Journal of Paediatrics and Child Health

doi:10.1111/jpc.14704

ORIGINAL ARTICLE

Paediatric Buruli ulcer in Australia

Georgia Walker,[1] Deborah N Friedman,[2] Matthew P O'Brien [3], Chris Cooper,[1] Anthony McDonald,[4] Peter Callan[4] and Daniel P O'Brien [2,5,6]

Departments of [1]Paediatrics, [2]Infectious Diseases, [4]Plastic Surgery, Barwon Health, Geelong, [5]Department of Medicine and Infectious Diseases, Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, [3]Department of Infectious Diseases, Perth Children's Hospital, Perth, Western Australia, Australia and [6]Manson Unit, Médecins Sans Frontières, London, United Kingdom

Aim: This study describes an Australian cohort of paediatric Buruli ulcer (BU) patients and compares them with adult BU patients.

Methods: Analysis of a prospective cohort of all BU cases managed at Barwon Health, Victoria, from 1 January 1998 to 31 May 2018 was performed. Children were defined as ≤15 years of age.

Results: A total of 565 patients were included: 52 (9.2%) children, 289 (51.2%) adults aged 16–64 years and 224 (39.6%) adults aged ≥65 years. Among children, half were female and the median age was 8.0 years (interquartile range 4.8–12.3 years). Six (11.5%) cases were diagnosed from 2001 to 2006, 14 (26.9%) from 2007 to 2012 and 32 (61.5%) from 2013 to 2018. Compared to adults, children had a significantly higher proportion of non-ulcerative lesions (32.7%, $P < 0.001$) and a higher proportion of severe lesions (26.9%, $P < 0.01$). The median duration of symptoms prior to diagnosis was shorter for children compared with adults aged 16–64 years (42 vs. 56 days, $P = 0.04$). Children were significantly less likely to experience antibiotic complications (6.1%) compared with adults (20.6%, $P < 0.001$), but had a significantly higher rate of paradoxical reactions (38.8%) compared with adults aged 16–64 (19.2%) ($P < 0.001$). Paradoxical reactions in children occurred significantly earlier than in adults (median 17 vs. 56 days, $P < 0.01$). Cure rates were similarly high for children compared to adults treated with antibiotics alone or with antibiotics and surgery.

Conclusions: Paediatric BU cases in Australia are increasing and represent an important but stable proportion of Australian BU cohorts. Compared with adults, there are significant differences in clinical presentation and treatment outcomes.

Key words: Australia; Buruli ulcer; paediatrics; paradoxical reaction.

What is already known on this topic

1 Buruli ulcer (BU) is a neglected tropical disease affecting all ages.
2 BU is increasing in incidence, severity and number of geographic hotspots in Australia.
3 Destructive skin lesions pose risks of long-term morbidity, psychosocial and financial consequences.

What this paper adds

1 This is the first large-scale study to describe paediatric BU in Australia.
2 Paediatric disease is more commonly non-ulcerative and severe at diagnosis than adult disease, despite being diagnosed earlier.
3 Paediatric BU is ordinarily curable with antibiotic therapy alone, although paradoxical reactions frequently complicate therapy.

In Victoria, Australia, there is a rapidly growing epidemic of Buruli ulcer (BU),[1] a destructive infection of skin and subcutaneous tissue which, if not promptly diagnosed and treated, can result in permanent disability, deformity, protracted healing and costly treatment.[2,3] BU (also known as Bairnsdale ulcer, Daintree ulcer and Searls ulcer) is caused by *Mycobacterium ulcerans*, and is the third most common cause of mycobacterial infection in immunocompetent patients globally.[4] *M. ulcerans* produces mycolactone, a potent macrolide exotoxin which causes necrosis of skin and subcutaneous tissues, especially fat.[5] This process typically results in a painless nodule which erodes the overlying skin and ulcerates.[6] BU most commonly occurs on the limbs, but is also occasionally seen on the face, and less commonly on non-exposed areas of skin.[7–9]

Classified as one of the neglected tropical diseases by the World Health Organization (WHO),[10] BU is a major threat to public health in sub-Saharan Africa and discrete non-tropical settings in Australia, especially the Bellarine and Mornington Peninsulas of South-Eastern Victoria.[2,7,11] Australian BU cases are steadily increasing in number, severity and geographical location.[1,7] Prompt identification of suspicious lesions, early referral for laboratory diagnosis and institution of targeted treatment is vital for early disease control and minimisation of complications.[1]

Paediatric disease

Internationally, BU has been most commonly reported in children in Africa.[8,12] In African studies of BU, the median age of

Correspondence: Associate Professor Daniel P O'Brien, Department of Infectious Diseases, Barwon Health, PO Box 281, Geelong, Vic. 3220, Australia. Fax: +61 34215 2377; email: daniel.obrien@amsterdam.msf.org

Conflict of interest: None declared.

Accepted for publication 3 November 2019.

patients is 12–15 years, most cases identified are severe, and in children non-ulcerated lesions (plaque or oedematous) and upper body location are more common than in adults.[8,12–14]

In contrast, Australian BU cases are more commonly reported in adults and the proportion of cases classified as severe is approximately 20%.[7] A recent study of BU in Victoria showed a median age at diagnosis of 58 with only 9% of patients aged ≤15 years.[7] It is not clear if this epidemiological disparity between African and Australian paediatric cases can be completely explained by age-related population statistics.

Despite the global burden of paediatric BU, there is limited knowledge of how its natural history compares with adult disease, and why the age and severity at diagnosis differs greatly between African and Australian populations. To date, there have been no large-scale studies of Australian paediatric BU, and it is not well known whether BU diagnosis and treatment outcomes vary between children and adults.

This study aims to describe the epidemiology, clinical features, diagnosis, treatment and outcomes in Australian paediatric BU patients and compare them to adult patients from the same 20-year cohort of BU cases collected from the Bellarine and Mornington Peninsulas in Victoria, Australia. We also aim to provide clinicians with practical recommendations for diagnosis and treatment of BU in children.

Methods

Case-patient identification

All patients with confirmed *M. ulcerans* disease managed by Barwon Health clinicians between 1 January 1998 and 31 May 2018 were included in this study. Children were defined as ≤15 years of age.

Data collection

Data were prospectively collected using Epi Info Version 6 (CDC, Atlanta, Georgia, USA). These data included patient age; gender; geographic location; medical comorbidities; duration of symptoms at diagnosis; lesion type, size, clinical location and WHO category at diagnosis; mode of diagnosis; treatment and outcomes.

Definitions

Disease severity was defined using the WHO classification system where 'non-severe' is utilised for category 1 disease and 'severe' for categories 2 or 3 disease (a single lesion ≥5 cm or occurring at a critical site (eye, genitalia, breast, osteomyelitis), or multiple lesions of any size).[7,11] Immunosuppression was defined as any child with a primary or secondary immunodeficiency.

Standard drug dosages included rifampicin 10 mg/kg/day (maximum 600 mg per day), clarithromycin 7.5 mg/kg twice daily (maximum 500 mg per dose), ciprofloxacin 15 mg/kg twice daily (maximum 500 mg per dose). A complication of antibiotic therapy was defined as an adverse event attributed to an antibiotic that required its cessation as determined by the treating clinician.

Definitions of surgical methods were as previously described.[15] Treatment success was defined as complete healing of the lesion without the occurrence of a culture positive *M. ulcerans* lesion within 12 months of commencing antibiotic treatment. Paradoxical reactions were defined by the presence of one or both of the following features: (i) clinical: an initial improvement with antibiotic treatment in the clinical appearance of a *M. ulcerans* lesion followed by a clinically significant deterioration of the lesion or its surrounding tissues in terms of oedema or tissue necrosis, or the appearance of a new lesion(s); and (ii) histopathology: examination of excised tissue from the clinical lesion showing evidence of an intense inflammatory reaction consistent with a paradoxical reaction.[15]

Statistical analysis

Categorical values were compared using the Mantel–Haenszel test and median values for non-parametric variables were compared using the Wilcoxon rank-sum test.

Ethics approval

This study was approved by the Barwon Health Human Research and Ethics Committee. All data were de-identified prior to analysis.

Results

The study population included 565 patients: 52 (9.2%) children, 289 (51.2%) adults aged 16–64 years and 224 (39.6%) adults aged ≥65 years.

Baseline characteristics of children

Baseline characteristics of children are shown in Table 1. The median age of the 52 children was 8.0 years (interquartile range (IQR) 4.8–12.3 years), 50% of whom were female. A total of 20 (38.5%) cases occurred in children aged ≤5 years, 12 (23.1%) in children aged 6–10 years, and 20 (38.5%) in children aged 11–15 years. Total case numbers have increased from six cases (11.5%) between 2001 and 2006, 14 (26.9%) between 2007 and 2012, and 32 (61.5%) between 2013 and 2018, while the proportion of children in the cohort has remained stable (6.7–9.9%) (Table 1). Median time to diagnosis was 42 days (IQR 28–60 days), with no statistically significant difference between paediatric age-groups. None of the cohort was immunosuppressed.

At diagnosis, two-thirds (35, 67.3%) of lesions were ulcers, and the remainder (17, 33.7%) were non-ulcerative. The majority of lesions occurred on the lower limb, over one-third overlaid a joint, and over one-quarter were classified as severe. There was no statistically significant difference in severity stratified by child's age group ($P = 0.40$), nor by site of the lesion ($P = 0.29$). The proportion of severe disease increased over time from 16.7% from 2001 to 2006; 21.4% from 2007 to 2012 and 31.3% from 2013 to 2018.

Diagnosis, treatment and cure

A total of 50 (96.2%) children were diagnosed on the basis of a positive IS2404 PCR from swab (37, 74.0%) or biopsy (13, 26.0%), and 2 (3.8%) on histopathology demonstrating a necrotic ulcer with the presence of acid-fast bacilli. Most patients (28, 53.8%) were treated with antibiotics alone, 21 (40.4%) with antibiotics plus surgery and 3 (5.8%) with surgery alone. Initial antibiotic regimens were rifampicin and clarithromycin in 44 (89.8%) cases and rifampicin and

Table 1 Baseline characteristics for patients with Buruli ulcer from the Barwon Health Cohort 1 January 1998 to 31 May 2018

	Age group, years			
Characteristics	0–15	16-64	≥65	*P* value
Gender, *n* (%)				
Male	26 (50.0)	132 (45.7)	115 (51.3)	0.43
Female	26 (50.0)	157 (54.3)	109 (48.7)	
Time period, *n* (%)				
1998–2006	6 (6.7)	37 (41.1)	47 (52.2)	0.10
2007–2012	14 (9.3)	84 (56.0)	52 (34.7)	
2013–2018	32 (9.9)	168 (51.7)	125 (38.5)	
Lesion type, *n* (%)				
Nodule	6 (11.5)	10 (5.5)	15 (6.7)	<0.001
Oedema	10 (19.2)	13 (4.5)	24 (10.8)	
Plaque	1 (1.9)	2 (0.7)	1 (0.5)	
Ulcer	35 (67.3)	263 (91.3)	183 (82.1)	
WHO category, *n* (%)				
1	38 (73.1)	220 (81.2)	152 (71.4)	0.005
2	8 (15.4)	37 (13.7)	28 (13.2)	
3	6 (11.5)	14 (5.2)	33 (15.5)	
Median duration of symptoms, days (IQR)	42 (28–60)	56 (30–84)*	35 (21–60)**	
Lesion position, *n* (%)				
Upper limb	15 (28.9)	80 (27.7)	70 (31.3)	0.94
Lower limb	36 (69.2)	204 (70.6)	150 (67.0)	
Head/Trunk	1 (1.9)	5 (1.7)	4 (1.8)	
Joint	18 (34.6)	103 (35.6)	89 (39.7)	0.59
Multiple lesions, *n* (%)				
No	51 (98.1)	279 (96.5)	206 (92.0)	0.04
Yes	1 (1.9)	10 (3.5)	18 (8.0)	
Diabetes, *n* (%)	0 (0.0)	11 (3.8)	33 (14.7)	<0.001
Immune suppressed, *n* (%)	0 (0.0)	13 (4.8)	35 (17.3)	<0.001

*P =0.04; **P =0.39. IQR, interquartile range; WHO, World Health Organization.

ciprofloxacin in 5 (10.2%) cases. The median antibiotic duration was 56 days (IQR 54–84). Three (6.1%) of those who received antibiotics developed an antibiotic complication: all involved gastrointestinal intolerance to clarithromycin. Of the 24 patients (46.2%) who underwent surgery, the specific surgical intervention was documented in 16 patients (66.6%); 11 (68.8%) underwent curettage or debridement, 3 (18.8%) conservative excision, 2 (12.5%) wide excision. Nine of the 24 surgical patients (37.5%) required split skin grafting and 1 (4.2%) required a vascularised tissue flap. Paradoxical reactions were observed in 19 of the 49 (38.8%) patients who received antibiotics with a median onset on day 17 of therapy (IQR 14–62). There were no deaths in this cohort.

Cure was achieved in 51 patients (98.1%). The remaining child, a 17-month-old male, was initially treated with 56 days of oral antibiotic therapy (rifampicin and clarithromycin), although he experienced culture positive disease recurrence 4 months later. Retreatment with the same oral antibiotic regimen and duration was successful and the lesion healed by secondary intention 16 months after commencement of initial therapy.[16]

Comparison to adults

There was no difference in the gender balance between children and adults. Children had a significantly higher proportion of non-ulcerative lesions and severe lesions, but a significantly lower proportion of multiple lesions, compared with adults. The median duration of symptoms prior to diagnosis was shorter for children. There was no difference in the lesion position or the proportion of lesions located over a joint. (Table 1).

Similar proportions of children and adults received treatment with antibiotics alone, antibiotics plus surgery or surgery alone. (Table 2) Children were significantly less likely to experience an antibiotic complication, and had a significantly higher rate of paradoxical reactions compared to adults aged 16–64, but similar to adults ≥65 years. In addition, paradoxical reactions occurred earlier in children (range 3–88 days) than in adults. Cure rates were similarly high for children and adults treated with antibiotics alone or antibiotics plus surgery. However, when treated with surgery alone, cure rates were significantly higher for children.

Discussion

Our study's findings confirm a steadily growing epidemic of paediatric BU, with a fivefold increase in case numbers over the last decade. The growth of the paediatric epidemic is proportional to the observed increase in adult cases, suggesting that the epidemic's underlying cause is common to children and adults. The proportion of severe disease among children and adults has increased

Table 2 Comparison of treatment and outcomes for children and adults in the Barwon Health Buruli Ulcer Cohort 1 January 1998 to 31 May 2018

	Age group, years			
Treatments and Outcomes	0–15	16–64	≥65	*P* value
Antibiotics alone treatment, *n* (%)	28 (53.9)	166 (58.5)	119 (53.9)	0.37
Antibiotics + surgery treatment, *n* (%)	21 (40.4)	90 (31.7)	86 (38.9)	
Surgery alone treatment, *n* (%)	3 (5.8)	28 (9.9)	16 (7.2)	
Antibiotic complication, *n* (%)				
Yes	3 (6.1)	38 (15.0)	56 (27.5)	<0.001
No	46 (93.9)	215 (85.0)	148 (72.6)	
Paradoxical reaction, *n* (%)				
Yes	19 (38.8)	49 (19.2)	69 (34.5)	<0.001
No	30 (61.2)	206 (80.8)	131 (65.5)	
Median time to paradoxical reaction, days (IQR)	17 (14–62)	53 (29–74)*	58 (28.5–86)**	
Outcome antibiotics alone, *n* (%)				
Cure	27 (96.4)	165 (99.4)	111 (96.5)	0.18
Not cure	1 (3.6)	1 (0.6)	4 (3.5)	
Outcome antibiotics plus surgery, *n* (%)				
Cure	21 (100.0)	88 (100.0)	83 (98.8)	0.52
Not cure	0 (0.0)	0 (0.0)	1 (1.2)	
Outcome surgery alone, *n* (%)				
Cure	3 (100.0)	27 (84.3)	12 (44.4)	<0.01
Not cure	0 (0.0)	5 (15.7)	15 (55.6)	

*$P < 0.01$; **$P < 0.01$. IQR, interquartile range.

over time, possibly indicating enhanced pathogenicity of circulating *M. ulcerans* strains.[7]

In comparison to paediatric BU in African settings, Australian paediatric disease is less common, and less frequently severe at diagnosis (27% compared with >50%).[11] It has been postulated that African strains of *M. ulcerans* are more virulent than strains endemic to Australian settings,[17] which may explain the difference in disease severity. An alternative explanation is that delays in accessing diagnostics and treatment in resource-limited African settings could contribute to this discrepancy. In further contrast to African BU which more commonly affects male children,[12] Australian disease appears as likely to affect female children. The disparities in disease burden by age and sex between the continents may indicate differences in environmental exposures and transmission mechanisms.

We identified several differences between paediatric and adult disease in our cohort. Firstly, children were found to have higher rates of non-ulcerative lesions with the disease manifesting as a nodular or oedematous lesion in one third of cases. Despite its name, BU is often non-ulcerative, particularly in children, and importantly diagnostic swabs of the surface of non-ulcerated lesions can lead to initial false negative results.[18] Children are at higher risk of severe disease than adults aged 16–64 years, a finding which was not caused by diagnostic delay, as children were diagnosed a median of 2 weeks earlier than adults. We hypothesise that the increased severity of paediatric disease may relate to immaturity of the developing immune system. This propensity would mirror the increased rate of severe disease reported in the elderly, which is felt to result from a waning of immune function as well as increased rates of comorbid disease.[7,19]

More than half the children in our cohort were successfully treated with antibiotic therapy alone. This represents a major evolution in BU treatment strategy away from surgery as the primary therapeutic strategy as described in a 1995 case series of eight children treated for BU at The Royal Children's Hospital in Melbourne between 1967 and 1993. In this series, all eight children underwent surgical excision, six (75.0%) required split skin grafting and three (37.5%) received adjunctive antibiotic therapy.[20] At that time, antibiotic therapy alone was thought to be ineffective, and the authors supported treatment involving radical excision to deep fascia, which usually required grafting.[20] In contrast, our paediatric cohort demonstrates the effectiveness of antibiotic therapy alone. The contemporary backbone of BU treatment is rifampicin-based antibiotic therapy, with surgical intervention reserved to promote healing by removal of necrotic tissue.[11,15,16] Aggressive surgical resection of lesions is no longer recommended. The important role of surgery lies in improving the rate of wound healing, and preventing further tissue loss associated with severe paradoxical reactions. Surgery without antibiotics may be an effective option for selected small lesions; however, aggressive surgical resection is no longer required for most cases.[15] Globally, this change in therapeutic strategy towards medical or combined therapy has resulted in reduced rates of invasive surgery and general anaesthesia, as well as reduced incidence of disability, disfigurement and disease recurrence.[8,21] In resource-limited settings of Western Africa, this also represents major advantages for children and families by reducing the financial strain of accessing limited and overburdened surgical services, and reducing the barriers to education and employment that disability, disfigurement and recurrent disease can pose.[8,11,22,23]

International BU studies report rates of paradoxical reactions with antibiotic therapy for BU between 1.9 and 26%.[8] In contrast, 38.8% of the children in our cohort developed a

Table 3 Paediatric Buruli ulcer (BU) – Advice for clinicians

Clinical presentation
- BU affects children of all ages, occurs equally in males and females, and is predominantly a disease of immunocompetent children
- Two thirds of children present with an ulcer, usually painless and featuring necrotic slough and undermined edges[4]
- The remaining third mostly present with non-ulcerative nodular or oedematous lesions, though occasionally with plaques
- There is usually only one lesion
- Almost all lesions occur on the limbs (legs more than arms) and are commonly found over joints
- The lesion may have been present for 1–2 months prior to presentation, and may present as cellulitis not responding to routine therapy
- BU should be considered as a differential diagnosis in all children with skin ulcers or presumed cellulitis, particularly if exposed to endemic regions including the Bellarine and Mornington Peninsulas in Victoria, and Northern Queensland

Diagnosis
- Polymerase chain reaction (PCR) is the gold standard diagnostic test
- In the case of ulcerative lesions, diagnostic samples can be collected from purulent fluid, or a swab from the ulcer's undermined edge
- For non-ulcerative lesions a biopsy should be performed as surface swabs may commonly result in false-negative results
- The initial PCR may be negative (usually due to diagnostic technique). If the initial PCR result on a suspicious lesion is negative it should be repeated, preferably with testing performed on a biopsy specimen[18]
- Adjunctive diagnostic tests are smear microscopy and culture (with Ziehl-Nielsen staining to detect acid-fast bacilli), and histopathology

Treatment
- BU is curable, usually without the need for surgery
- The treatment modality depends on lesion type, location, and severity, as well as patient factors and family preference[25]
- We recommend urgent referral to a specialist experienced in BU management for commencement of oral antibiotic therapy. Most children can be managed as out-patients, with regular review
- Rifampicin-based combination therapy has been demonstrated to be highly effective. First-line therapy is rifampicin 10 mg/kg/day (maximum of 600 mg per day) plus clarithromycin 7.5 mg/kg twice daily (maximum 500 mg/dose) for 8 weeks (56 days)[25]
- Aggressive surgical resection of lesions is no longer recommended. Adjunctive surgery by surgeons experienced in managing BU may be considered in specific circumstances
- Paradoxical reactions (a clinical deterioration in BU lesions related to antibiotic treatment) are especially common in children, and do not indicate failing antibiotic therapy
- Regular wound care is an important element of BU management

paradoxical reaction, which was double the rate of our adult population. Prior to the recognition of paradoxical reactions, clinical deterioration following antibiotic commencement was frequently misdiagnosed as treatment failure, and the treatment strategy was often unnecessarily altered.[24] With improved recognition of paradoxical reactions, clinicians have been able to successfully monitor and initiate earlier treatment. Mild paradoxical reactions may be managed with observation alone although moderate to severe reactions often require steroid suppressive therapy, for example prednisolone 0.5–1 mg/kg, and potentially longer antibiotic treatment durations of up to 12 weeks.[25]

Conclusions

This study aimed to provide a framework for conceptualising paediatric BU, and for guiding its diagnosis and clinical management. Table 3 provides advice for clinicians about the clinical features, diagnosis and treatment of paediatric BU, based on current local evidence.

Our study is limited by the fact that we have not managed all BU cases acquired in the Bellarine and Mornington Peninsulas, since visitors generally present to clinical services where they live. However, as we manage almost all of the residents of the endemic areas that we service, we feel our findings are representative of the overall BU-affected population. Additionally, being a service with expertise in managing BU, there may be a referral bias for severe cases. However, as we almost exclusively see residents this bias is likely to be non-significant.

Access to early diagnostic testing and effective treatment are undoubtedly essential elements of the public health response to BU. While local research into transmission and environmental reservoirs are ongoing, disease control relies on both local and international cooperative research to answer these crucial questions.[1] It is hoped that this study serves to increase clinician awareness about paediatric BU, and facilitates discussion about future research.

References

1 O'Brien DP, Athan E, Blasdell K, De Barro P. Tackling the worsening epidemic of Buruli ulcer in Australia in an information void: Time for an urgent scientific response. *Med. J. Aust.* 2018; **208**: 287–9.
2 Global Buruli Ulcer Initiative, World Health Organization. *Buruli Ulcer (Mycobacterium ulcerans Infection): Fact Sheet*. Geneva, Switzerland: World Health Organization; 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/buruli-ulcer-(mycobacterium-ulcerans-infection) [accessed 10 March 2019].
3 Pak J, O'Brien DP, Quek T, Athan E. Treatment costs of *Mycobacterium ulcerans* in the antibiotic era. *Int. Health* 2012; **4**: 123–7.
4 Van der Werf TS, Van der Graaf WT, Tappero JW, Asiedu K. *Mycobacterium ulcerans* infection. *Lancet* 1999; **354**: 1013–8.
5 George KM, Chatterjee D, Gunawardana G *et al*. Mycolactone: A polyketide toxin from *Mycobacterium ulcerans* required for virulence. *Science* 1999; **283**: 854–7.
6 Boyd SC, Athan E, Friedman ND *et al*. Epidemiology, clinical features and diagnosis of *Mycobacterium ulcerans* in an Australian population. *Med. J. Aust*. 2012; **196**: 341–4.
7 Tai AYC, Athan E, Friedman ND, Hughes A, Walton A, O'Brien DP. Increased severity and spread of *Mycobacterium ulcerans*, southeastern Australia. *Emerg. Infect. Dis.* 2018; **24**: 58.
8 Yotsu RR, Richardson M, Ishii N. Drugs for treating Buruli ulcer (*Mycobacterium ulcerans* disease). *Cochrane Database Syst. Rev.* 2018; 8.
9 Yerramilli A, Tay EL, Stewardson AJ *et al*. The location of Australian Buruli ulcer lesions – Implications for unravelling disease transmission. *PLoS Negl. Trop. Dis.* 2017; **11**: e0005800.
10 Crompton D, Daumerie D, Savioli L; World Health Organization, Department of Control of Neglected Tropical Diseases. *Working to Overcome the Global Impact of Neglected Tropical Diseases: First WHO Report on Neglected Tropical Diseases*, 172. Geneva, Switzerland: World Health Organization; 2010.

11 Global Buruli Ulcer Initiative, World Health Organization. *Treatment of Mycobacterium ulcerans Disease (Buruli Ulcer): Guidance for Health Workers*. Geneva, Switzerland: The Organization; 2012.
12 Vincent QB, Ardant M-F, Adeye A *et al*. Clinical epidemiology of laboratory-confirmed Buruli ulcer in Benin: A cohort study. *Lancet Glob. Health* 2014; **2**: e422–30.
13 Maman I, Tchacondo T, Kere AB *et al*. Risk factors for *Mycobacterium ulcerans* infection (Buruli ulcer) in Togo – A case-control study in Zio and Yoto districts of the maritime region. *BMC Infect. Dis.* 2018; **18**: 48.
14 N'krumah RTAS, Koné B, Cissé G *et al*. Characteristics and epidemiological profile of Buruli ulcer in the district of Tiassalé, South Côte D'ivoire. *Acta Trop.* 2017; **175**: 138–44.
15 O'Brien DP, Callan P, Friedman ND, Athan E, Hughes A, McDonald A. *Mycobacterium ulcerans* disease management in Australian patients: The re-emergence of surgery as an important treatment modality. *ANZ J. Surg.* 2018; **89**(6): 653–8.
16 Friedman ND, Athan E, Walton AL, O'Brien DP. Increasing experience with primary oral medical therapy for *Mycobacterium ulcerans* disease in an Australian cohort. *Antimicrob. Agents Chemother.* 2016; **60**: 2692–5.
17 Mve-Obiang A, Lee RE, Portaels F, Small PLC. Heterogeneity of mycolactones produced by clinical isolates of *Mycobacterium ulcerans*: Implications for virulence. *Infect. Immun.* 2003; **71**: 774–83.
18 O'Brien DP, Globan M, Fyfe JM *et al*. Diagnosis of *Mycobacterium ulcerans* disease: Be alert to the possibility of negative initial PCR results. *Med. J. Aust.* 2019; **210**(9): 416.
19 O'Brien DP, Friedman ND, Cowan R *et al*. *Mycobacterium ulcerans* in the elderly: More severe disease and suboptimal outcomes. *PLoS Negl. Trop. Dis.* 2015; **9**: e0004253.
20 Goutzamanis JJ, Gilbert GL. *Mycobacterium ulcerans* infection in Australian children: Report of eight cases and review. *Clin. Infect. Dis.* 1995; **21**: 1186–92.
21 Klis S, Ranchor A, Phillips RO *et al*. Good quality of life in former Buruli ulcer patients with small lesions: Long-term follow-up of the BURULICO Trial. *PLoS Negl. Trop. Dis.* 2014; **8**: e2964.
22 Asiedu K, Etuaful S. Socioeconomic implications of Buruli ulcer in Ghana: A three-year review. *Am. J. Trop. Med. Hyg.* 1998; **59**: 1015–22.
23 de Zeeuw J, Omansen TF, Douwstra M *et al*. Persisting social participation restrictions among former Buruli ulcer patients in Ghana and Benin. *PLoS Negl. Trop. Dis.* 2014; **8**: e3303.
24 O'Brien DP, Robson ME, Callan PP, McDonald AH. "Paradoxical" immune-mediated reactions to *Mycobacterium ulcerans* during antibiotic treatment: A result of treatment success, not failure. *Med. J. Aust.* 2009; **191**: 564–6.
25 O'Brien DP, Jenkin G, Buntine J *et al*. Treatment and prevention of *Mycobacterium ulcerans* infection (Buruli ulcer) in Australia: Guideline update. *Med. J. Aust.* 2014; **200**: 267–70.