

# Clinical features and epidemiology of chikungunya infection in Singapore

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## ABSTRACT

**Chikungunya is a re-emerging mosquito-borne viral infection that has spread from East Africa to Indian Ocean islands and re-emerged in India since 2004. In Malaysia, chikungunya re-emerged after a hiatus of seven years, causing a localised outbreak in a north-western coastal town in 2006 and subsequently widespread outbreaks in 2008. Since the first local outbreak of chikungunya in Singapore in January 2008, chikungunya infections have been increasingly reported in Singapore. In this case series, five patients aged 37–62 years, with chikungunya infection confirmed in August 2008, were reported. Three of the five were male, and only one had medical comorbidities. Two had a travel history to Johor, Malaysia, where local outbreaks of chikungunya had been reported. Fever, arthralgia and rash were the most common symptoms. Fever lasted four to five days while viraemia lasted four to 11 days, persisting two to three days after defervescence in three patients. A biphasic pattern of fever was observed in two patients. Leucopenia was noted in all patients, while mild thrombocytopenia and transaminitis occurred in three of five patients. Two patients had persistent polyarthralgia at two to three weeks after the onset of symptoms. Fever, arthralgia and rash should prompt consideration of acute chikungunya in Singapore. While taking the travel history, doctors should be mindful that indigenous chikungunya cases can occur.**

**Keywords:** arbovirus, arthralgia, chikungunya, infection outbreaks, mosquito-borne viral infection

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## INTRODUCTION

Chikungunya fever is caused by the chikungunya virus, an arthropod-borne *Alphavirus* of the *Togaviridae* family. “Chikungunya”, from the Bantu language of the Makonde people in Tanzania, means “that which bends up,” referring to the stooped posture adopted by affected individuals

with severe arthralgia.<sup>(1)</sup> Chikungunya fever was first reported in Tanzania in 1952.<sup>(1)</sup> Epidemics occurred in many African countries in the 1950s to 1970s, Thailand in 1958 and 1962, India in 1963 and 1973, Cambodia and Vietnam in 1963, Sri Lanka in 1965, and the Philippines in 1968.<sup>(2)</sup> Since the 1970s, only occasional outbreaks have been reported: Senegal in 1982 and 1996, Indonesia in 1985 and 2001, the Philippines in 1985, Thailand in 1995, Malaysia in 1998, and Congo in 1999.<sup>(2)</sup> More recently, it has re-emerged, spreading from Kenya in 2004, to Reunion Islands in 2005 and India in 2006.<sup>(3)</sup> This more recent outbreak has affected travellers from Germany,<sup>(4)</sup> Italy<sup>(5)</sup> and France,<sup>(6,7)</sup> and caused a local outbreak in Italy where *Aedes albopictus* can be found.<sup>(8)</sup>

In Malaysia, chikungunya re-emerged after a hiatus of seven years and caused an outbreak in the isolated north-western coastal town of Bagan Panchor in March 2006.<sup>(9,10)</sup> Subsequent outbreaks were reported in the Kinta district in December 2006.<sup>(11)</sup> Since early 2008, widespread chikungunya outbreaks have been reported in many states in peninsular Malaysia.<sup>(12)</sup> Although Singapore has had an active laboratory-based chikungunya surveillance system in place since 2006, only ten imported chikungunya cases were detected in 2007. In January 2008, the first local outbreak of chikungunya was reported in Little India.<sup>(13,14)</sup> Since then, chikungunya infections have been increasingly reported in Singapore. We report five cases of chikungunya infection in Singapore, which were admitted to the Communicable Disease Centre, Tan Tock Seng Hospital, between August 1 and August 28, 2008. The patients described here illustrate the typical clinical presentation and epidemiological link of chikungunya infection in Singapore. Table I summarises pertinent demographical, epidemiological, clinical and laboratory data of the cases.

## CASE SERIES

### Case 1

A previously-well, 37-year-old Malay woman who lived in Pontian, Malaysia, commuted daily to work in Singapore. She presented with fever, myalgia and arthralgia of the right shoulder, bilateral knees, ankles, wrists and small joints of her hands. She had backache but no gastrointestinal symptoms. She had been in

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**Fig. 1** Case 1. Photograph shows swelling of the left ankle, compared to the unaffected right ankle.



**Fig. 2** Case 2. Photograph of the back shows generalised erythema; pressure on the rash caused blanching which brought out the imprint of the examiner's right hand.



**Fig. 3** Case 2. Photograph shows maculopapular rash on the limb.



**Fig. 4** Case 3. Photograph shows bilateral conjunctival injection.



**Fig. 5** Case 4. Photograph shows bilateral palmar erythema.

contact with cases of chikungunya in her Pontian neighbourhood. Examination revealed posterior auricular lymphadenopathy and left ankle swelling (Fig. 1). She later developed a maculopapular rash over her limbs on Day 6 of the illness. Investigations showed lymphopenia without thrombocytopenia. Nadir lymphocyte count of  $0.40 \times 10^9/L$  occurred on Day 3 of the illness. Liver function tests were normal. The duration of viraemia was defined as the amount of time the chikungunya polymerase chain reaction (PCR) test remained positive. For this patient, chikungunya PCR test was positive till Day 7 of the illness. She was given analgesics for her arthralgia. On follow-up on Day 21 of the illness, she still had arthralgia over her right shoulder, right knee and wrists, affecting her housekeeping job. No joint swelling was observed.

#### Case 2

A previously-well, 50-year-old Malay Singaporean man who worked as a manager in Kranji was referred by the Ministry of Health Singapore (MOH) for screening, following the detection of two cases of chikungunya in Kranji. He reported fever, myalgia and arthralgia involving the heels, shoulders and finger joints. He had

a headache without gastrointestinal symptoms. He later developed generalised erythema (Fig. 2), a maculopapular rash on his limbs (Fig. 3) with erythema of his palms. He had no joint swelling or palpable lymphadenopathy. He was febrile till Day 4 of the illness, but had a re-spike of temperature to  $38^\circ C$  on Day 7 of the illness, demonstrating a biphasic pattern of fever. Investigations revealed leucopenia and thrombocytopenia, with a platelet nadir of  $133 \times 10^9/L$  on Day 8 of the illness. Alanine transaminase (ALT) was normal and aspartate transaminase (AST) was mildly raised at 50 U/L. He was discharged well but was subsequently lost to follow-up.

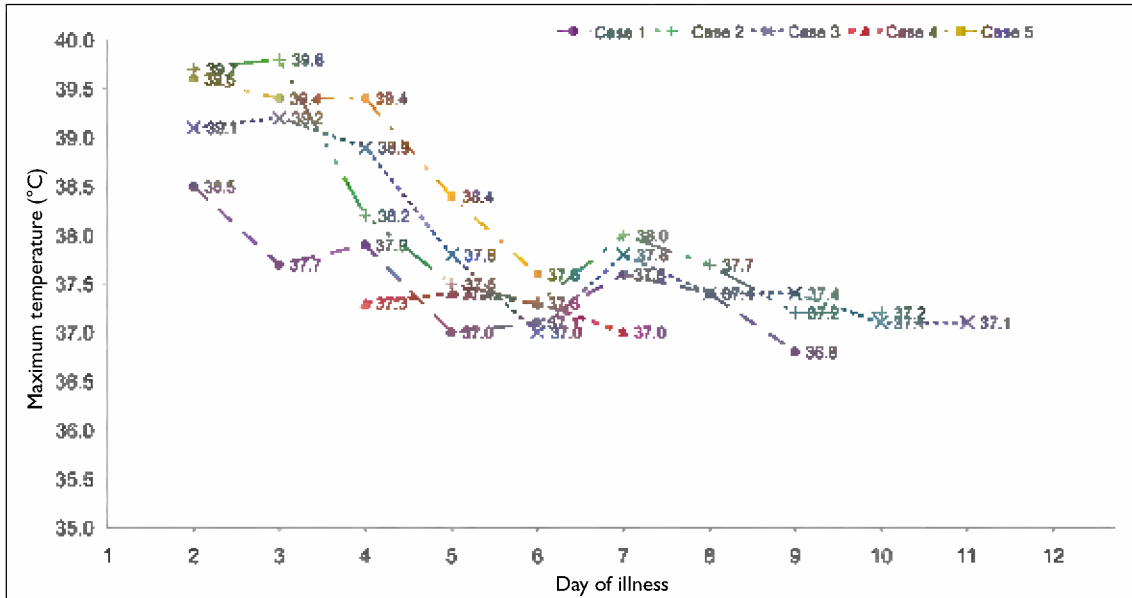


Fig. 6 Graph shows the trends of the maximum temperature by day of illness for the five cases.

### Case 3

A previously-well, 62-year-old Chinese Singaporean man, who worked at the Pasir Panjang wholesale market, presented with fever, myalgia, backache and polyarthralgia. His daughter had been recently diagnosed with chikungunya fever at another hospital. He reported red eyes, but without eye pain. He had no gastrointestinal symptoms. On admission, he had conjunctival injection (Fig. 4) and a maculopapular rash. He had swelling of the finger joints. He was febrile till Day 5 of the illness, with the recurrence of a low-grade temperature of 37.8°C on Day 7. Investigations showed mild lymphopenia and mild thrombocytopenia, with a platelet nadir of  $149 \times 10^9/L$  on Day 6 of the illness. Liver function was normal. His rash, joint swelling and conjunctivitis resolved in a week.

### Case 4

A 49-year-old Chinese man, who briefly stepped out of his car near the site of the Kranji chikungunya outbreak four days prior to his illness onset, presented with four days of fever, arthralgia involving the left knee and myalgia, and one day's duration of generalised rashes. He was noted to have red palms (Fig. 5) with a maculopapular rash and cervical lymphadenopathy on admission. He also had conjunctival injection. His fever had settled on admission on Day 4 of the illness. Investigations showed leucopenia, with a nadir white cell count of  $2.4 \times 10^9/L$  on Day 6 of the illness and very mild thrombocytopenia, with a nadir platelet count of  $164 \times 10^9/L$  on Days 6 and 7 of the illness. He had normal ALT and marginally-elevated AST of 44 U/L. He fully recovered on follow-up three weeks after symptom onset.

### Case 5

A 48-year-old Chinese woman with hyperlipidaemia and gout, presented with fever, myalgia, lower back pain and polyarthralgia involving her bilateral knees, metatarsophalangeal joints, shoulders, wrists and finger joints. She is a permanent resident who commuted weekly to Pontian, Malaysia to visit her family. She noted an intermittent dry cough, and reported knowledge of local chikungunya cases in Pontian at that time. On admission, she was observed to have a generalised macular rash, mild conjunctival injection, and swelling of both knees, finger joints and right metatarsophalangeal joint. She had mild leucopenia without thrombocytopenia. AST was marginally elevated at 44 U/L, but her liver function was otherwise normal. On follow-up three weeks later, she had mild, persistent joint pain involving the same joints. No discernible swelling was noted.

## DISCUSSION

Malaysia recorded its first chikungunya epidemic in 1998.<sup>(9)</sup> It re-emerged in April 2006 and genomic sequences of recovered isolates confirmed the outbreak originated locally.<sup>(10)</sup> In December 2006, chikungunya outbreaks in the Kinta district of Malaysia were caused by the Central/East African genotype.<sup>(11)</sup> Since early 2008, widespread chikungunya outbreaks have been reported in many states in Peninsular Malaysia, including Johor, Melaka, Perak, Negri Sembilan, Selangor, Pahang and Penang.<sup>(12)</sup>

In Singapore, the first autochthonous transmission of chikungunya fever was reported in January 2008,<sup>(13,14)</sup> although imported chikungunya cases have been notified since 2006. As of September 24, 2008, 231 cases were

**Table I. Demographical, epidemiological, clinical and laboratory data of five patients with acute chikungunya infection in Singapore.**

Case no.	Age (years)	Gender	Ethnic group	Comorbidity	Travel history	Duration of fever (days)	Duration of viraemia (days)	Onset of rash (day of illness)	Persistent arthralgia at follow-up (weeks after symptom onset)
1	37	Female	Malay	Nil	Johor, Malaysia	4	7	6	Yes (3 weeks)
2	50	Male	Malay	Nil	Nil	4	8	7	Lost to follow-up
3	62	Male	Chinese	Nil	Nil	5	11	2	No (1 week)
4	49	Male	Chinese	Nil	Nil	4	5	3	No (3 weeks)
5	48	Female	Chinese	Hypertension, gout	Johor, Malaysia	5	4	2	Yes (3 weeks)

notified to MOH this year. Of these, 108 were imported cases, with a history of travel to Malaysia, Indonesia, Sri Lanka, India and the Maldives.<sup>(15)</sup> Two of our five cases here illustrate the close relationship between Malaysia and Singapore. Many Malaysian workers commute daily from southern Johor to Singapore for work, and many more Singaporeans and Malaysians residing in Singapore visit Malaysia for leisure or work. At the Woodlands Checkpoint alone, the traveller volume was about 90 million in 2007.<sup>(16)</sup>

In previous reports, chikungunya fever has been observed to have an average incubation period of 2–4 days.<sup>(3)</sup> Fever was common, occurring in 89%–100% of the cases. Joint pain was reported in 96%–100% of the cases,<sup>(8,17,18)</sup> while joint swelling was less frequently reported, at between 32% and 40%.<sup>(17,18)</sup> Headache was noted in 31%–51% of the cases, while rashes in 28%–52%.<sup>(8,17,18)</sup> Fever lasted a mean of 4–5 days.<sup>(4,6)</sup> In our case series, all five patients had fever, which lasted 4–5 days (Table I). Two of our patients had a biphasic pattern, with a transient spike of temperature 2–3 days after the fever defervesced (Fig. 6). All had joint pain, involving multiple joints including the ankle, knee, shoulder, wrist and fingers. Rash was observed in all the patients, with morphology ranging from flushing, to maculopapular rash and palmar erythema. In our study, two out of four patients who attended follow-up at 1–3 weeks after symptom onset, reported persistent polyarthralgia (Table I). Other studies have reported similar findings, with joint pain persisting > 2 weeks in 4%,<sup>(9)</sup> > 3 weeks in 10%,<sup>(18)</sup> > 1 month in 53%,<sup>(5)</sup> > 2 months in 69%, and > 6 months in 13% of the cases.<sup>(4)</sup>

In a study of 88 patients from Reunion Island at 19 months' follow-up, persistent joint pain which was noted in 64% of cases was symmetrical in 64% and polyarticular in 100%. Joint swelling was noted in 16%. Activities of daily living were impaired in 46%.<sup>(19)</sup> In 47 French travellers, arthralgia was noted in 100% of the cases, of which 87% was bilateral and 41% was associated with

joint swelling. However, joint effusion, mainly in the knees, was detected only in 15%. Joint pain was persistent in 86% at three months and 48% at six months.<sup>(7)</sup> In our series, all our five patients had leucopenia (nadir white cell count  $1.6\text{--}3.9 \times 10^9/\text{L}$ ), while three out of five patients had mild thrombocytopenia (nadir platelet count  $133\text{--}164 \times 10^9/\text{L}$ ). Mild transaminitis was noted in three of the five patients (peak AST level 44–50 U/L). Mild leucopenia and thrombocytopenia, and mild to moderate transaminitis have also been reported in other studies.<sup>(4,6,17)</sup>

Chikungunya infection can be confirmed by PCR or serology. However, the use of serology is limited by the significant cross-reactivity of the assay with other alphaviruses. Viral antigen detection via PCR may be positive for more than seven days,<sup>(18)</sup> and up to nine days from the onset of the illness.<sup>(10)</sup> Of note, one of our patients had a positive chikungunya PCR test up to Day 11 of the illness. In addition, persistent viraemia beyond the febrile period was noted in three of five patients, with their chikungunya PCR tests remaining positive for 2–3 days post-defervescence. Panning et al reported that chikungunya IgM may be positive from Day 2 of the illness and chikungunya IgG from Day 3,<sup>(20)</sup> although other reports documented detectable IgM from Day 4<sup>(4,21)</sup> and IgG from Days 6–10.<sup>(4,21,22)</sup> Of note, antibodies can persist for many months – IgM up to Day 170 and IgG up to Day 252.<sup>(20)</sup>

With the establishment of autochthonous chikungunya transmission in Singapore, distinguishing chikungunya fever from hyperendemic dengue fever poses a clinical challenge. One comparative study from Thailand showed a significantly greater proportion of chikungunya patients with conjunctivitis, maculopapular rash and myalgia/arthralgia, when compared with patients with dengue haemorrhagic fever.<sup>(23)</sup> A comparison of PCR-confirmed chikungunya and dengue cases at Tan Tock Seng Hospital showed that vomiting and abdominal pain were more common in dengue patients and rash was more frequent in chikungunya patients. Chikungunya patients had an odds

ratio of 10 of developing myalgia/arthralgia compared with dengue patients. Higher nadir platelet and leucocyte counts were noted in chikungunya patients (median platelet  $168 \times 10^9/L$ , range  $102\text{--}376 \times 10^9/L$ ; median leucocyte  $3.4 \times 10^9/L$ , range  $1.0\text{--}13.0 \times 10^9/L$ ) compared with dengue patients (median platelet  $30 \times 10^9/L$ , range  $7\text{--}206 \times 10^9/L$ ; median leucocyte  $2.5 \times 10^9/L$ , range  $1.0\text{--}5.0 \times 10^9/L$ ).<sup>(24)</sup> Although differentiation of chikungunya from dengue may not alter supportive management, it would be useful in the diagnosis and advice to patients of the expected clinical course.

Excess mortality was observed in population studies during chikungunya outbreaks in Reunion Island,<sup>(25)</sup> India<sup>(26)</sup> and Mauritius.<sup>(27)</sup> Severe atypical chikungunya cases were reported from Reunion Island comprising mainly cardiovascular and neurological disorders.<sup>(28)</sup> Severe chikungunya infections requiring admission to the intensive care unit was also reported in Reunion Island.<sup>(29)</sup> Uveitis<sup>(30)</sup> and optic neuritis<sup>(31)</sup> have also been previously documented. There is currently no antiviral treatment for chikungunya fever, and treatment for polyarthralgia is largely symptomatic with analgesics and non-steroidal anti-inflammatory drugs.<sup>(2,3)</sup> Increased cases of bowel perforation as a result of non-steroidal anti-inflammatory drug and corticosteroid use for chikungunya were noted in India.<sup>(2)</sup> Chloroquine was used in ten patients for chronic arthritis associated with chikungunya,<sup>(32)</sup> but its efficacy has not been proven.<sup>(3)</sup>

Since January 2008, Singapore has experienced autochthonous transmissions of chikungunya virus in areas where *Aedes albopictus* and *Aedes aegypti* mosquitoes were present. Chikungunya may become endemic in Singapore, and doctors should be aware of its clinical features and complications. Fever, arthralgia and rash are the three most common symptoms. While taking a travel history, doctors should be mindful that indigenous chikungunya cases can occur.

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