Enemy in our midst?

A Review of Leptospirosis
Epidemiology, Transmission and Risk Factors  See page 111

Risk of *Anopheles sinensis* as an Emerging Malaria Vector in Singapore  See page 128

Lassa Fever: Risk Assessment for Disease Importation into Singapore  See page 118

Plus

Risk of *Anopheles sinensis* as an Emerging Malaria Vector in Singapore  See page 128

Lassa Fever: Risk Assessment for Disease Importation into Singapore  See page 118
Our theme for this edition of ENB Quarterly is rodent-borne diseases. According to the US CDC, many infections can be directly or indirectly transmitted by rodents, especially rats. They include hantavirus pulmonary syndrome, haemorrhagic fever with renal syndrome, lassa fever, plague, rat bite fever, murine typhus and scrub typhus.

Our lead article reviews the epidemiology, transmission, and risk factors of leptospirosis. Despite being an under-reported disease, leptospirosis is now widely recognized as one of the more prevalent zoonoses worldwide. The main modes of transmission to humans are via water and soil contaminated with rat faeces or urine. Raising public awareness through health education should be a key intervention. The second article is a scientific contribution which provides the risk assessment for Lassa fever, an acute viral haemorrhagic fever. While the overall risk of an imported case of Lassa fever into Singapore is considered to be low, vigilance for emerging infections is key. In a world increasingly connected by trade and travel, it is important that we remain quick to detect, respond to, and contain such threats.

In addition to rodent-borne diseases, we have a scientific contribution that looks at the role of Anopheles sinensis mosquito species in Singapore. In 2009, three clusters of P. falciparum malaria cases were reported and An. sinensis was the predominant Anopheline found in two of the affected areas in Singapore. Further research done showed that An. sinensis was equally competent in transmitting P. vivax. While there has not been reports of indigenous cluster of cases in recent years, this study has revealed that An. sinensis could pose a malaria threat to urban Singapore if the risks are not managed.

We hope you enjoy reading this epidemiological bulletin as much as we did putting it together. Thank you for your continued support. Your feedback is always welcome!

Steven
Enemy in our midst?
A Review of Leptospirosis Epidemiology, Transmission and Risk Factors

Alvin Kuo Jing Teo*, Alexandra Bramley*, Zul-Azri As-Saad Sa’at, Charlene Judith Fernandez, Wenya Charmaine Chng, Brian Zi Yan Tan, Li Yang Hsu, Junxiong Pang, Steven Peng-Lim Ooi

1Saw Swee Hock School of Public Health, National University of Singapore, 2Communicable Diseases Division, Ministry of Health, 3Agri-Food & Veterinary Authority of Singapore, 4National Centre for Infectious Diseases

*Joint first authors

INTRODUCTION

Leptospira spp. are mobile, slow-growing, obligate aerobic spirochetes that measure 0.1 μm in diameter. The use of genetic tools has resulted in the modern reclassification of Leptospira into more than 19 species, which can be further categorized into at least 24 serogroups and 250 serovars. The species that are associated with both animal and human disease other than L. interrogans are L. borgpetersenii, L. santarosai, L. noguchii, L. weilii, L. kirschneri, and L. alexanderi. Other known species are either commonly associated with animals only or are saprophytic in nature.

Over 100 years ago, scientists from both Europe and Japan identified Leptospira spp. as the causative agent of Weil's disease, a term currently used to describe severe leptospirosis. Leptospirosis – despite being an under-reported disease – is now widely recognized as the most prevalent zoonosis worldwide.

The disease is approximately 10 times more prevalent in tropical climates compared to temperate climates. The World Health Organization's (WHO) Leptospirosis Burden Epidemiology Group estimated that there were 1.03 million cases with 58,900 deaths worldwide annually, resulting in approximately 2.9 million Disability Adjusted Life Years (DALYs) lost each year.

CLINICAL MANIFESTATIONS

Humans

The clinical course of leptospirosis is variable, and most cases are mild, self-limiting or subclinical. The incubation period ranges from 2-26 days (average 10 days). Fever, chills, headache, severe myalgia, conjunctival suffusion, anorexia, nausea, vomiting, and prostration are common features. Leptospirosis can also be complicated by jaundice and renal failure (Weil’s disease), pulmonary haemorrhage and acute respiratory distress syndrome. Other complications include uveitis, optic neuritis, rhabdomyolysis, myocarditis and peripheral neuropathy.

A study done by Bal and colleagues showed that the Leptospira can be detected in the urine via Polymerase Chain Reaction (PCR) several weeks after the onset of illness. Leptospira antibodies can be detected in blood 5-7 days after the onset of symptoms. The serological gold standard test is microscopic agglutination test (MAT) which is difficult to perform, hence Leptospira IgM Enzyme-Linked Immunosorbent Assay (ELISA) are commonly done in clinical labs for diagnosis. Leptospira can also be cultured from clinical samples (e.g. blood and urine), but this generally requires special culture media and the sensitivity is not high.
Animals
There are different animal species that can act as both maintenance and incidental hosts of various *Leptospira* spp. Animals can be ac clinical as maintenance hosts or become sick by becoming an incidental host. Small mammals (i.e. dogs, monkeys, rats and squirrels) are maintenance hosts and are able to spread leptospirosis to domestic livestock, household pets, and humans by shedding of the bacteria through urine. Transmission is either through direct contact or by contact of contaminated soil and water.

A decade-long study in Switzerland showed that dogs diagnosed with leptospirosis had a 10% risk of mortality. All dogs suffered from acute kidney injury and had clinical manifestations that were similar to human leptospirosis, including 8.7% that presented with the involvement of the liver, lungs, and blood.

Environment
A recent systematic review reported that contact with contaminated water due to floods and recreational activities such as swimming in lakes, rivers and ponds, fishing, kayaking, surfing, canoeing, rafting, and triathlons were associated with increased risk of leptospirosis. For example, the Eco-Challenge in Sabah in 2000 resulted in 42% of those who swam in contaminated water being infected with *Leptospira* spp.

Occupational environments, especially in the developing countries, that may have direct or indirect contact with rodent urine, such as those of sewage workers (odds ratio [OR] 3.0), garbage collectors (OR 4.0), and agricultural workers (OR 2.5) demonstrated an increased risk of leptospirosis infection. Manual labourers tend to be more prone to skin abrasions, and this may increase the risk of infection. Increased shedding of the pathogen into the environment results in a heightened risk of both occupational and non-occupational exposure to *Leptospira* spp. in both rural and urban settings.

Increased rates of leptospirosis occur in tropical countries, especially after extreme rainfall. *Leptospira* spp. can remain infectious in wet soil for 43 days and approximately 20 months in freshwater.

---

**Figure 1. Reported human leptospirosis cases in Singapore, 2017 (n=53)**
reported more than 30,000 cases between 2011 and 2016, mainly attributed to heavy rainfall, flooding, recreational activities, poor hygiene and increased rat population. Singapore – a tropical country with a warm and humid climate – is optimal for Leptospires. However *Leptospira* spp. can also be found in temperate climates, sporadically causing human disease in agricultural workers in particular.24

Mwachui and co-workers stated that the increased risk of leptospirosis among residents in the rural areas compared to residents in the urban areas was likely independent of geographical location.18 This was likely due to the larger number and diversity of peridomestic animals in the urban environment that act as potential sources for leptospirosis.25,26 Epidemics in urban areas are attributable to rats in slums and sewer systems that are frequently flooded during heavy storms, increasing the risk of infection through direct contact with rat urine-contaminated water and soil.20 With the prediction of the world’s slum population doubling to 2 million by 203027, urban epidemics will likely continue to increase.

**Animals**

*Leptospira borgpetersenii* (mainly host-to-host transmission) and *Leptospira interrogans* (mainly via contaminated water) are the two most common pathogenic species causing leptospirosis in animals.28 Generally, all animal pathogenic strains can be transmitted and be pathogenic to humans.29

Rats, and other rodents are known to be maintenance hosts for *Leptospira* spp. Studies have shown that these animals are chronic carriers of *Leptospira* spp., commonly not manifesting any signs of infection when examined.30 In particular, rats are the main reservoir hosts for *L. interrogans* serovar icterohaemorrhagiae which is one of the most virulent *Leptospira* spp. in humans.31 Rats are deemed to be the most important animal host for the spread of leptospirosis due to the fact they contaminate both food and water.32

**Companion dogs**

There is increasing awareness that companion dogs are a potential source of leptospirosis. A study conducted in Switzerland showed increasing canine infections and the need to heighten awareness and promote early diagnosis of leptospirosis among the dog owners.18,33 Meeyam et al reported a 11% seroprevalence of *Leptospira* antibodies, of serogroups not covered by existing vaccines, among dogs randomly selected from the Small Animal Hospital in Chiang Mai, Thailand.34 The study observed playing in sewage, staying outdoors more than 50% of the time, and consuming raw meat increased the risk of leptospirosis antibodies in dogs.

The Agri-Food & Veterinary Authority (AVA) of Singapore reported a rise in the number of suspected leptospirosis cases in dogs in 2016 that was associated with a daycare centre for dogs.35 Infected dogs might exhibit signs such as fever, vomiting, diarrhoea, loss of appetite, and changes in frequency/amount of urination.36 The risk of leptospirosis in dogs can be reduced by eliminating the potential source of infection, and through annual vaccination.35-37

Vaccination is a key strategy to prevent disease in companion dogs and reduce the risk of transmission to humans, but protection is serovar-specific.26,38 At the current time, vaccines containing serovars *L. interrogans*, *L. Canicola*, *L. Grippotyphosa* and *L. Pomona* are available in Singapore for vaccination of dogs against leptospirosis. Pet owners should actively practice hygiene measures and wash hands with soap and water after handling dogs’ excreta. Protective coverings such as gloves should be worn when dealing with the excreta of infected dogs.

**Stray dogs**

Similar to companion dogs, stray dogs pose risks of harboring and transmitting leptospirosis. In 2009, Jittapalapong and colleagues reported an 83.5% seroprevalence of *Leptospira* antibodies among 230 stray dogs that they examined in Bangkok.39 Akin to the findings in Bangkok, studies in Mexico and Trinidad and Tobago also indicated that dogs were potential sources of leptospirosis in humans.40,41 In the Pacific Islands, New Caledonia, Gay and colleagues suggested that dogs were vectors for leptospirosis and a prominent link between environmental reservoirs and humans.42

Currently, there are an estimated 7,000 stray dogs in Singapore.43 Whilst no evidence of stray dogs being a prominent source of *Leptospira* infections in Singapore is reported, their potential role as a bridge between other reservoirs and susceptible humans cannot be ruled out.

**HUMAN LEPTOSPIROSIS CASES IN SINGAPORE**

Prior to 28 September 2016, human leptospirosis was not a notifiable disease in Singapore. Notifications were sporadic and done voluntarily by clinicians and/ or hospital laboratories. The Ministry of Health (MOH) reviewed the list of notifiable diseases in 2016, and leptospirosis was included since then. A total of 53 lab confirmed cases were notified in 2017 (Figure 1). 32 were Singapore residents, comprising 19 local and 13 imported cases. The remaining 21 cases were 15 foreigners who worked in Singapore and six foreigners
who came to Singapore for medical treatment. Of the 15 foreigners who worked in Singapore, ten were local cases and five were imported cases. A total of three deaths were reported, of which two were classified as local cases and the remaining one as imported.

HUMAN-TO-HUMAN TRANSMISSION

Human to human transmission is possible but rare, with a case report in 1988 purporting sexual transmission of Leptospira spp. Another case report described transmission through lactation, while others showed probable transplacental transmission causing stillbirth.

HUMAN LEPTOSPIROSIS PREVENTION MEASURES

Leptospirosis is preventable, and measures should be based on local risk and epidemiology factors. Effective risk communications and health education for at-risk groups — those travelling to other endemic areas, participating in outdoor recreational activities, and those working or living in areas with increased risk — are essential components to prevent and control the disease. Mitigation strategies include using protective clothing and footwear, covering open wounds, and using chemoprophylaxis.

Pre-exposure prophylaxis in humans

A clinical trial comparing prophylaxis with doxycycline 200mg/week with placebo was conducted in 1982 among United States of America soldiers deployed for jungle training, and a significantly lower attack rate (0.2% vs 4.2%) was reported in the intervention group. In another high-endemic setting, the disease attack rate was significantly lower (3.1% vs 6.8%) in the doxycycline group, indicating that doxycycline prophylaxis might reduce morbidity and mortality during outbreaks. A retrospective study conducted amongst athletes who participated in the Eco-Challenge-Sabah also reported that doxycycline prophylaxis before and during the race was protective (RR 0.4, 95% CI 0.1 – 1.1) against leptospirosis infections.

Leptospiral vaccines for humans are available only in a few countries. Spirolept®, a monovalent (Icterohaemorragiae) vaccine, is currently available in the French market, but it is restricted to individuals working in high-risk areas such as sewer workers. In Cuba, Vax-Spiral®, a trivalent (Icterohaemorragiae, Canicola, Pomona) vaccine was included in the National Leptospirosis Prevention and Control Program in 1998, with a consequent decrease in disease incidence. However, immunity induced by the vaccines is serовар-specific and provides a relatively short protection period. Furthermore, the efficacy of currently available killed, whole-cell vaccine is limited.

Post-exposure prophylaxis in humans

The effect of doxycycline 200mg single dose was investigated in Thailand after a flood in 2014. The non-randomized trial reported a protective effect of doxycycline single dose prophylaxis for leptospirosis infection among participants with lacerations and who were exposed to flood water. Likewise, the use of doxycycline after exposure to contaminated water was examined in Brazil, and a protective effect was suggested, although the results were not statistically significant. However, the protective effect of chemoprophylaxis was not demonstrated in a case-control study conducted in India.

The evidence for doxycycline prophylaxis, in particular post-exposure, is inconclusive. The potential benefit of chemoprophylaxis must be weighed against other considerations such as the risk of adverse reactions. Regular use of doxycycline was associated with increased risk of gastrointestinal side effects. Notwithstanding this, chemoprophylaxis for high-risk individuals was found to be cost-effective in preventing the serious health complications of leptospirosis. The US Centers for Disease Control and Prevention (CDC), advised the use of doxycycline 200mg per week through the period of potential exposure for high-risk individuals. The use of doxycycline prophylaxis is also recommended by a few other leptospirosis-endemic countries, should chemoprophylaxis is considered.

CONCLUSION

Leptospirosis is an underreported infection that nonetheless poses a significant public health burden, resulting in an estimated 2.9 million DALYs worldwide. Occupational groups that are at risk of skin abrasions, such as manual labourers and construction workers, faced an increased risk of leptospirosis. Recreational activities have also been linked to leptospirosis infections, and it is plausible that a similar link exists here in Singapore.

Further epidemiological studies may help us to establish risk factors and modes of transmission in Singapore. The evidence for pre- and post-exposure prophylaxis as well vaccination against leptospirosis remains inconclusive, and therefore preventable measures such as public health awareness through education should be the key intervention.
Leptospirosis is a neglected infectious disease and the local epidemiology – especially in terms of respective risk factors and transmission patterns related to human, animals and environment – requires more research in order to develop evidence-based public health interventions where necessary.

ACKNOWLEDGEMENT

We are grateful to our National Environment Agency colleagues at the Environmental Health Institute and Environmental Public Health Division for their comments to the paper.

REFERENCES


Lassa Fever: Risk Assessment for Disease Importation into Singapore

Olivia Oh, Marc Ho, Jeffery Cutter, Lyn James, Derrick Heng

Public Health Group, Ministry of Health

INTRODUCTION

Lassa fever is an acute viral haemorrhagic fever (VHF) caused by the Lassa virus of the Arenavirus family. A 1955 to 1956 outbreak of encephalomyelitis in Sierra Leone was postulated to have had represented the first recorded clinical description of Lassa fever. The virus was, however, not identified until 1969 when it was isolated from the blood of an American missionary nurse medically evacuated to New York from Jos, Nigeria.\textsuperscript{1} She had become ill after caring for two other nurses who had died from a hitherto unrecognised haemorrhagic fever.\textsuperscript{2} The transmission chain was eventually traced to an obstetric patient who had sought treatment for a septic abortion, and the virus was named after the village, Lassa, where she had resided.\textsuperscript{3}

Lassa fever has an incubation period of around 10 days, with a range between two and 21 days. Approximately 80\% of infected persons develop mild or no clinical symptoms. Early signs and symptoms are non-specific and include fever, headache and general malaise, followed by sore throat, nausea, vomiting, and diarrhoea in some cases. Less than one-third of Lassa fever patients develop haemorrhage, however bleeding is a predictor of disease severity and a significantly higher risk of death. The overall case-fatality rate for Lassa fever is around 1 to 2\%, but can reach up to 20\% in hospitalised cases, reflecting the consequence of severe disease. In fatal cases, death usually occurs within 14 days of disease onset.\textsuperscript{4}

New-onset deafness of varying severity is a common feature in the convalescent phase, and occurs in approximately one-third of Lassa fever patients. Hearing loss is permanent in many cases, and there appears to be no correlation between severity of infection and development of deafness. Furthermore, Lassa fever is exceptionally severe in pregnant women, with fatality rates of 30\% in the last trimester, and 50\% for women who had delivered within one month of illness. This contrasts with a 13\% mortality rate among non-pregnant women hospitalised with severe disease. Spontaneous abortion is a serious complication of Lassa fever with foetal mortality rates ranging from 75\% to 95\%, depending on the stage of pregnancy.\textsuperscript{6,7}

The current treatment of choice for Lassa fever is intravenous ribavirin. Administration of intravenous ribavirin within the first six days of disease onset has been shown to significantly reduce the mortality rate of cases with severe disease. Unfortunately, Lassa fever is often misdiagnosed as influenza, typhoid or malaria in the early stages, resulting in many patients failing to receive appropriate medical treatment in time.\textsuperscript{4} Nevertheless, case-fatality has been shown to still be reduced in patients given ribavirin at day seven or later to a lesser extent.

Oral ribavirin is less efficacious compared to the intravenous form.\textsuperscript{8} It is also frequently given after potential exposure to Lassa virus. However, no clinical data exist on the efficacy of post-exposure prophylaxis in humans, and guidelines vary on indicators for use, dose and duration of therapy.\textsuperscript{9} The low secondary attack rate of the disease in most circumstances and infrequency of high risk exposures make anecdotal observations difficult to interpret. Adverse reactions are common, which not only lead to decreased adherence, but may pose a challenge in distinguishing these events from the early non-specific symptoms of Lassa fever. Experts
### Table 1. Imported cases of Lassa fever worldwide, 1969-2018

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Country of infection</th>
<th>Country imported to</th>
<th>Traveller Details</th>
<th>Departure flight details (where available)</th>
<th>Fatal</th>
<th>Number of contacts (where available)</th>
<th>Secondary cases in destination country (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1969</td>
<td>Nigeria</td>
<td>United States</td>
<td>Nurse</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1971</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Nurse</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1971</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Physician</td>
<td>Commercial flight on day 4 of illness</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1972</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Nurse</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1974</td>
<td>Nigeria</td>
<td>Germany</td>
<td>Physician</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1975</td>
<td>Sierra Leone</td>
<td>United States</td>
<td>Aid worker</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1975</td>
<td>Nigeria</td>
<td>United Kingdom</td>
<td>Physician</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1976</td>
<td>Nigeria</td>
<td>United Kingdom</td>
<td>Engineer</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1976</td>
<td>Sierra Leone</td>
<td>United States</td>
<td>Aid worker</td>
<td>Medical evacuation</td>
<td>No</td>
<td>552 including 29 high risk</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>1980</td>
<td>Burkina Faso</td>
<td>Netherlands</td>
<td>Aid worker</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1982</td>
<td>Nigeria</td>
<td>United Kingdom</td>
<td>Teacher</td>
<td>Commercial flight on day 7 of illness</td>
<td>No</td>
<td>173 including 124 high risk</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>1982</td>
<td>Nigeria</td>
<td>United Kingdom</td>
<td>Diplomat</td>
<td>Commercial flight before illness onset</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1984</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Geologist</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1985</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Nurse</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1987</td>
<td>Sierra Leone</td>
<td>Japan</td>
<td>Engineer</td>
<td>Commercial flight before illness onset</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1987</td>
<td>Sierra Leone, Liberia</td>
<td>Israel</td>
<td>Engineer</td>
<td>Commercial flight before illness onset</td>
<td>No</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>1989</td>
<td>Nigeria</td>
<td>Canada</td>
<td>Agricultural worker</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1989</td>
<td>Nigeria</td>
<td>United States</td>
<td>Attended funeral</td>
<td>Commercial flight before illness onset</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2000</td>
<td>Ghana, Burkina Faso, Côte d’Ivoire</td>
<td>Germany</td>
<td>Student</td>
<td>Commercial flight on day 6 of illness</td>
<td>Yes</td>
<td>232 including 30 high-risk Probable (1)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>2000</td>
<td>Sierra Leone</td>
<td>Netherlands</td>
<td>Physician</td>
<td>Commercial flight on day 4 of illness</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>2000</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Aid worker</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>125 including 10 high risk</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>2000</td>
<td>Nigeria</td>
<td>Germany</td>
<td>Nigerian national</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>2003</td>
<td>Sierra Leone</td>
<td>United Kingdom</td>
<td>Peacekeeper</td>
<td>Illness onset after return from duty</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2004</td>
<td>Sierra Leone, Liberia</td>
<td>United States</td>
<td>Businessman</td>
<td>Commercial flight on day 3 of illness</td>
<td>Yes</td>
<td>188 including 5 high risk</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>2006</td>
<td>Sierra Leone</td>
<td>Germany</td>
<td>Tourist</td>
<td>Commercial flight on day 6 of illness</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>2007</td>
<td>Nigeria</td>
<td>South Africa</td>
<td>Physician</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>2009</td>
<td>Nigeria</td>
<td>United Kingdom</td>
<td>Tourist</td>
<td>Commercial flight during illness</td>
<td>Yes</td>
<td>328 (none were high risk)</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>2009</td>
<td>Mali</td>
<td>United Kingdom</td>
<td>Aid worker</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>123 including 7 high risk</td>
<td>No</td>
</tr>
<tr>
<td>29</td>
<td>2010</td>
<td>Liberia</td>
<td>United States</td>
<td>Visiting family</td>
<td>Commercial flight on day 1 of illness</td>
<td>No</td>
<td>141 including 1 high risk</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>2011</td>
<td>West Africa (unspecified)</td>
<td>Sweden</td>
<td>Aid worker</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>2013</td>
<td>Liberia</td>
<td>Ghana</td>
<td>Peacekeeper</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>2013</td>
<td>Liberia</td>
<td>Ghana</td>
<td>Peacekeeper</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>2014</td>
<td>West Africa (unspecified)</td>
<td>United States</td>
<td>Unknown</td>
<td>Commercial flight during illness</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>2015</td>
<td>Liberia</td>
<td>United States</td>
<td>Mining industry worker</td>
<td>Commercial flight before illness</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>2016</td>
<td>Togo</td>
<td>Germany</td>
<td>Physician</td>
<td>Medical evacuation</td>
<td>Yes</td>
<td>52</td>
<td>Yes (1)</td>
</tr>
<tr>
<td>36</td>
<td>2016</td>
<td>Togo</td>
<td>United States</td>
<td>Physician</td>
<td>Medical evacuation</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>2016</td>
<td>Liberia</td>
<td>Sweden</td>
<td>Tourist</td>
<td>Commercial flight before illness</td>
<td>No</td>
<td>75</td>
<td>No</td>
</tr>
</tbody>
</table>
have hence recommended ribavirin as post-exposure prophylaxis exclusively in the event of a definitive high risk exposure.\textsuperscript{10}

**TRANSMISSION**

The natural reservoir of Lassa virus is the multimammate rat *Mastomys natalensis*. The geographic range of these rodents extends throughout West, Central, and East Africa. These commensal rodents are mainly confined to human dwellings and surrounding habitats, and tend to aggregate in houses during the dry season and then disperse into surrounding fields during the wet season.\textsuperscript{12,13} Infected rodents remain persistent carriers of the virus throughout their lives and shed the virus through urine, saliva and respiratory secretions.

Although *M. natalensis* rats are ubiquitous in sub-Saharan Africa, Lassa virus infected rodents have thus far only been reported in West African countries including Guinea, Sierra Leone, Nigeria and Mali.\textsuperscript{13,14} Consequently, Lassa fever is almost exclusively seen in West Africa, especially in distinct hyperendemic areas in Nigeria and countries of the Mano River Union comprising Liberia, Sierra Leone and Guinea.\textsuperscript{6}

Zoonotic transmission of the virus from the rodent reservoir to the human host presumably occurs through contact with rats or their excreta. This can be via inhalation of primary aerosols from infected rodent urine, when cleaning dust contaminated by rodent excreta, by ingestion of unprotected food contaminated by rodent excreta, or by direct contact of broken skin with rodent excreta. Person-to-person transmission may occur via direct contact with blood or other body fluids, although chains of transmission are often limited.\textsuperscript{15,16}

**RISK FACTORS FOR HUMAN TRANSMISSION**

The risk factors for human infection are largely distinct, with zoonotic transmission driven mainly by environmental factors, and secondary human-to-human transmission driven by human behaviours and contact patterns.\textsuperscript{14} Persons at greatest risk of primary infection are those living in rural areas where *M. natalensis* can be found, especially in areas of poor sanitation or crowded living conditions where the risk of rodent infestation increases.\textsuperscript{17,18} The incidence of human infection is the highest during the dry seasons from November to May when the changing availability of food drives the habitat change of *M. natalensis* rodents from surrounding fields into houses, thereby leading to increased chance encounters with infected rodents and their excreta during these periods.\textsuperscript{19}

Given the high titres of Lassa virus that are excreted in the urine by infected *M. natalensis* rodents, it has been assumed that contamination of food with rodent excreta is the main mode of rodent-to-human transmission in endemic areas.\textsuperscript{20} The hunting of peridomestic rodents and consumption of their meat has also been statistically linked as a risk factor for transmission of Lassa fever in Guinea where rodents represent nearly one third of the meat market. While hunting and preparation of rodent meat pose specific risks of being bitten and coming into contact with infected rodent blood and urine, oral transmission of the virus from consumption of meat itself may occur only if the meat is undercooked, as the virus is heat-labile.\textsuperscript{21,22}

Lassa virus has been isolated from blood, faeces, urine, throat swabs, vomit, semen and saliva of infected persons, and has been found to persist in human urine for up to three months.\textsuperscript{6,15,23} There is no evidence that Lassa fever patients are infectious before they develop symptoms, and transmission has not been reported in persons who had contact with an infected case prior to the onset of symptoms. While the risk of secondary transmission is highest during the later stages of disease when vomiting, diarrhoea, shock or haemorrhage is present, it is difficult to judge when the symptoms indicate infectiousness. Contact with bodily fluids or droplets is necessary for transmission, and the risk level of secondary transmission depends on the closeness, nature and duration of contact. Sexual contact with someone convalescent with Lassa fever also appears to be a significant risk factor, although the extent of such sexual transmission is unknown. There is no credible epidemiological evidence of airborne person-to-person transmission of Lassa virus as attack rates are low and sporadic even in crowded lodgings.\textsuperscript{23}

Due to its potential for human-to-human transmission, Lassa fever has been associated with nosocomial outbreaks since its discovery. In particular, large outbreaks with high fatalities had occurred, leading to the perception that the virus was highly contagious and virulent. Nevertheless, overall evidence suggests nosocomial transmission of Lassa fever occurred less frequently than previously supposed. Outbreak hospitals were typically inadequately equipped and staffed, with poor infection control practices.\textsuperscript{24,25} Recent genetic sequencing of a large dataset of Lassa virus genomes suggested that majority of human infections were independent transmission events from
the rodent reservoir, thereby indicating that human-to-human transmission chains are the exception rather than the rule.\textsuperscript{25}

**EPIDEMIOLOGY**

Since its discovery in 1969, the endemic areas for Lassa fever had been historically constricted to two geographically distinct regions in West Africa, namely the Mano River region comprising Liberia, Guinea and Sierra Leone in the West; and Nigeria in the East.\textsuperscript{37} This is an apparent disparity from the widespread distribution of *M. natalensis* in West, Central, and East Africa. Consequently, it has been suggested that some West African countries are likely to be underreporting cases due to less established surveillance as opposed to true absence of the virus taking into consideration their proximity to other endemic countries, environmental suitability, and low healthcare expenditure.\textsuperscript{14}

In recent years, sporadic cases and outbreaks have increasingly been reported from other West African countries that separate the two regions including Burkina Faso (in 1980 and 2017), Mali (in 2009), Ghana (in 2011), Benin (in 2014, 2016 and 2017) and Togo (in 2016 and 2017).\textsuperscript{1,28-33} A sporadic case reported in the Democratic Republic of the Congo in 2011 was the first - and thus far the only - time that Lassa fever was documented in Central Africa.\textsuperscript{34} While there is some serological evidence of human infection with Lassa fever or a closely related virus in the Central African Republic, conversely, there have been negative serological studies in other Central African countries including Cameroon, Equatorial Guinea, Congo and Gabon.\textsuperscript{13,35}

The true disease burden of Lassa fever across West Africa is unknown, with the estimated annual incidence of Lassa fever ranging from 100,000 to three million annual cases, and 5,000 to 67,000 deaths.\textsuperscript{5,15} However, these numbers remain as crude estimates given that the surveillance for the disease is inadequate and not uniformly performed. Risk mapping of Lassa fever based on environment data of hyperendemic areas shows that abiotic persistence of the Lassa fever virus in the general environment was restricted to particular moisture or rainfall conditions. With consideration of the distribution of the *Mastomys* rodents, areas favourable for Lassa virus endemicity in West Africa covers 80% of Sierra Leone and Liberia, 50% of Guinea, 40% of Nigeria, 30% each of Cote d’Ivoire, Togo and Benin, and 10% of Ghana.\textsuperscript{13} Small areas in Mali, Senegal, Guinea-Bissau, Niger, Ghana, as well as Cameroon in Central Africa have also been predicted to be environmentally suitable for the zoonotic transmission of Lassa fever.\textsuperscript{14} Climate change, alongside population increases, is predicted to double the incidence of Lassa fever by 2070 and drive an expansion of the areas of West Africa considered high risk for Lassa fever.\textsuperscript{36}

**PREVENTION**

No licensed Lassa fever vaccine is currently available although many candidates have been developed.\textsuperscript{37} In the absence of a vaccine, rodent control, behavioural changes and infection control in healthcare facilities are the most efficient ways to reduce the risks of Lassa fever infection. Travellers to West Africa, and Central Africa to a lesser extent, should be informed of the risk of exposure to Lassa fever, particularly in areas currently experiencing outbreaks, and adopt appropriate personal protective measures. Preventive measures are based on the reduction of exposure to rodents and their excreta (e.g. avoiding consumption of food and drink contaminated by rodent droppings; avoiding exposure to rodents) and to persons presenting with haemorrhagic fever symptoms.\textsuperscript{16} Exposure is not likely to occur in cities, and seasonal flare-ups are typically observed in the dry season from November to May. The main traveller groups at risk for Lassa fever infection are missionaries and aid-workers, healthcare workers, peacekeepers and military personnel, as well as other travellers to rural areas where sanitary conditions are basic.\textsuperscript{38}

When caring for patients with suspected or confirmed Lassa fever, the risk of infection among healthcare workers can be reduced through strict isolation of cases, appropriate use of infection control precautions including the use of personal protective equipment, and application of strict barrier nursing.\textsuperscript{16} Laboratory workers are also at risk of infection. Two cases among research staff in a research institute were reported in the United States (US) in 1969 prior to the development of biosafety standards for Lassa fever.\textsuperscript{39,40} As the risk of transmission increases considerably following death, and body fluids remain contagious post-mortem, safe burial practices should be followed.\textsuperscript{41}

**RISK ASSESSMENT**

**Risk of primary infection in Singapore**

Though arenaviruses are generally considered to be a rodent-transmitted infection, most of these viruses are only associated with one specific rodent reservoir species. As such, although the Lassa virus antigen has been previously detected in very few *Rattus* and *Mus*
genera rodents, live virus had only been isolated from *Mastomys* rodent species. This suggests that while there was a possibility for non-*Mastomys* rodents to be occasionally and transiently infected with Lassa virus in spill-over infections, these rodents do not serve as a host reservoir. In addition, several studies have reported a correlation between the absence of *Mastomys* rodents and low human Lassa virus seroprevalence, further supporting *M. natalensis* as the only reservoir host of virus.\textsuperscript{42,43}

There is no evidence that the tropical environmental conditions in South-East Asia including Singapore can support the maintenance of Lassa fever, or its reservoir, *M. natalensis*. Local rodent species are unlikely to be able to serve as reservoir hosts for the virus. As such, the risk of primary infection with Lassa virus in community settings in Singapore is virtually non-existent.

**Risk of importation via travel to Singapore**

International travel presents opportunities for the importation of Lassa fever to non-endemic areas via infected travellers. Notably, Lassa fever was the first VHF to be identified in a traveller and remains the most common VHF with the capacity for human-to-human transmission among international travellers, disproportionately affecting health care workers and those working in rural settings such as humanitarian aid workers and peacekeepers.\textsuperscript{38} From 1969 to date, a total of 37 cases of imported Lassa fever have been reported in 11 countries, mostly in Europe and North America (Table 1). Sierra Leone (12), Nigeria (11) and Liberia (5) were the places of infection for 28 of the 37 imported cases, while the United Kingdom (UK) (13), the US (9) and Germany (5) received the largest number of imported cases. Notably, the UK and the US were also the top final destination countries for air travellers originating from Sierra Leone, Nigeria and Liberia (travel data not shown).

In 2017, Singapore received a monthly average of 743 travellers from countries in West and Central Africa that reported confirmed Lassa fever cases, had serological evidence of Lassa fever endemicity or were environmentally suitable for the zoonotic transmission of Lassa virus (Table 2). This comprised 0.04% of the total number of international travellers to Singapore as a final destination (monthly average of 2 million; annual volume of 24 million from January to December 2017). The largest proportions of travellers from the affected African countries were from Nigeria (32.0%) which is hyperendemic for Lassa fever with outbreaks of various magnitudes and severity occurring almost annually in different parts of the country; followed by Ghana (27.9%) which has reported sporadic cases in recent years.
The importation of a human case of Lassa fever in Singapore is possible as demonstrated by reports of imported cases notably in countries – such as Israel, Sweden and Japan – that have similarly low travel volume to the Lassa fever hyperendemic regions (travel data not shown). Nonetheless, while systemic febrile illnesses occur more frequently among ill travellers from Sub-Saharan Africa compared to other regions, febrile travellers are still more likely to be diagnosed with malaria than Lassa fever or another VHF.44,45 The overall risk of contracting Lassa fever has been conservatively estimated at less than one in one million travel episodes to African countries with endemic disease.38

On balance, the overall likelihood of such importation into Singapore is low based on historical trends, and low travel volume between affected countries in West and Central Africa, and Singapore.

Risk of secondary spread in the event of an imported case

To assess the likelihood of secondary spread in Singapore in the event of an imported case, reports of imported Lassa fever cases were analysed for the number of contacts generated, and consequent secondary infections. Of nine importation events for which information were available, the number of contacts generated by each imported case ranged from 30 to 552 (total number 1,892; mean of 210 contacts and median of 173 contacts) (Table 1). 13.4% of contacts (206 of 1534 contacts with detailed information) were classified as high-risk contacts. Despite numerous reports of high-risk exposures or close physical contact with imported cases prior to clinical suspicion of Lassa fever infection, only two instances of secondary transmission, both in Germany, have been documented thus far.46-52

First transmission event

The first instance was a probable asymptomatic case in January 2000 involving a physician who had treated a female German student. The student had lived in the Ivory Coast for several months and travelled to Ghana and Burkina Faso in the month prior to her illness. She developed a sudden onset of high fever and flu-like symptoms while in Abidjan, Ivory Coast where a presumptive diagnosis of malaria was made at a local hospital. The case then returned to Frankfurt, Germany on day 6 of her illness. She was admitted on arrival, and was transferred to a specialist hospital for tropical diseases in Würzburg three days later when her condition deteriorated. Lassa fever was considered on day 10 of illness, and confirmed through polymerase chain reaction (PCR) the next day. Intravenous ribavirin treatment was started, however, the case died of massive haemorrhage and organ failure on day 14 of illness.53

No symptomatic secondary infections were observed among 232 contacts of the index case. High-risk exposures were reported by 18 contacts, but all tested negative for Lassa fever by serology. Close physical contact was reported by 12 healthcare workers and family members. Among these, serological testing revealed one probable transmission to a physician from the specialist hospital. The physician had performed a physical examination and procedures including an insertion and administration of an infusion without gloves or a protective mask. She recalled exposure to cough of the index case during inspection of the latter’s throat. The physician received ribavirin prophylaxis 36 hours post exposure once Lassa fever was diagnosed in the index patient. She did not develop symptoms of Lassa fever but presented with specific IgG antibodies to the virus. The physician had also never travelled to Africa, nor had previous infection with Lassa virus or other related African arenavirus. Lassa virus-related lymphocytic choriomeningitis virus, endemic in central Europe, was excluded by serology. Nonetheless, since transmission could not be definitely proven according to the serological criteria for acute infection (IgM detection or demonstration of IgG seroconversion), and the lack of clinical symptoms, she was classified as having a probable secondary infection. No evidence of further transmission was found. All airplane passengers tested had negative serological test results.54

Second transmission event

The second instance was in March 2016. The index case involved an American missionary healthcare worker medically evacuated from Togo where he worked as a surgical assistant, to Cologne for treatment of complicated falciparium malaria. He passed away from severe multi-organ failure a day after arriving in Germany, and his body was transferred to a funeral home specialising in conditioning corpses for repatriation flights six days later. Lassa fever was only confirmed 12 days post-mortem following signs of haemorrhagic fever in autopsy findings. Since Lassa fever had previously never been reported in Togo, it was not initially considered as a differential diagnosis.

An employee of the funeral home, tasked with preparing the corpse, contracted the infection. He had reportedly worn gloves, and did not recall exposure to bodily fluids. He already had symptoms of an upper respiratory infection when he had contact with the body, and was negative for Lassa fever when tested 10 days following exposure. However, as his symptoms persisted, a second test was performed five days
later and infection was confirmed through PCR. Two additional contacts exposed to the corpse tested positive for Lassa fever IgM antibodies, although these were later deemed false-positive, and both tested negative by PCR.16,55 A second American healthcare worker in Togo who provided care to the index case developed similar symptoms. He was medically evacuated to Atlanta, US, in strict isolation, and tested positive for Lassa fever infection.56

No further cases have been detected in Germany or the US in relation to these events.55 Overall, investigations of imported cases were consistent with a time-dependent risk of transmission, with absence of transmission in the early phase of disease, and increased risk during late illness in keeping with disease progression.54

Hence, if a case were to occur in Singapore, those most at risk of secondary infection would be persons in closest contact with the case or with body fluids during the period of symptomatic illness. These include healthcare workers and also family members or other individuals who had provided direct nursing care, laboratory workers handling specimens, and persons handling or preparing the body of a deceased case. Invasive procedures and emergency resuscitations performed on patients with severe haemorrhage in well-resourced settings may pose risks for healthcare workers that were different from those in smaller hospitals in endemic countries, where such procedures may not be available.16

In the event of an imported case, there are well-established infection control practices in our healthcare institutions that would help limit its spread. However, this would need to be coupled with an index of suspicion, particularly with a relevant travel history. Delays in the identification of cases can pose risks to healthcare facilities. Experiences of nosocomial transmission in Germany suggest that even well-resourced settings with well-trained healthcare personnel can be vulnerable to secondary transmission of Lassa fever, especially when there is low clinical suspicion of a VHF infection.

Overall risk assessment for Singapore

As such, the recent geographical expansion of Lassa fever to areas in West Africa where it has not been recognised previously is of particular concern as the lack of a “relevant” travel history may elude the rapid identification of an infection. The recent Lassa fever outbreak in Cologne, highlighted that Lassa fever should be considered as a differential diagnosis for any patient originating from West Africa region and presenting with suggestive symptoms.16 Similarly, a Lassa fever case imported into the UK from Mali in 2009 represented the first human case from the country, though previous serological evidence had suggested that the virus was likely present in the country. In the same fashion, the risk of Lassa fever was initially considered to be low, and was only upgraded after the case developed multi-organ failure.29

While the likelihood of exposure to Lassa fever during travel increases during times of outbreaks or seasonal flare-ups, the risk of acquisition and subsequent transmission of the infection can be significantly reduced by well-informed travellers and healthcare providers. This includes maintaining basic hygiene and precautionary measures while overseas, and infection prevention and control measures when dealing with the sick.

The overall public health impact of an imported case of Lassa fever into Singapore is considered to be low. Nevertheless, given the stigma of VHFs especially arising from large Ebola virus outbreaks in the last decade, public perception of an epidemic spread by such a pathogen can achieve an impact out of proportion to the actual danger presented. In a world increasingly connected by trade and travel, where emerging infectious diseases spread more rapidly across continents, it is important that Singapore remains vigilant to quickly detect, respond and contain threats such as Lassa fever.

REFERENCES


Risk of *Anopheles sinensis* as an Emerging Malaria Vector in Singapore

*Lee-Ching Ng*1,2, *Sook Cheng Pang*1

1National Environment Agency, Environmental Health Institute, 2School of Biological Sciences, Nanyang Technological University, Singapore

**INTRODUCTION**

Singapore has been certified malaria free since November 1982 by the World Health Organization (WHO).1 Despite the successful elimination of malaria, occasional small outbreaks occur, with the most recent one in 2009. Field investigations of the 2009 outbreak revealed *Anopheles (An.) sinensis* as a potential vector in Singapore.2

In the middle of 2009, three clusters with a total of 29 *Plasmodium (P.) vivax* malaria patients, with no recent travel history, were identified by the Ministry of Health (MOH). Interestingly, molecular epidemiology using the msp3a and msp1 genes of the parasite confirmed two independent local transmissions in the Mandai-Sungei Kadut cluster and the Sembawang cluster. The predominant Anopheline found in the two areas was *An. sinensis*, a mosquito that had not been previously recognised as a vector in Singapore. Malaria vectors are typically members of the Anopheline family, and the known vectors found in Singapore are *Anopheles epioroticus* (formally known as *Anopheles sundaicus*), *Anopheles maculatus* and *Anopheles letifer*.1 Malaria transmission in the Jurong cluster could not be confirmed as the infecting parasite from the human cases showed no genetic link. Correspondingly, no *Anopheles* vector, including *An. sinensis*, was found in the vicinity.

*Anopheles sinensis* has been incriminated as a secondary vector in China and South Korea.4-9 However, there were no reports of *An. sinensis* being a primary vector in Southeast Asia. In the Malayan region, including Singapore, *An. sinensis* had not been considered a vector, since it was found to be more zoophagic and no malaria parasite sporozoite has been found in the mosquito.10,11 In Thailand, *An. sinensis* has been considered only as a secondary *P. vivax* vector with weak transmission capability.10,12

Vector competence variation within the species of mosquitoes has been demonstrated by an experiment which found that *An. sinensis* from South Korea was able to develop oocysts and sporozoites, when fed with blood containing local strain of *P. vivax* and those from Thailand. In contrast, *An. sinensis* from Thailand failed to develop sporozoites when fed with the Thai strain of *P. vivax*.13

To understand the vector capacity of Singapore *An. sinensis*, a study was initiated at the Environmental Health Institute (EHI), National Environment Agency (NEA). In collaboration with Shoklo Malaria Research Unit (SMRU) from Mae Sot, Thailand, this study involved artificially infected Singapore strain *An. sinensis* with *Plasmodium vivax* from Thai-Myanmar border. The results are important for local risk assessment of malaria transmission in Singapore.

**METHODS AND RESULTS**

Singapore *An. sinensis* is competent in transmitting *vivax* malaria

Wild *An. sinensis* larvae, collected by NEA field officers during their routine inspection, were used for colonisation of the mosquito at the EHI insectary. The identification of the mosquitoes was determined by morphological examination using a taxonomic key14, and confirmed by Deoxyribonucleic acid (DNA) sequencing of the *CO1* and *ITS2* genes.15,16 Working
in collaboration with SMRU, these mosquitoes were fed with blood collected from *P. vivax* cases who had gametocytaemia along the Thai-Myanmar border. *Anopheles cracens*, which is a known *P. vivax* vector in Thailand, was used as a control and was fed with the same samples of blood. Seven independent experiments consistently showed that by day 6 post-feeding, the *P. vivax* malaria oocytes were found in the gut of 50-100% of the mosquitoes that were dissected. By day 15 post-feeding, sporozoites were found in the salivary glands of the blood-fed mosquitoes (Figure 1). In the four sets of experiments which detected sporozoites, the average number of sporozoites ranged from 703 to 14,538 per mosquito, a level lower than that of *An. cracens* (2,812 to 76,764 per mosquito).20

For transmission to occur, a malaria parasite has to undergo a complex process involving the development of oocytes in the gut of mosquitoes and invasion of the salivary glands by the resultant sporozoites. The infectious sporozoites are then ready to be injected into a vertebrate host. The ability of the parasite to invade into the salivary gland of a mosquito provides strong evidence that Singapore’s *An. sinensis* has the competency in transmitting malaria parasite, if they get into contact with malaria cases with gametocytaemia.

### Spatial distribution of *An. sinensis* in Singapore

Based on two years of field survey, using modified Centres for Disease Control and Prevention (CDC) light traps at 38 sites throughout the island state, the presence of *An. sinensis* adults was detected in 15 sites. Further investigations around the sites revealed that the breeding habitats of *An. sinensis* were typically freshwater ponds with thick mats of algae or grassy pools of water (Figure 2). The habitats found were consistent with the typical rice fields ecology described in China, South Korea, Japan and Thailand.5,10,17-19 Using these data, NEA is working on a map to capture areas with potential breeding habitats for *An. sinensis*. This map will be used to guide surveillance of the *An. sinensis* mosquitoes in Singapore and to implement control measures to prevent *An. sinensis* breeding.

Consistent with previous findings in 2009: An. sinensis were found to bite humans as early as 1900 hours and were active till midnight. The studies6,7 showed that the removal of the algae and grasses from the water bodies rapidly and effectively reduced *An. sinensis* mosquito population to almost undetectable levels (NEA unpublished data). It was also shown that though its potential breeding habitats are common in Singapore, *An. sinensis* population in urban setting can be easily controlled through environmental management, such as managing the growth of algae and vegetation in the water bodies.2

### Risk of malaria transmission in Singapore

Interestingly, despite a widespread presence of *An. sinensis*, and being a competent vector of *P. vivax* malaria as shown in this study, there have been no reports of indigenous cases of malaria in recent years. There are two postulations regarding the absence of transmission. Firstly, there is a low chance of contact between gametocytaemia cases and the *An. sinensis* mosquito. This can be attributed to a small number of gametocytaemia cases in the community, a small population of *An. sinensis* which is only restricted to pockets of areas in Singapore, and a wide range of hosts that *An. sinensis* is attracted to for blood meals. Secondly, there is a low chance of contact between an infectious *An. sinensis* mosquito and a susceptible person. While the broad biting host range of *An. sinensis* can also lower the chance of this transmission process, the lifespan of the vector in the field is a critical factor. The lifespan of *An. sinensis* in the Singapore’s environment remains unknown and is under investigation. The extrinsic incubation period, during which sporozoites develop and invade the salivary glands, is typically long for malaria parasites. A short life span of the mosquito would certainly impose a constraint on the population of infectious mosquitoes.
DISCUSSION

Notwithstanding the above-mentioned observations and suppositions, this study has revealed that *An. sinensis* could pose a malaria threat in urban Singapore, if the risks are not managed. Freshwater bodies such as ponds in parks, large water tanks in fish farms and water pools in the forest are common. Our heterogeneous community and status as a regional travel hub present an opportunity for gametocytæmia cases from endemic countries to come in contact with the vector, which could trigger transmission. A feasible and important strategy to reduce contact between potential carriers and mosquitoes is to reduce the
vector population through good maintenance and management of water bodies. This is especially essential in Singapore's urban setting with relatively high human population density.

Studies are ongoing to gain an in-depth understanding on the potential impact of the changed entomological landscape on the risk of malaria transmission in Singapore. Complementing vector population control with vigilance in the medical community on early case identification and prompt treatment is paramount in our efforts to keep malaria transmission at bay.

REFERENCES


NOTES FROM THE FIELD
City's Most Unwanted Inhabitants

Reported by Jiaying Wong
Communicable Diseases Division, Ministry of Health

Oh Rats! When rodents invade...
Curious on how rodents are controlled in Singapore?
Do you have the guts and patience to hunt them down in the silence of the night?
INTRODUCTION

Rodents such as rats and mice spread diseases worldwide. Some of these diseases may spread to humans directly, through contact with the rodents themselves, or their faeces, urine, saliva, and bites. Other diseases may also spread to humans indirectly, through ticks, fleas or mites that have fed on an infected rodent. These rodent-borne diseases include, but are not limited to hantavirus, leptospirosis, murine typhus, and plague.

In Singapore, disease surveillance and control for rodent-borne diseases are shared across three agencies - the Ministry of Health (MOH), the National Environment Agency (NEA), and the Agri-Food & Veterinary Authority of Singapore (AVA). Disease surveillance and epidemiological investigation of human cases of rodent-borne disease is under the purview of MOH, while AVA is responsible for the same in animal cases of rodent-borne disease, and the NEA undertakes the integrated vector surveillance and control comprising environmental management and source reduction. All three agencies work together under the auspices of the One Health framework to tackle the issues related to rodent-borne disease surveillance and control.

OVERVIEW

Before commencing on a rodent control exercise, it is essential for the Field Epidemiology Training Programme (FETP) trainees to understand the vectors, in this case the rodents, and what to look out for. The trainees including myself were briefed by NEA officer Mr Jason Tan, Manager of the Rodent Control Unit based in the South-East Regional Office to learn more about rodents and NEA’s rodent control strategy. Rodents such as rats are nocturnal creatures, and usually search for food between dusk and dawn. They may also be seen in the daytime when unable to find sufficient food due to crowded conditions, and their presence in the daytime may indicate rat infestation.

Figure 1. The three main rodent species in Singapore and its droppings
Rats have a well-developed sense of smell, hearing and touch, and are light sensitive despite having poor eyesight and being colour blind. They move about in the dark along walls using their whiskers and tend to use established routes, during which oil and dirt on their bodies rub off onto walls and result in rub marks. Their continuously growing teeth must be kept short by gnawing, and gnaw marks are often found in areas with rat infestation as well.

**COMMON RODENTS FOUND IN SINGAPORE**

There are three main types of rats found in Singapore, the sewer rat (*Rattus norvegicus*), roof rat (*Rattus rattus* spp), and the house mouse (*Mus musculus*) (Figure 1). Sewer rats are burrowers and often associated with drains or sewers, while roof rats are climbers that mainly live indoors in elevated settings such as ceilings and roofs. The house mouse lives both indoors and outdoors, often within or in the vicinity of stored food such as grains. Also worthy of mentioning is the Asian House Shrew (*Suncus murinus*), which are often mistaken as rats. They can be found in burrows or houses but primarily eat insects, and are considered a pest instead of a vector. Rats reproduce quickly and can have up to six litters each year, with up to eight pups per litter.

**RODENT OPERATION**

The FETP trainees proceeded to outfield to experience how rodent control inspection was carried out at the hawker centre and its vicinity. The inspection was conducted at night when the hawker centre was closed and rats were more active. Areas of inspection included the individual hawker stalls, refrigerator/freezer areas, refuse areas, and common turf areas, bin chutes and bin centres. To enhance our inspection, modified tools such as action cameras on extended poles were used to inspect elevated areas such as roof beams, areas above refrigerators or freezers, and hawker stall signboards (Figure 2). Specialised equipment such as flexible probes were also used to capture images and videos inside burrows to check for rodent activities (Figure 3). The use of specialized tools and technology helped to improve the efficiency of the inspection, and...
Figure 3. Viewing video footage taken using the probe.

Figure 4. A shrew spotted at the entrance of a burrow.
reduced the amount of physical work required of the inspection officers.

During the inspection, rat droppings were observed in areas such as the electrical risers, along dark corners of the hawker centre, in the vicinity of the refuse areas and inside the bin chutes. A shrew was also spotted in a burrow, found at the common turf area adjacent to the hawker centre (Figure 4). Subsequent to the rodent control inspections, the responsible agencies or companies such as the Town Councils or the mall managements will be informed to carry out control measures such as setting up baiting, glue boards, rat cages and dusting.

**REFLECTIONS AND CONCLUSIONS**

Rodent control inspection is a tough job. Officers usually carry out inspections in premises such as hawker centres and shopping malls at night to reduce any public disturbance to the operations, and also in order to catch the rodents in action as they are nocturnal creatures. Inspection of smaller premises such as hawker centres may take two to three hours, whereas large premises like shopping malls may even take up to five to six hours with a team of officers. Experience and knowledge of the rodents are important in sniffing out rodent activity. Continued vigilance and NEA’s integrated rat control efforts are key in our fight against rodent-borne diseases.

**ACKNOWLEDGEMENT**

Special acknowledgement goes to colleagues at NEA’s Rodent Control Unit for their guidance and assistance in the preparation of this report.
FAST FACTS

PRIME MINISTER LEE HSIEN LOONG’S NATIONAL DAY RALLY 2018

Keeping Healthcare Affordable

Enhanced schemes and subsidies to keep costs low
- Subsidies of up to 80% in hospitals, and for primary and long-term care
- Strengthened 3M framework

Upgraded MediShield to MediShield Life
- Higher payouts, lifetime protection
- Almost 200,000 Singaporeans benefitted from MediShield Life last year, amounting to over $800 million in payouts

Extended CHAS for all Singaporeans
- Generous subsidies at GP clinics
- All Singaporeans with chronic conditions will be covered

More will benefit from CHAS as our population ages

More and better polyclinics
- Building new polyclinics
- Patients can enjoy better facilities and improved services

Better long-term care with CareShield Life
- ElderShield revamped to CareShield Life
- Higher payouts, for as long as you live
- Generous subsidies for premiums

New polyclinics
- By 2020
- By 2023

For more information, visit bit.ly/ndr18 or scan QR code on the internet.
### Infectious Diseases Update
As of E Week 39 (23-29 Sep 2018)

#### SURVEILLANCE SUMMARY

**ENB Quarterly | Vol 44 (4) | 139**

**Preliminary figures, subject to revision when more information is available.**

**Updated case counts due to change in case definitions w.e.f 1 Jan 2018**

<table>
<thead>
<tr>
<th>Disease</th>
<th>E Week 39</th>
<th>Cumulative first 39 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2018*</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
</tr>
</tbody>
</table>

#### FOOD/WATER-BORNE DISEASES

- **Acute Hepatitis A**: 1 0 0 56 63 62
- **Acute Hepatitis E**: 0 0 0 45 60 49
- **Campylobacteriosis**: 11 17 8 308 356 347
- **Cholera**: 0 0 0 2 1 1
- **Paratyphoid**: 1 0 0 13 16 18
- **Poliomyelitis**: 0 0 0 0 0 0
- **Salmonellosis**: 28 27 39 1201 1529 1472
- **Typhoid**: 1 0 0 31 47 47

#### VECTOR-BORNE DISEASES

- **Chikungunya Fever**: 0 0 0 6 20 31
- **Dengue Fever**: 40 39 257 2081 2098 12008
- **Dengue Haemorrhagic Fever**: 0 0 NA 0 0 NA
- **Japanese Encephalitis**: 0 0 NA 32 40 NA
- **Leptospirosis**: 0 1 NA 24 28 40
- **Murine Typhus**: 0 0 NA 9 0 NA
- **Nipah virus infection**: 0 0 0 0 0 0
- **Plague**: 0 0 0 0 0 0
- **Yellow Fever**: 0 0 0 0 0 0
- **Zika Virus Infection**: 0 0 NA 1 66 NA

#### AIR/DROPLET-BORNE DISEASES

- **Avian Influenza**: 0 0 NA 0 0 NA
- **Diphtheria**: 0 0 0 2 0 0
- **Ebola Virus Disease**: 0 0 NA 0 0 NA
- **Haemophilus influenzae type b**: 0 0 0 3 6 5
- **Hand, Foot And Mouth Disease**: 622 672 672 33276 27004 21592
- **Legionellosis**: 2 1 0 16 15 15
- **Measles**: 0 0 1 29 58 56
- **Melioidosis**: 0 1 1 22 36 34
- **Meningococcal Disease**: 0 0 0 6 6 4
- **Mumps**: 8 14 12 381 402 395
- **Pertussis**: 2 1 1 85 52 41
- **Pneumococcal Disease (invasive)**: 2 4 1 100 125 112
- **Rubella**: 1 0 0 10 13 15
- **Severe acute respiratory syndrome**: 0 0 0 0 0 0
- **Tetanus**: 0 0 0 1 0 0

#### OTHER DISEASES

- **Acute hepatitis B**: 1 2 1 35 30 40
- **Acute hepatitis C**: 1 0 0 11 13 9
- **Botulism**: 0 0 NA 0 0 NA

#### POLYCLINIC ATTENDANCES - AVERAGE DAILY NUMBER

- **Acute upper respiratory infections**: 2767 2686 2384 NA
- **Acute conjunctivitis**: 79 80 91 NA
- **Acute Diarrhoea**: 571 483 483 NA
- **Chickenpox**: 15 10 NA NA

#### HIV/STI/TB NOTIFICATIONS

- **2018 Aug Cumulative 2018**
- **HIV/AIDS**: 22 204
- **Legally Notifiable STIs**: 850 68 14
- **Tuberculosis**: 161 1086
## Influenza Surveillance

Average daily number of patients seeking treatment in the polyclinics for Acute Respiratory Infection (ARI) peaked in July and declined to below the 70th percentile in August. The proportion of patients with influenza-like illness (ILI) among the polyclinic attendances for ARI is 1.9%. Overall positivity rate for influenza among ILI samples (n=186) in the community was 19.9% in the past 4 weeks. Of the specimens tested positive for influenza in September 2018, these were positive for influenza A (H1N1)pdm09 (37.2%), influenza B (25.6%), and influenza A (H3N2) (37.2%).
Dengue Surveillance

The number of dengue notifications remained low, well below the mean + 1 standard deviation (SD) level, from July to September. Preliminary results of all positive dengue samples serotyped in September 2018 showed DEN-1, DEN-2, DEN-3 and DEN-4 at 47.2%, 44.4%, 5.6% and 2.8%, respectively.

Zika Surveillance

As of 29 September 2018, there was 1 case of Zika reported. There were 67 cases reported in 2017.
Surveillance of Other Selected Diseases

**Typhoid**

- 2017
- 2018

**Paratyphoid**

- 2017
- 2018

**Hepatitis A**

- 2017
- 2018
SURVEILLANCE SUMMARY

Measles

Rubella

Pneumococcal Disease (Invasive)
ENB Quarterly is published in Jan, Apr, Jul and Oct every year by the Ministry of Health, Singapore. Readership includes physicians, epidemiologists, microbiologists, laboratorians, researchers, scientists, and public health practitioners. Correspondence address: The Editor (ENB Quarterly), Public Health Group, Ministry of Health, 16 College Road, College of Medicine Building, Singapore 169854. A downloadable electronic format is provided free of charge at our website: https://www.moh.gov.sg/content/moh_web/home/Publications/epidemiological_news_bulletin.html

Contribution by authors of articles to ENB Quarterly is a public health service and does not preclude subsequent publication in a scientific peer-reviewed journal. Opinions expressed by authors do not necessarily reflect the position of the Ministry. The material in ENB Quarterly may be reproduced with proper citation of source as follows:

[Author]. [Article title]. Epidemiol News Bull [Year]; [Vol]:[inclusive page numbers]

Summary statistical data provided in ENB Quarterly are provisional, based on reports to the Ministry of Health. For more current updates, please refer to our MOH Weekly Infectious Diseases Bulletin: https://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html

Do you have any ideas or suggestions? Your views are important to us.

Please contact us at ENB_Quarterly@moh.gov.sg