pictures

More comprehensive investigations can be submitted as Original Research.

Surveillance Report

A summary and interpretation of surveillance data over a given period of time. A description of the surveillance system and the limitations of the data collected must be included.

- Unstructured abstract of ≤ 250 words
- Word limit: ≤ 2000 words
- ≤ 15 references
- ≤ 10 figures/graphs/pictures

Surveillance System Implementation/Evaluation

An article describing the implementation of a new surveillance system or an evaluation of an existing surveillance system used to detect public health events.

- Unstructured abstract of ≤ 250 words
- Word limit: ≤ 2000 words
- ≤ 15 references
- ≤ 3 figures/graphs/pictures

Risk Assessments

An article detailing a risk assessment of a public health threat or event.

- Structured article with an abstract ≤ 250 words and sections for introduction (including risk question/s), risk assessment methodology, results, discussion and recommendations
- Structured abstract with objectives, method, results and discussion
- The results should include an assessment and/or characterization of the hazard, exposure and context, as well as the level of risk or risk characterization. The limitations must also be included. Risk management may be included in the discussion.
- Word limit: ≤ 3000 words
- ≤ 30 references
- ≤ 3 figures/graphs/pictures

Original Research

Original research articles may include epidemiological studies including outbreak investigations.

- Structured article with an abstract of ≤ 250 words and sections for introduction, methods, results and discussion
- Structured abstract with objective, methods, results and discussion
- Word limit: ≤ 3000 words
- ≤ 40 references
- ≤ 5 figures/graphs/pictures

Lessons from the Field

An article describing a problem faced in field epidemiology or during a public health event and the experience in trying to overcome the problem.

- Structured article with an abstract ≤ 250 words and sections for problem, context, action, lesson(s) learnt or outcome and discussion
- Structured abstract with the headings of problem, context, action, lesson(s) learnt and discussion
- Word limit: ≤ 2000 words
- ≤ 15 references
- ≤ 3 figures/graphs/pictures

Perspectives

An unstructured article discussing an issue regarding the surveillance of and response to public health events. The scope of the discussion must be clearly defined.

- Word limit: ≤ 1000 words
- ≤ 10 references
- ≤ 1 illustration

Case Report or Case Series

An unstructured article describing an unusual case or series of cases of public health significance. Subheadings may be used to increase the readability of the article.

- Unstructured abstract of ≤ 250 words
- Word limit: ≤ 2000 words
- ≤ 15 references
- ≤ 3 figures/graphs/pictures

Regional Analysis

An article providing an analysis of a topic for the Western Pacific Region, typically authored by WHO staff as part of their routine work on behalf of Member States. Regional Analyses do not undergo peer review.

Letter to the Editor

A letter commenting on a previously published article OR a letter commenting on the theme of the issue. Letters do not undergo peer review.

- Word limit: ≤ 500 words
- ≤ 5 references
- ≤ 1 illustration

News, Meeting and Conference Reports

News items and meeting and conference reports do not undergo peer review. Please contact the Coordinating Editor at WPSAR@wpro.who.int if you intend on submitting such an article.

Illustrations

Refer to the article type for the limit on illustrations (figures/graphs/pictures). Please insert all illustrations at the end of the article with titles. Each illustration must be referred to in the text and must be understood on its own. Use Microsoft® Office Excel for graphs and Microsoft® Office Word for tables and diagrams. Additionally, please provide a Microsoft® Office Excel spreadsheet of the data used to create a graph. Footnotes should be placed under the illustration and should use the following symbols in superscript format: *, †, ‡, §, ‖, **, ††, etc.

References

Reference the most recent and relevant publications. Please use the Vancouver referencing style with in-text citations and a bibliography at the end of the text. Sample references can be viewed on the National Institutes of Health website.

Place the bibliography at the end of the article text and not as footnotes. Write journal names in full. Use superscript sequential numbering for citing references in the text. Place the number after any punctuation. For example:

> These results are consistent with the original study.[11]

Reference personal communication in the text only and include the person's full name and institution.

Caution should be used in referencing websites; it should be done only when their content has been substantially described in the article.

Peer review process

Every article is initially screened by the Editorial Team to ensure it fits the scope of the journal. All articles, with the exception of regional analyses, letters to the editor, news items and meeting and conference reports, then undergo external peer review by two reviewers. This blind peer review process ensures that the reviewer does not know the identity of the author(s) and the author(s) do not know the identity of the reviewer. Significant effort is made to make this process timely, but since it relies on the availability and cooperation of persons external to the journal, it can take considerable time.

Upon receipt of the reviews, the Coordinating Editor assesses the comments and recommendations made by the reviewers, and then decides on the outcome of the peer review process. One of four options will be chosen: accept submission, accept with revisions, submit for review, or decline submission. The corresponding author will be advised of this outcome.

If the article has been accepted or accepted with revisions are required, you will be invited to revise your article according to the reviewer comments. A separate MS Word document outlining how you addressed each of the reviewer comments is also required. You must indicate the page and paragraph numbers where the changes were made and should provide reasons for not making a suggested change. Both the changes and reasons will be assessed

against the reviewer comments by the Coordinating Editor and may require further clarification from the authors. Once all comments have been adequately addressed, the article will commence the publication process.

If the outcome of the review process is "submit for review", then the same process is followed. However, the resubmitted article and responses to the reviewer comments are sent back to the original reviewers for another round of peer review. You will be asked to respond to a second round of reviewer comments, which will again be assessed by the Coordinating Editor. Once both sets of reviewer comments have been adequately addressed, the article will commence the publication process.

The publication process comprises rigorous editing for content and style by an external technical editor, followed by layout and proofreading. Authors may be asked to provide further information or clarifications during these stages. An article is not formally accepted for publication until these stages have been completed and approval has been granted by the Editorial Team. The authors will also have an opportunity to approve the final proof prior to publication on the WPSAR website. The article will be batched with others in the next quarterly issue.

Authorship

As per the International Committee of Medical Journal Editors (ICMJE), all authors should have contributed significantly to the article through one or more of the following in each category A, B and C:

A

- Study design
- Data collection
- Data analysis
- Data interpretation

B

- Drafting the article
- Critically revising the article

C

- Final approval of the article for submission

Any other contributors may be listed in the Acknowledgements section.

Acknowledgements

Contributors who do not fulfil the authorship requirements may be acknowledged. Permission from all contributors in the acknowledgement section should be sought. We assume that permission has been granted and will not follow up with the authors to confirm.

Ethics and permissions

It is the responsibility of authors to gain appropriate ethics approval for their work. A statement of ethics approval obtained or an explanation of why ethics approval was not required should be included for all articles during the submission process.

License for publication

Prior to publication, all authors are asked to sign a licence to publish that grants exclusive copyright license to the World Health Organization.

Conflicts of interest

A conflict of interest is defined by ICMJE as "when an author or author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions". Conflicts of interest may be financial, institutional, research or personal. A relationship does not always represent a conflict of interest and does not necessarily preclude publication in WPSAR. All authors and reviewers will be required to state any potential conflicts of interest, which will be assessed by the Editorial Team.

Funding

Authors will be required to state the sources of funding for their work.

Photographs for cover

If authors have taken photographs that are relevant to their article, they may be submitted for consideration for publication on the cover of the issue. Submission of a photograph does not guarantee its publication.

Language

Articles should be written in English. Authors who require assistance with preparing their articles in English should contact WPSAR at WPSAR@wpro.who.int. Once published, all abstracts and most articles are translated into Chinese.

Article submission process

Submit articles to the Coordinating Editor through the online journal management system on the WPSAR website. When submitting the article, you will be requested to provide the following:

- a cover letter describing the article and why it should be published;
- a title page with:
  - the article title,
  - a short title,
  - a brief description of the article of ≤ 50 words,
  - ≤ 7 keywords,
  - full names of all authors and institutions,
  - full contact details of the corresponding author,
  - data in an MS Excel spreadsheet for any graphs
  - names and e-mail addresses of two suggested reviewers (optional but recommended);
- acknowledgements, conflicts of interest, ethics statement and funding information (attached as a separate file to ensure a blind review);
- an MS Word file or equivalent of the article; and
- a scanned copy of the WPSAR licence for publication signed by all authors.

With the online journal management system, you will be able to track the progress of your article through the editorial process. If you encounter any difficulties with this system, please refer to our *WPSAR online journal system – User guide for authors*.

Corrections

If authors of a published article become aware of any errors with the article, they should contact the Coordinating Editor at WPSAR@wpro.who.int. Corrections will be published online.

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