Buruli Ulcer in Australia

Paul D. R. Johnson

1 Bairnsdale Ulcer and the Discovery of *Mycobacterium ulcerans*

“Bairnsdale ulcer” (synonymous with Buruli ulcer (BU)) was first recognised and named as a distinct clinical entity in the late 1930s by General Practitioners working in Bairnsdale—a regional town in east Gippsland, Victoria, Australia [1, 2] (Fig. 1). They suspected their patients were suffering from a new type of infection caused by an acid-fast bacillus, but with clinical features distinct from tuberculosis and leprosy. Pathology specimens forwarded to the University of Melbourne and the transfer of patients from Bairnsdale to the Alfred Hospital in Melbourne provided researchers with clinical samples from which the microbiology and pathology of *Mycobacterium ulcerans* infection were first definitively described [3]. Although not listed as authors on the original 1948 publication “A New Mycobacterial Infection in Man” the contribution of these doctors was pivotal in the discovery of *M. ulcerans*. Glen Buckle, who with Jean Tolhurst first isolated *M. ulcerans* in pure culture, later drew special attention to the important contribution of Drs D. S. Alsop, L. E. Clay and J. R. Searls of Bairnsdale, and Dr. K. E. Torode of Colac [1].

In their initial research, Buckle and Tolhurst showed that *M. ulcerans* was able to grow on media that supported other pathogenic mycobacteria provided the incubation temperature was kept at 30–33 °C. They noted that growth slowed above 35 °C and that cells started to slowly die above 37 °C. They went on to establish experimental infections in mice, rats and rabbits and observed that while local lesions were produced at the site of subcutaneous inoculations, when inoculated into the

P. D. R. Johnson (✉)

Infectious Diseases Department, Austin Health and University of Melbourne,
Heidelberg, VIC, Australia

WHO Collaborating Centre for *Mycobacterium ulcerans*, VIDRL, Peter Doherty Institute for
Infection and Immunity, Melbourne, VIC, Australia

e-mail: Paul.Johnson@austin.org.au

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Fig. 1 Australia with locations of confirmed BU acquisition since 1937 shown in red

peritoneal cavity, peripheral lesions developed on distant extremities in cooler body areas (scrota, tails). Sir Frank Fenner, a renowned Australian scientist who later worked on the eradication of smallpox, studied *M. ulcerans* in the 1950s. Fenner demonstrated that an inoculum of only 5–10 cells would reliably produce lesions in mice that appeared after at least 150 days (5 months) and that BCG was protective in an animal model at low but not higher inoculums [2]. Interestingly, the very low inoculum required to produce an experimental infection has recently been confirmed in new research that demonstrated a mosquito could initiate an *M. ulcerans* infection in a mouse-tail coated with *M. ulcerans* cells. In these experiments, the calculated effective inoculum size was in the range of just 2–3 cells [4].

Between 1948 and 1975 Radford reported 39 human cases of BU in Australia: 12 from Victoria including those in the original report, 4 from the Northern Territory (three from Croker Island and one from the coastal mainland near Darwin) and at least 20 from near Rockhampton and near Cairns in Queensland. A single case report from New South Wales (NSW) was published in 1954 but was thought likely to be an imported infection as the patient had epidemiological links to Papua New Guinea [2].

The Bairnsdale region in Victoria (latitude 38°S) is approximately 2000 km by road from Rockhampton in Queensland (latitude 23°S) and almost 3000 km from Cairns (latitude 17°S) (Fig. 1). There are large continuous human populations along the NSW Coast between the Victorian and Queensland endemic regions, yet locally acquired BU remains almost unknown there with the exception of one published confirmed case [5] and a small number of others from southern coastal NSW very close to the Victorian border. There has also been only one confirmed case from the

northern tropical coast of Western Australia but no local transmission in the more populated temperate areas further south [6]. BU does not occur in South Australia or Tasmania, western Victoria or anywhere in the dry Australian interior. The reason for this patchwork focal distribution within and between states is unknown, but the geographic pattern has remained stable from the 1950s, except in Victoria.

All Australian isolates of *M. ulcerans* belong to the virulent so called “Classical Lineage” that also causes BU in Africa [7, 8], but there are small differences at the genomic level that allow location of Australian clinical isolates to specific geographic regions. Variable number of tandem repeat (VNTR) typing has been used to successfully attribute region of acquisition when newly diagnosed patients report multiple potential exposures [9]. More recently a detailed investigation using whole genome sequencing of 178 *M. ulcerans* isolates from different regions of Australia spanning 70 years has been conducted [10]. The results strongly support single introduction events into each of the major Australian endemic areas with subsequent local evolution. It also appears that *M. ulcerans* first reached Australia in the north, possibly from Papua New Guinea and has moved in large skip-steps down the east coast of Australia and along the Southern coast of Victoria as far as Melbourne. These introductions are historically recent and may have been assisted by coastal shipping activities down the east coast since European settlement. In Victoria movement from east to west along the southern mainland coast is continuing with the most recent recognised introduction event occurring in about 2003 to Rye on the Mornington peninsula [10] (Figs. 1 and 2).

Fig. 2 Sketch map showing of southern approaches to the city of Melbourne including Port Phillip Bay, Western Port, the Mornington and Bellarine Peninsulas and towns mentioned in the text

2 Buruli Ulcer in Queensland

Buruli ulcer was recognised in Queensland from the early 1950s and possibly even earlier [3, 11]. In Queensland, the local names Daintree ulcer or Mossman ulcer have been used in preference to Bairnsdale ulcer [12]. To avoid confusion in this chapter, the term “Buruli ulcer” refers to all cases of *M. ulcerans* infection acquired in Australia, past and present.

Two separate endemic areas were recognised in Queensland from the early 1950s, one in the Douglas Shire just north of Cairns, particularly between Mossman and the Daintree River [13, 14], and a second on the Capricorn Coast near Rockhampton and Yeppoon [2, 11]. There have also been single cases or small clusters linked to Nambour near Brisbane, the Glass House Mountains (Sunshine Coast), Maryborough (Fraser Coast), Townsville [15, 16], and Port Douglas near Cairns and Mossman [2, 11, 16, 17]. However, due to the long incubation period of BU [18] it is difficult to confirm that any one location is endemic based on a single case unless a detailed travel history is obtained that excludes contact with all other regions or there is other evidence such as strain typing of the isolate to support geographic attribution. For most historical cases, these details are no longer available.

The most active recent Queensland focus of *M. ulcerans* transmission is in the far north of the state, from Mossman to the Daintree River in the Douglas Shire. The great majority of infections associated with this region have occurred in permanent residents rather than visitors [12]. In her Master of Science thesis published in 1996, May Smith, for many years Director of Nursing at Mossman Hospital, reported 41 cases of BU acquired in this small geographic region [13]. The first likely case occurred in 1952 and the first confirmed case in 1964. However, local aboriginal people had been aware of a disease resembling BU in this region for several generations. Subsequently, Steffen *et al.* reviewed five decades of BU in the far North Queensland endemic area and reported a gradual increase from approximately one case every 2 years in the 1960s and 1970s to approximately two cases per year in the 1980s rising to approximately four cases per year in the 2000s [12]. Subsequently the incidence reduced again to an average of two cases per year with the notable exception of 2011 and 2012 when there were 61 and 11 confirmed cases respectively [17]. Since then, the usual pattern has resumed with only 6, 2 and 1 new diagnoses in 2013, 2014 and 2015. In the 2011 Australian census, the permanent population of the Douglas Shire was just over 11,000. From this a crude annual incidence of BU for the Douglas Shire can be estimated to range from 9 to 550 per 100,000 population.

Steffen and Freeborn proposed that the exceptional year of 2011 followed an unusually long and unusually wet 2010/2011 rainy season that may have led to an abrupt temporary expansion of an unknown reservoir or vector. Interestingly, most cases in the exceptional year of 2011 were diagnosed in the dry season (winter) which is likely explained by a surge in transmission during their unusual wet season (summer) followed by a delay of several months attributable to the long incubation period of BU and an additional pre-diagnostic interval [18]. Despite the very

different climate and geography, exactly the same temporal pattern is observed in temperate Victoria with peak transmission likely occurring in summer but most new diagnoses made in winter and early spring [19, 20].

3 Buruli Ulcer in Victoria

In the original definitive description of *Mycobacterium ulcerans* published by MacCallum et al. in 1948, 6 patients were described, 5 from “in and around” the town of Bairnsdale and a sixth case from Colac over 400 km to the west of Bairnsdale by road (Fig. 2). It was noted that the Bairnsdale cases were from separate households unknown to each other, suggesting from the outset chance exposure to a dispersed environmental pathogen rather than exposure to single point source or person to person transmission [3]. Also noted at the time was the wide age distribution with the disease affecting children and adults and both genders equally which has remained a consistent pattern in Victoria since then [21–23]. John Hayman, a pathologist with a long-standing interest in BU, reported 42 cases in Victoria, all from the general Bairnsdale region, including the original 5 from the 1930s to 1990. Notably only 14 of these were directly linked to the town of Bairnsdale itself, 8 were from the nearby lakeside hamlet of Loch Sport but others were from up to 50 km to the east of Bairnsdale. In seeking to understand the distribution he observed, Professor Hayman proposed proximity of cases to relict rain forest and suggested this was intermittently disturbed through fire or flooding leading to temporary seeding of lower lying areas near human habitation with *M. ulcerans*. He also proposed that *M. ulcerans* may be distributed through aerosols generated by wind action over water bodies that were supporting temporary blooms of *M. ulcerans* recently dislodged from its usual rainforest habitat upstream [24].

From 1990 there was a notable change in the epidemiology of BU in Victoria as *M. ulcerans* appeared to switch its behaviour from low level endemicity in a fixed geographic region to high-level transmission in completely new regions not previously endemic. Initially, a handful of new cases were identified by John Hayman around Tooradin and Warneet on the shores of Western Port, 240 km to the west of Bairnsdale [25] (Fig. 2). Next, at East Cowes (known as “Silverleaves”) on Phillip Island a local General Practitioner, Dr. Paul Flood, recognised a cluster of unusual ulcers in patients in his practice from late 1992 which were subsequently confirmed by histology and culture to be caused by *M. ulcerans* [26]. From 1992–1995 there were at least 25 new cases, almost all within a very small region surrounding a golf course and a newly formed shallow lake that had developed following the construction of a fire access track [27]. The golf course was irrigated with treated recycled water purchased from the Phillip Island sewerage facility which was delivered to a permanent dam on the golf course and allowed to mix there with natural ground water before the dam contents were pumped to sprinklers on the greens and fairways. Victorian public health authorities arranged for improved drainage of the newly formed lake behind the access track in 1993 and altered the way recycled water was used on the golf course from 1995. This was followed by a sustained

reduction in new cases linked to Phillip Island in subsequent years [21] and east Cowes/Silverleaves is currently disease free.

We attempted to support the hypothesis that the golf course irrigation system and/or shallow lake that formed behind the fire access track close to houses where people had acquired BU had become contaminated with *M. ulcerans* initially with direct culture of environmental samples and later by direct detection with PCR in water samples collected from the outbreak region. In a pilot study aimed at developing a PCR method to detect *M. ulcerans* in environmental samples we discovered the insertion sequence (IS) 2404 and developed an IS2404-based PCR assay in 1995 [28, 29]. We then investigated whether *M. ulcerans* was present in stored samples obtained from the dam and golf course irrigation system. In the first ever example of environmental detection of *M. ulcerans*, we identified PCR-positive water samples from the Cowes golf course pumping system and ground water that had collected behind the fire access track the previous year [28, 29]. Our attempts to directly culture *M. ulcerans* from environmental samples were unsuccessful.¹

Clinical samples supplied by Professor John Hayman were crucial in the initial validation of the new PCR assay and it was quickly appreciated that IS2404 PCR would be an excellent rapid diagnostic test for BU and soon become the diagnostic test of choice in Australia, due to its quick turn around and exceptional sensitivity and specificity. PCR based on the IS2404 target is now also the gold standard for BU diagnosis in reference laboratories worldwide [16, 28, 30, 31].

The sudden appearance of a new focus of transmission at Cowes, Phillip Island, the high attack rate (up to 6% of the permanent population of east Cowes were affected) [21] and the recognition of infection in visitors who may have spent only brief periods in the outbreak area has become a hallmark of the new epidemiology of BU in Victoria since 1990. At the same time as the Phillip Island outbreak, there was a similar less intense outbreak over a slightly longer period (1990–1996) at Frankston/Langwarrin on the Mornington peninsula [25]. Dr. Mark Veitch, an epidemiological intelligence officer with the Department of Human Services in Victoria described the detailed epidemiology of the Cowes outbreak, and made an interesting link between the two outbreaks (Frankston/Langwarrin from 1990, East Cowes from 1992) noting that sand mined near Langwarrin had been used in the construction of a new road system in East Cowes (Silverleaves) just prior to the outbreak there [21].

Between 1995 and early 2000s there were very few cases of BU in humans in Victoria and the disease returned to its former obscurity. However, the situation changed again abruptly with large new outbreaks on the Bellarine Peninsula and most recently on the Mornington Peninsula (Fig. 2). At the time of writing (late 2017) there has been an exponential increase in cases in Victoria for the past 4 years (Fig. 3), and several new endemic areas have become established. The re-emergence began in 1998 when cases of BU were linked to St Leonards. St Leonards is a small town on the Bellarine Peninsula with a permanent population of 2480 (2016 Census) and like Cowes on Phillip Island also a popular summer holiday destination. The outbreak at

¹This work was performed by scientists at the Mycobacterium Reference Laboratory, then located at Fairfield Infectious Diseases Hospital.

Fig. 3 Cases (n) of confirmed BU in Victoria by year 1940 to November 2017. Cases prior to 1992 courtesy private database created by Professor John Hayman

St. Leonards was investigated by the Victorian Department of Human Services Communicable Diseases Branch. There were two cases in 1998, one more in 2000 and then 11 diagnosed in 2001. Environmental PCR was attempted following the success at Phillip Island but no positive results were obtained from low-lying water sources or from the local golf course irrigation system (recycled water not used).

Cases have continued to occur at St Leonards since 1998 albeit at low intensity after 2001. Possible explanations to explain the outbreak at the time included much higher than usual rainfall and local reports of high mosquito numbers. A small proportion of mosquitoes trapped in CO₂ traps at St. Leonards were subsequently shown to harbour *M. ulcerans* DNA [32].

In 2002 new cases of BU abruptly appeared at Point Lonsdale, 20 km around the coast to the south of St Leonards (Fig. 2) heralding the onset of an intense, sustained outbreak that peaked in 2011 and is slowly abating now, but has been an important local public health issue at Point Lonsdale for 15 years [23]. Point Lonsdale is a small seaside resort town with a permanent population of around 2684 (2016 census) which increases significantly during the summer. The crude incidence in 2011 was estimated as 770/100,000 of the permanent population (C. Lavender *personal communication*). Many of the local population are retirees and a feature of the Point Lonsdale outbreak was the high attack rate in older people with up to 3.7% of all

residents aged over 75 requiring treatment for BU [22]. A second notable feature at Point Lonsdale and elsewhere in Victoria since 1990 has been the high proportion of visitors who developed BU [22]. At Point Lonsdale in the first 2 years of the outbreak only local residents were affected but after 2004 this changed with both an increase in outbreak intensity and the appearance of disease in visitors and residents in almost equal proportions [22].

The changing epidemiology of BU in Victoria and concern from local councils and influential residents prompted the creation of a series of Victorian Government Public Health Grants to investigate the new epidemiological patterns of disease. From 2001 diagnostic PCR for BU became a standard diagnostic test performed at the Victorian Infectious Diseases Reference Laboratory, and from January 2004 in response to increased local concern BU became a legally notifiable infection in Victoria which has greatly aided mapping of cases and new endemic areas. In 2005 a new BU focus appeared at Barwon Heads (and the adjacent town of Ocean Grove) a further 10 km around the coast from Point Lonsdale (Fig. 2). From 2012 onwards new endemic foci have appeared along the Mornington Peninsula affecting towns including Sorrento, Blairgowrie, Rye Tootgarook, Mornington, Frankston and surrounding suburbs, and further north at Seaford and Beaumaris, just 24 km from the centre of Melbourne.

In 2007 two important studies from the Bellarine Peninsula were published which have changed our understanding of likely modes of transmission of BU in Victoria. Quek et al. conducted a case control study that examined risk factors in 49 cases and 609 controls. The key new finding of this research was a statistically significant association between mosquito bites and risk of BU. In their final multivariate model being bitten by mosquitoes was found to increase risk (odds ratio 2.60 [95% c.i. 1.22–5.53]) and use of insect repellent to reduce risk (odds ratio 0.37 [95% c.i. 0.19–0.69]) [33]. In the second study conducted at Point Lonsdale between 2004 and 2007, 11,500 mosquitoes were trapped of which approximately 4/1000 were PCR-positive for IS2404 and in a subset of samples there was molecular evidence that we were detecting the human outbreak strain of *M. ulcerans* [22, 30]. At the time of writing the detection of *M. ulcerans* in several species of mosquitoes has been repeatedly confirmed in Victoria [32] but similar studies have so far been negative in Africa [34].

4 Buruli Ulcer in Animals in Victoria

During the 1980s, in the Bairnsdale region of Victoria, *M. ulcerans* infection was identified in 11 Koalas (arboreal marsupials) from a population of about 200 animals on Raymond Island, just a few km southeast of Bairnsdale [35–38]. This was the first recognition of naturally occurring BU in any species other than humans anywhere. The affected animals were mature, usually male and it was suggested that lesion distribution was consistent with wounds acquired during social behaviour such as fighting.

In the late 1990s after the decline in human cases at Phillip Island, several sick adult possums (also native arboreal marsupials) were detected at Phillip Island with ulcerative disease, at least three of which were confirmed to have *M. ulcerans*

infection by histology and PCR [35]. Although brushtail possums had previously been shown to be susceptible under experimental conditions to *M. ulcerans* infection and to transmit the infection to other co-housed individuals [39], this was the first recognition of natural infection in possums. There is a koala reserve at Phillip Island just 2 km from the endemic area in east Cowes, yet no cases of BU in this koala population were observed despite notification to local wild life officers of the presence of the disease in local humans and possums.

Subsequently, while seeking possible environmental sources of mosquito exposure to *M. ulcerans* we identified positive PCR signals in environmental samples at Point Lonsdale, with by far the strongest signals arising from possum excreta. This led to a systematic investigation of the possible role that possums may play as a reservoir and environmental amplifier of *M. ulcerans* in Victoria. We performed environmental surveys and trapped and screened 63 possums (42 ringtail, 21 brushtail). During the surveys, we discovered that 42% of possum excreta samples collected at Point Lonsdale were strongly PCR-positive for *M. ulcerans* compared with <1% in non-endemic areas. Further, 9/42 trapped ringtail possums had clinical BU lesions confirmed by PCR as did 1/21 brushtail possums. Additional trapped animals without clinical lesions were found to be excreting high levels of *M. ulcerans* DNA in their faeces. This research confirmed the validity of using possum excreta surveys as a proxy for mapping the occurrence of BU in possum populations, and for the first time suggested that BU may be a zoonosis with humans acting as spill-over hosts connected directly or indirectly to possums via mosquitoes [40]. In 2011, just prior to the surge in new cases in Victoria on the Mornington Peninsula, Carson *et al.* validated this model in a new endemic area by showing that possum excreta at Sorrento and Blairgowrie on the Mornington peninsula was strongly PCR-positive close to the location of new human cases of BU [41]. Interestingly, no analogous small animal reservoir has yet been identified in Africa [42] but there is recent evidence that bandicoots² in the far north Queensland endemic focus of BU also excrete *M. ulcerans* in their faeces [43].

In Victoria, but not elsewhere in Australia several other naturally acquired BU infections have been reported in animals including at least three species of possums [44]. On the Bellarine Peninsula four domestic dogs have been diagnosed with BU [45], there has been a confirmed case in a cat from eastern Victoria [46], a long footed potoroo (small terrestrial marsupial) from eastern Victoria [46], two horses from eastern Victoria and at least three alpacas (Bellarine Peninsula and eastern Victoria) [35, 44–47]. Notably these animal infections have occurred across the same geographical region that is endemic for humans in Victoria (Fig. 1). Given the relatively wide experimental host range of *M. ulcerans* (lizards, amphibians, chick embryos, possums, armadillos, rats, mice, rabbits, guinea pigs, pigs and cattle [35, 48, 49]) it is surprising that naturally acquired disease in animals appears to be relatively rare and restricted. The failure (so far) to identify natural infections in animals outside Victoria is also surprising and remains unexplained. Possible explanations include the particular susceptibility of humans (and possums), something specific about Victorian strains of *M. ulcerans* compared with Queensland and Northern

²Bandicoots are small to medium sized native terrestrial marsupials.

Fig. 4 Proposed transmission pathways of *M. ulcerans* between the environment, mosquitoes, possums and humans in Victoria Australia PLOS Neglected Tropical Diseases 2010 doi:<https://doi.org/10.1371/journal.pntd.0000791.g005>

Territory strains [6], or that the concentration of *M. ulcerans* that accumulates in the environment in Victoria is higher than elsewhere. It is also possible that the disease does occasionally occur in animals outside Victoria but is not recognised or not brought to the attention of veterinarians familiar with the disease (Fig. 4).

5 Recent Epidemiology of Buruli Ulcer in Victoria

The rapid expansion of BU endemic areas and recent exponential increase in numbers of cases in humans is unprecedented and a significant cause of local concern. There is published and unpublished evidence that possums carry and excrete *M. ulcerans* DNA in high concentration in faeces at Point Lonsdale, Barwon Heads, Sorrento, Blairgowrie, Beaumaris and near Rosebud - all places where human BU has become endemic since 2002 (Fig. 2). Similar surveys outside endemic areas yield negative results [40]. The frequent acquisition of BU by visitors to endemic areas in Victoria as well as local people in almost equal proportion suggests that transmission of *M. ulcerans* is a chance event and that risk may not be present throughout the year. Possums are likely to carry *M. ulcerans* disease over prolonged periods yet from what we understand so far, the risk of acquiring infection appears to occur mainly in summer for both residents and visitors as cases in both groups present to doctors at similar times (winter and spring). This may be explained by an increase in vector activity in warmer weather [22] combined with greater exposure to the outdoor environment and/or less use of protective clothing. Interviews with visitors have identified very short exposure periods in some cases which have allowed us to estimate a median incubation period of 4.5 months but a range up to 9 months. A recent study of 649 BU lesions in 579 patients identified a highly non-random distribution with BU lesions in Victoria preferentially occurring

Fig. 5 Lesion distribution from 649 BU lesions occurring in 579 patients, Victoria, Australia. PLOS Neglected Tropical Diseases 2017; doi: <https://doi.org/10.1371/journal.pntd.0005800.g002>

on ankles, back of calves, forearms and elbows but rarely on the soles of feet, palms of hands or parts of the body that usually remain covered [19] (Fig. 5). One explanation for this distribution is targeting behaviour by biting insects although it is possible that there is more than one mode of transmission. A recent study of family clusters of BU in Victoria has suggested that exposure risk per household lasts only a short time and provides molecular typing evidence to support the long-standing epidemiological observation that *M. ulcerans* is not transmitted between individuals within a household [50].

6 Clinical Management of Buruli Ulcer in Australia

The large number of recent cases in Australia, particularly in Victoria and the relative complexity of treating BU has meant that a small group of Infectious Diseases Physicians and Surgeons have greatly increased their clinical experience and

understanding of the management of BU. Much of this experience has been captured in a number of recent publications. We are fortunate to have universal health-care coverage and rapid access to doctors and diagnostic tests. Many recently diagnosed cases are WHO category I (<5 cm), nevertheless from time to time we also see severe cases, sometimes due to delayed diagnosis or acute oedematous disease which appears in every respect to be similar to severe cases in Africa [19, 51]. National treatment guidelines have been developed [52, 53] and there is now general agreement that all-oral antibiotic regimens based on rifampicin with a companion drug (generally clarithromycin) are highly active against *M. ulcerans* [14, 54, 55], and that medical therapy alone is frequently curative without surgical intervention. However, drug therapy is not straightforward particularly in the elderly [51, 56] and patients with larger lesions often appear to deteriorate during treatment due to paradoxical inflammatory reactions [57, 58]. Short courses of oral steroids may help these reactions to settle [59, 60]. The optimal role and timing of surgery has still to be established but clearly surgery has an important role in assisting with healing through removing extensively necrotic tissue and to repair large skin defects. For small lesions the decision to treat with primarily surgical or medical therapy is partly determined by patient and clinician preference as both approaches are curative in the majority of cases. Relapse is more common if antibiotics are not used [17, 61, 62].

7 Buruli Ulcer: The Australian Paradox

BU is classified by WHO as a neglected tropical disease with most cases occurring in poor subsistence farming families in tropical river land regions in West and Central Africa. For unknown reasons rates of BU in Africa are now static or may even be in decline after significant epidemics during the past 20–30 years. In contrast, the south-eastern Australian state of Victoria is temperate and economically developed, yet case numbers are exponentially increasing. Most people affected live in or visit affluent coastal resort towns that have become newly endemic. Despite the contrast in epidemiology between Africa and Victoria the disease is quite similar in its clinical appearance, the suffering it causes and the complexity of treatment of severe forms of BU [63, 64].

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