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Juliana M Betts, Ee Laine Tay, Paul D R Johnson, Caroline J  
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Health Protection Policy Branch  
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CANBERRA ACT 2601

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# Buruli ulcer: a new case definition for Victoria

Juliana M Betts, Ee Laine Tay, Paul D R Johnson, Caroline J Lavender, Katherine B Gibney, Daniel P O'Brien, Maria Globan, Nectaria Tzimourtas, Miriam A O'Hara, Simon R Crouch

## Summary

With increasing Buruli ulcer cases in Victoria, a new case definition will support ongoing surveillance activities and a better understanding of disease epidemiology.

## Abstract

Laboratory-confirmed infection with *Mycobacterium ulcerans* is currently notifiable to health departments in several jurisdictions. Accurate surveillance is imperative to understanding current and emerging areas of endemicity and to facilitate research into a neglected tropical disease with poorly-understood transmission dynamics. The state of Victoria currently reports some of the highest numbers of *M. ulcerans* cases in the world each year, with 340 cases notified in 2018 (an incidence of 5.5 per 100,000 population). In May 2019, a group of clinical, laboratory and public health experts met to discuss a new case definition for the surveillance of *M. ulcerans* disease in Victoria, incorporating clinical and epidemiological elements. The new case definition supports important public health messaging and actions for residents and visitors to popular tourist areas in Victoria.

## Introduction

Infection with *M. ulcerans* usually manifests as a painless skin nodule or plaque on the leg or arm, which then ulcerates over a period of weeks. The resulting condition is known as Buruli ulcer (BU); however, based on regions of endemicity, it has also been variably named Bairnsdale ulcer or Daintree ulcer in Australia. The condition can be disabling and requires a lengthy course of antibiotics, sometimes with adjunctive surgery,<sup>1</sup> and specialist follow-up resulting in considerable cost to individuals and the health system.<sup>2</sup>

As a neglected tropical disease, BU transmission dynamics remain poorly understood, which has implications for public health control strategies.<sup>3</sup> This is despite the fact that Australia recorded the third-highest case numbers globally in 2018, after Ghana and Nigeria.<sup>4</sup> The vast majority of these cases were from selected coastal regions of Victoria (340 cases in 2018, an incidence of 5.5 per 100,000 population) and marked a substantial increase from the 66 cases (incidence 1.1 per 100,000 population) notified in 2013.<sup>4,5,6</sup> There has also been a recent change in the geographical focus of the outbreak, with increasing cases in residents and visitors to the Mornington Peninsula, Frankston municipality and south-eastern Bayside suburbs of Melbourne, and a decrease in case numbers from the Bellarine Peninsula.<sup>6</sup> This changing epidemiology is likely due to the interplay of complex environmental and ecological factors.

## Discussion and conclusion

Adequate disease surveillance remains a critical aspect of the public health response to the outbreak. A central element of any disease surveillance system is the case definition, which aims to ensure consistency and reliability of surveillance data.<sup>7</sup> The case definition has significant implications for

the positive predictive value of a surveillance system (the proportion of notified cases that represent true cases of the disease).<sup>7</sup> As BU is not a nationally notifiable disease in Australia, there is no national case definition. BU is currently notifiable to local health departments as a subset of non-tuberculous mycobacteria in Queensland, the Northern Territory, and South Australia, and specifically as *Mycobacterium ulcerans* in Victoria. All jurisdictions have, until recently, based their case definitions for surveillance upon laboratory confirmation (positive isolation or detection of *M. ulcerans* by culture or polymerase chain reaction (PCR)).

**Box 1: Previous case definition for *M. ulcerans* surveillance in Victoria, Australia (2011–2019)**

**Confirmed case**

A confirmed case requires laboratory definitive evidence only.

**Laboratory evidence**

Detection and specific identification of *Mycobacterium ulcerans* by culture on a specimen of tissue or a swab from a lesion / ulcer, by the Mycobacterium Reference Laboratory (MRL)

OR

Detection of IS2404 by polymerase chain reaction (PCR)

BU has been notifiable in Victoria since 2004. Victoria's previous case definition (Box 1) was developed by the *Mycobacterium ulcerans* consensus conference, held in Melbourne in February 2006, and systematic collection and recording of enhanced surveillance data has been in place in Victoria since January 2011.

In Victoria, as case numbers have escalated in the last few years, an increasing number of

'inconclusive' cases of BU have been difficult to classify using the original case definition. Consequently, a need for a revised case definition was identified. From 2011 to 2018, there were 1,217 confirmed cases of BU in the Victorian surveillance system, with 35 additional notifications that did not meet the 'confirmed' case definition. In particular, it was not clear how patients with clinically-apparent disease and laboratory-suggestive evidence, such as histologically compatible results or a weak-positive PCR, should be designated. To discuss this issue, a group of experts including public health physicians, infectious diseases physicians, laboratory scientists, epidemiologists and public health officers met in Melbourne, Victoria, on 31 May 2019. Examples of demonstratively 'inconclusive' cases were presented and discussed and possible alternative case definitions considered (Table A.1, Appendix A).

It was noted that, despite the high sensitivity and specificity of PCR for *M. ulcerans* detection (with some reports approaching 100% for these properties),<sup>8</sup> other factors may impede the reliability of PCR results in determining a case of BU.<sup>9</sup> These factors include specimen collection technique; processing of the specimen prior to referral for PCR; and the possibility of commensal residence of the organism on skin. While PCR testing has recently been made available free of charge at the Victorian Infectious Diseases Reference Laboratory, the use of private pathology services for couriering samples may place a financial burden on patients. A more nuanced case definition—incorporating histological, clinical and epidemiological evidence—enables cases, where PCR costs have been prohibitive, to still be captured as probable cases, where appropriate. Furthermore, in some contexts overseas, the sensitivity of PCR for BU diagnosis has been suggested to be lower than previously thought (65%; 95% confidence interval (95% CI): 56–73%) when assessed against the opinions of an expert panel.<sup>10</sup> Clinical diagnosis by the treating clinician had the highest sensitivity of 92% (95% CI: 85–96%);<sup>10</sup> however, this analysis was undertaken in an endemic setting where clinicians were likely to be familiar with the clinical

## Box 2: Revised case definition for *M. ulcerans* surveillance in Victoria (effective from 1 January 2020)

### **Reporting**

Both confirmed and probable cases should be notified.

### **Confirmed case**

A confirmed case requires laboratory definitive-evidence AND clinical evidence.

### **Laboratory-definitive evidence**

1. Detection and specific identification of *Mycobacterium ulcerans* by culture on a clinical specimen from a lesion / ulcer, by a Mycobacterium Reference Laboratory (MRL)

OR

2. Detection of IS2404 by polymerase chain reaction (PCR)

(Note: see laboratory-suggestive evidence below for 'weak positive' PCR results)

### **Clinical evidence**

A clinician experienced in the management of Buruli ulcer makes a clinical diagnosis of Buruli ulcer, including appropriate clinical follow-up to ensure a consistent clinical course.

### **Probable case**

A probable case requires clinical evidence, laboratory-suggestive evidence AND epidemiological evidence.

### **Clinical evidence**

A clinician experienced in the management of Buruli ulcer makes a clinical diagnosis of Buruli ulcer, including appropriate clinical follow-up to ensure a consistent clinical course.

### **Laboratory-suggestive evidence**

1. Histological examination of biopsied tissue demonstrates the presence of acid-fast bacilli

OR

2. A 'weak positive' detection of IS2404 by PCR (where the cycle threshold is given, a cycle threshold of  $\geq 35$  would be considered a weak positive result).

### **Epidemiological evidence**

The case resides in an area of local transmission<sup>i</sup> or has visited an area of local transmission within the 12 months prior to symptom onset.

i an area of local transmission is defined as any suburb, or similar area, where two or more confirmed cases of Buruli ulcer have ever been notified within a 12-month period, where such cases have no known travel to an alternative current area of local transmission.

features of the disease and where the quality of PCR testing may have been less robust. With the changing epidemiology in Victoria, clinical evidence should be considered only from those who are experienced in the management of BU (including some general practitioners, surgeons and infectious diseases physicians).

As of January 2020, Victoria's revised case definition mandates the reporting of both confirmed and probable cases and necessitates the inclusion of clinical evidence (Box 2). The inclusion of a probable case definition allows recognition of cases that do not quite meet the threshold to be a confirmed case, but still permits these cases to inform public health actions. Reflective of the current notification data, the vast majority of cases will be PCR-positive and therefore designated as confirmed cases. Such cases will still be readily comparable with confirmed cases from other jurisdictions, and with historically-notified cases in Victoria, for epidemiological research purposes. It will also allow Victoria to continue international reporting obligations to the Global Buruli Ulcer Initiative<sup>ii</sup> which monitors the percentage of PCR-positive cases. Rejected cases which are PCR-positive, but which lack clinical evidence, are unlikely to detrimentally affect comparison with previously-classified data: such cases tended to be rejected prior to formal institution of the new case definition, and numbers rejected are likely to be few. Moreover, the inclusion of probable cases permits a more nuanced approach to classification and may provide additional insights into the epidemiological factors associated with this neglected tropical disease.

By including epidemiological evidence in the new case definition, a need to define local transmission became apparent. As outlined in Box 2, an area of local transmission is defined as any suburb, or similar area, where two or more confirmed cases of BU have ever been notified within a 12-month period, where such cases have no known travel to an alternative current

area of local transmission. The application of this definition enabled characterisation of two new areas of local transmission – Aireys Inlet on the Surf Coast and the Geelong suburb of Belmont, recording three and seven cases in 2019, respectively.<sup>11</sup> This marked a significant development in understanding the geographical spread of the disease, and subsequently prompted important public health messaging for residents and visitors to this popular tourist area.

The changes described to the case definition for BU are intended to increase the positive predictive value and sensitivity of Victoria's surveillance system by incorporating a range of evidence beyond laboratory test results. This is of high importance for a considerably debilitating condition, where disease transmission remains poorly understood and epidemiology appears to be rapidly changing.

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ii <https://www.who.int/initiatives/global-buruli-ulcer-initiative-gbui>.

## Author details

Dr Juliana M Betts, Public Health Medicine Registrar<sup>1,2</sup>

Dr Ee Laine Tay, Epidemiologist<sup>1</sup>

Professor Paul D R Johnson, Infectious Diseases Physician<sup>3</sup>

Caroline J Lavender, Medical Scientist<sup>4</sup>

Dr Katherine B Gibney, Infectious Diseases Physician<sup>1,3,5</sup>

Associate Professor Daniel P O'Brien, Infectious Diseases Physician<sup>6,7</sup>

Maria Globan, Senior Scientist<sup>4</sup>

Nectaria Tzimourtas, Manager, Communicable Disease Investigation and Response<sup>1</sup>

Miriam A O'Hara, Public Health Officer<sup>1</sup>

Dr Simon R Crouch, Public Health Physician<sup>1</sup>

1. Victorian Government Department of Health and Human Services.

2. School of Public Health and Preventive Medicine, Monash University, Melbourne.

3. Department of Infectious Diseases, Austin Hospital, Melbourne.

4. Mycobacterium Reference Laboratory, Victorian Infectious Diseases Reference Laboratory (VIDRL), at the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia.

5. The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Victoria, 3000, Australia.

6. Department of Infectious Diseases, University Hospital, Geelong.

7. Department of Medicine and Infectious Diseases, Royal Melbourne Hospital, University of Melbourne, Melbourne.

## Corresponding author

Dr Simon Crouch

Address: Department of Health and Human Services, 50 Lonsdale St, Melbourne, Vic 3000

Telephone: 0435 069 229

Email: [simon.crouch@dhhs.vic.gov.au](mailto:simon.crouch@dhhs.vic.gov.au)

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## Appendix A

Table A.1: Previously-inconclusive cases

Case number	Case details	Initial classification by old case definition	Classification by new case definition
1	One-year-old female residing in Mornington Peninsula. Presented to hospital with cellulitis of right hand. Two blisters on the area, one of which had ruptured. Swab collected for <i>M. ulcerans</i> (MU). Commenced on cephalixin. Improvement noted over the subsequent 2–3 days and patient discharged. Swab returned weak positive results for MU (cycle threshold (Ct) = 38.9). Continued to improve clinically over subsequent weeks – no further management required. Culture and smear negative for <i>M. ulcerans</i> at 3 months.	Confirmed	Rejected – laboratory-suggestive and epidemiological evidence but does not meet clinical evidence.
2	Eighty-four-year-old female residing on the Bellarine Peninsula. Presented to GP with a 2-week history of ulcerated lesion to left forearm (< 5cm). Wound swab PCR weak positive for MU (Ct = 36), on first extraction. Re-extracted and obtained similar result (Ct = 38). Referred to Infectious Diseases at a public hospital. Biopsy specimen PCR negative and histology consistent with carcinoma.	Confirmed	Rejected – laboratory-suggestive and epidemiological evidence but does not meet clinical evidence
3	Fifty-six-year-old female from south east Melbourne with no history of travel to endemic areas. Presented to Hospital with a 1-month history of right lower leg changes: swelling and erythema. Managed as cellulitis. Initial PCR weakly positive (Ct = 34). Cellulitis resolved with standard therapy. Repeat PCR and tissue culture both negative for <i>M. ulcerans</i> .	Confirmed	Rejected – laboratory-suggestive evidence but does not meet clinical or epidemiological evidence.
4	Fifty-eight-year-old male with multiple visits to the Mornington Peninsula over the past 12 months. Presented to GP with an ulcerated lesion to left lower leg that seemed to have started from an insect bite. Punch biopsy demonstrated numerous acid-fast bacilli (on Wade-Fite and Ziehl-Neelsen stains) consistent with <i>M. ulcerans</i> . Referred to Infectious Diseases at a public hospital, successfully managed with antibiotics (rifampicin and clarithromycin) and dressings.	Suspected	Probable
5	Sixty-five-year-old male from Melbourne. Multiple visits to Frankston over the past 12 months, where he undertakes gardening. Presented with a 2-month history of an ulcer on left forearm (< 5 cm). PCR negative. Histology suggestive of MU with acid-fast bacilli seen on microscopy, dermal necrosis with some granulomatous inflammation. Treated with rifampicin and clarithromycin and narrow surgical excision with good effect.	Suspected	Probable