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**Mycobacterium ulcerans** infection (Buruli ulcer) in French Guiana, South America, 1969–2013: an epidemiological study

Maylis Douine, Rodolphe Gozlan, Mathieu Nacher, Julie Dufour, Yann Reynaud, Eric Elguero, Marine Combe, Camilla J Velvin, Christine Chevillon, Alain Berlioz-Arthaud, Sylvain Labbé, Dominique Sainte-Marie, Jean-François Guégan, Roger Pradinaud, Pierre Couppié

**Summary**

**Background** *Mycobacterium ulcerans* infection is the third most common mycobacterial disease in the world after tuberculosis and leprosy. To date, transmission pathways from its environmental reservoir to humans are still unknown. In South America, French Guiana has the highest reported number of *M ulcerans* infections across the continent. This empirical study aimed to characterise the epidemiology of *M ulcerans* infection in French Guiana between 1969 and 2013.

**Methods** Data were collected prospectively mainly by two dermatologists at Cayenne Hospital’s dermatology department between Jan 1, 1969, and Dec 31, 2013, for age, date of diagnosis, sex, residence, location of the lesion, type of lesion, associated symptoms, and diagnostic method (smear, culture, PCR, or histology) for all confirmed and suspected cases of *M ulcerans*. We obtained population data from censuses. We calculated mean *M ulcerans* infection incidences, presented as the number of cases per 100 000 person-years.

**Findings** 245 patients with *M ulcerans* infections were reported at Cayenne Hospital’s dermatology department during the study period. *M ulcerans* infection incidence decreased over time, from 6·07 infections per 100 000 person-years (95% CI 4·46–7·67) in 1969–83 to 4·77 infections per 100 000 person-years (3·75–5·79) in 1984–98 and to 3·49 infections per 100 000 person-years (2·83–4·16) in 1999–2013. The proportion of children with infections also declined with time, from 42 (76%) of 55 patients in 1969–83 to 26 (31%) of 84 in 1984–98 and to 22 (21%) of 106 in 1999–2013. Most cases occurred in coastal areas surrounded by marshy savannah (incidence of 21·08 per 100 000 person-years in Sinnamary and 21·18 per 100 000 person-years in Mana). Lesions mainly affected limbs (lower limbs 161 [66%] patients; upper limbs 60 [24%] patients). We diagnosed no bone infections.

**Interpretation** The decrease of *M ulcerans* infection incidence and the proportion of children with infections over a 45 year period in this ultra-peripheral French territory might have been mostly driven by improving living conditions, prophylactic recommendations, and access to health care.

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**Introduction** *Mycobacterium ulcerans* infection (Buruli ulcer) is the third most common mycobacterial disease in the world, after tuberculosis and leprosy.1 The causal pathogen, *M ulcerans*, produces a toxin called mycolactone, which leads to tissue destruction, resulting in skin ulcers and sometimes bone infection.2 Skin infections are generally ulcerative and large, with undermined edges, generally following nodules, plaques, or oedema. Osteomyelitis can occur when the ulcer invades the bone beneath a skin lesion or when the infection is bloodborne.3 When not properly treated, these lesions can lead to deformities, disabilities, and disfigurement. Although findings from several studies22–24 have shown that *M ulcerans* is an environmental mycobacterium that can be associated with a large array of taxa from the aquatic community, the transmission pathways from its environmental reservoir to human beings are still unknown, but evidence suggests a transmission pathway directly through the aquatic environment.24 Until 2004, the standard treatment was surgical debridement, but WHO now recommends that two antibiotics should be given for at least 8 weeks in association with surgery to promote wound healing and prevent deformity.21,26

Classified as a neglected tropical disease in 1998 by WHO, *M ulcerans* infection has been reported in at least 34 countries, mainly in Africa and Australia.2 In South America, only a few cases have been reported so far in Suriname and Peru, but the highest incidence has been reported in French Guiana,10,11 a French ultra-peripheral territory, located on the coast between Suriname and northern Brazil. French Guiana is a wide area mostly covered by Amazonian rainforest where most inhabitants reside along the coastal strip, which is mainly composed of marshy savannah and mangroves. Several communities live in French Guiana, including...
Evidence before this study
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Added value of this study
Our study, to our knowledge, is the first description of the epidemiology of $M$ ulcerans infection on the South American continent. Moreover, the extended study period, 45 years of monitoring, provides a unique view of the epidemiological trends across time with the evolution of socioeconomic and environmental contexts. The study findings show an epidemiological transition from the African-like epidemiology, with mostly children infected, to the Brazilian-like epidemiology, with mostly adults infected. This long-term view is of interest for the scientific community working on $M$ ulcerans.

Implications of all the available evidence
The study generates further research avenues to better understand than at present the transmission method of $M$ ulcerans: notably the link between socioeconomic and environmental factors. Clinically, the absence of bone lesions in this series also raises the hypothesis of specific strains of $M$ ulcerans in South America. That French Guiana concentrates most of the cases of $M$ ulcerans in South America remains striking. Either it is underdiagnosed and unreported in most of the continent or the specific environmental conditions of French Guiana represent a unique niche for the disease to appear.

For the National Institute of Statistics and Economic Studies see https://www.insee.fr/en/accueil

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time period across all districts divided by the sum of yearly exposed populations for that time period. This calculation allowed a mean \( M \) ulcerans infection incidence to be obtained, which we presented as the number of cases per 100,000 person-years. We calculated age-specific incidence with the number of cases for an age class divided by the sum of the yearly exposed population of that age class for a time period. We classified patients younger than 15 years old as children. We compared qualitative data using a \( \chi^2 \) test. We evaluated temporal changes of mean incidence and age using univariate linear regression. We tested the slope of the regression line (\( \beta \)) for significance. We used a Pearson’s goodness of fit test. The significance threshold for the \( p \) value was 0·05.

<table>
<thead>
<tr>
<th>Period</th>
<th>Total (n=245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969–83 (n=55)</td>
<td>1984–98 (n=84)</td>
</tr>
<tr>
<td>Population</td>
<td>906.443</td>
</tr>
<tr>
<td>Incidence of Mycobacterium ulcerans</td>
<td>6·07 (4·46–7·67)</td>
</tr>
<tr>
<td>Incidence of ( M ) ulcerans per region*</td>
<td>3·10 (1·67 to 4·53)</td>
</tr>
<tr>
<td>Cayenne</td>
<td>9·43 (3·64 to 22·5)</td>
</tr>
<tr>
<td>Mana</td>
<td>53·02 (32·24 to 73·80)</td>
</tr>
<tr>
<td>Sinnamary</td>
<td>5·01 (0·11 to 9·91)</td>
</tr>
<tr>
<td>Kourou</td>
<td>2·37 (0·04 to 4·7)</td>
</tr>
<tr>
<td>Rural areas</td>
<td>9·6 (6–14)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>9 (6–14)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>15 (19·3)</td>
</tr>
<tr>
<td>Children younger than 15 years</td>
<td>42 (76%)</td>
</tr>
<tr>
<td>Sex</td>
<td>55 (52%)</td>
</tr>
<tr>
<td>Male</td>
<td>27 (49%)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (51%)</td>
</tr>
<tr>
<td>Localisation of ( M ) ulcerans lesions</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Face</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Chest</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>34 (62%)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>21 (38%)</td>
</tr>
<tr>
<td>Ulcers</td>
<td>54 (93%)</td>
</tr>
<tr>
<td>Nodules</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Plaques</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>21 (38%)</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (62%)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>26 (47%)</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (53%)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Method of diagnosis (positive/tested)</td>
<td>3 (40%)</td>
</tr>
<tr>
<td>Culture</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PCR</td>
<td>24 (49%)</td>
</tr>
<tr>
<td>Smear</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Classification</td>
<td>28 (51%)</td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>27 (49%)</td>
</tr>
</tbody>
</table>

Data are n, mean (95% CI), median (IQR), mean (SD), n (%), or n/N (%). *n=242 (three cases missing data [two during 1969–83 and one during 1999–2013]). †Denominators are the numbers of lesions.

Table: Characteristics of the population of French Guiana studied and the Mycobacterium ulcerans lesions
This study was done at a single centre and resulted in anonymised patient records (the database did not include names or any variable that could allow precise identification of patients) as authorised by the French regulatory authorities. We declared the database to the Commission National Informatique et Libertés (CNIL number 3X#02254258) following French legal requirements. We analysed data with Stata 12 software.

**Results**

During the study period, 245 patients with an *M ulcerans* infection were diagnosed in the dermatology department at Cayenne Hospital (table). Microbiological results were positive to Ziehl-Neelsen (smear or histological examination, or both) in 131 (56%) of 233 cases. The numbers of positive Ziehl-Neelsen smears or histological examinations, or both, were similar before and after the year 2000 (the time that PCR became available; 75 [54%] of 139 vs 56 [60%] of 94; *p*=0·23). However, confirmed cases increased significantly with use of PCR, from 76 (52%) of 147 before 2000 to 90 (92%) of 98 after 2000 (*p*=0·005).

Age increased significantly with time between 1969 and 2013 (8·0·55; *p*=0·01; appendix). The proportion of children with *M ulcerans* infection decreased from 42 (76%) of 55 patients in 1969–83 to 26 (31%) of 84 in 1984–98 and to 22 (21%) of 106 in 1999–2013. Mean incidences by age between 1999 and 2013 generally showed a greater mean incidence for those 50 years of age or older than in those younger than 50 years of age, whereas before 1984, the main incidence peak was between 5 years and 9 years of age (figure 1). The highest number of cases was reported in Cayenne, where 113 cases were diagnosed; followed by Mana (48 cases), Sinnamary (39 cases), Kourou (27 cases), and finally rural areas (15 cases). The yearly number of cases varied widely, with no cases in some years and up to 27 in others (mean 5·4 cases per year [SD 5·3]; figure 2).

The mean incidence from 1969 to 2013 was 4·29 per 100 000 person-years. The highest mean incidence was in the western coastal area around Sinnamary (21·08 per 100 000 person-years) and Mana (21·18 per 100 000 person-years; appendix, figure 3). In Kourou, the mean incidence was 4·27 per 100 000 person-years, whereas it was 3·51 per 100 000 person-years in Cayenne and 1·04 per 100 000 person-years in rural areas. We observed an incidence peak in the Sinnamary area between 1974 and 1978 and another in the Mana area between 1984 and 1988. Despite periodical fluctuations over the years, the mean incidence has significantly decreased since 1969 across all districts (β –0·14; *p*=0·02; appendix).

The lower limbs were mostly affected, followed by the upper limbs, the chest, and the face (table; figure 4). The location of lesions differed slightly between sexes (*p*=0·04). Men were more often affected on the chest and upper limbs (47 [40%] of 118) than were women (27 [23%] of 117), who were mainly affected on the lower limbs (90 [77%] of 117 for women vs 71 [60%] of 118 for men). The location of lesions did not differ between geographical districts, time periods, or adults and children (appendix). Adults were significantly more often affected on the ankles than were children (21 [14%] of 154 vs four [4%] of 89; *p*=0·02), but we noted no significant difference for elbows (13 [8%] vs 12 [13%]; *p*=0·20).

20 (8%) patients had multiple *M ulcerans* lesions (two [18 patients], three [one patient], or six [one patient]), so 269 cutaneous lesions occurred on the 245 patients. Lesions were usually single ulcers (224 [83%] of 269) with undermined edges (157 [70%] of 224), but were sometimes nodules (22 [8%] of 269) with ulceration (16 [73%] of 22) or plaques (19 [7%] of 269) with ulceration (13 [68%] of 19; table; appendix). We observed no bone infections.

Two clusters of cases occurred during the study period. The first was in the Sinnamary district, where 23 cases were reported between 1969 and 1978, whereas only 20 were diagnosed in all other districts during the same time period. This represents a mean incidence of 71·8 cases per 100 000 person-years for that period in Sinnamary. During that time, 20 (87%) of 23 cases diagnosed in Sinnamary occurred in children and 16 (70%) of 23 lesions were located on the lower limbs. In this small sample, women (14 [61%] of 23) seemed to be more often affected than were men (nine [39%] of 23) in this cluster (*p*=0·03). The second cluster occurred in the Mana district, where 16 cases were diagnosed between 1984 and 1988, representing a mean incidence of 101·41 cases per 100 000 person-years. Eight (50%) of 16 patients from this second cluster were children and nine (56%) were women, with nine (56%) patients with lesions located on the lower limbs and four (25%) with
lesions located on the upper limbs. 27 other cases were diagnosed in other areas of French Guiana during the same time period: seven (26%) of 27 patients were children and 12 (44%) were women, with 21 (78%) patients with lesions located on the lower limbs and five (19%) with lesions located on the upper limbs.

Discussion
To our knowledge, this study is the first epidemiological study of *M ulcerans* infection in South America, covering a time span of 45 years, thus providing a unique perspective on this neglected tropical disease. Although the annual number of cases was small, some trends emerged, particularly the decreasing mean incidence over time, the decreasing proportion of children with infections over time, lesions mainly affecting the limbs, and the positioning of lesions differing by sex.

Over the 45 years, diagnostic methods changed. WHO put in place two main diagnostic criteria (direct smear examination and PCR) because of the low number of dermatologists and the scarcity of laboratories capable of growing mycobacteria or doing pathology examinations in Africa where most *M ulcerans* infections occur. But in French Guiana, the two head dermatologists of Cayenne Hospital are recognised *M ulcerans* infection experts. Therefore, even before the availability of PCR in 2000, cases were reported as suspected because of dermatologist expertise. PCR sensitivity generally reaches about 95% in specific studies with replicated samples. However, our study shows that in real-life situations, some samples are of different quality—eg, sometimes samples are taken too close to the surface (the bacteria grows mostly in the deep dermis and hypodermis). The sensitivity in our study of 88% is close to that observed in other studies in which it varied from 79% to 95%.

The mean incidence in French Guiana was 4.29 per 100,000 person-years between 1969 and 2013, but fluctuated, with a peak at around 100 per 100,000 person-years in Mana during the 1980s. This incidence is fairly close to that observed in Côte d’Ivoire, the most affected country in the world, with 1039 cases reported to WHO in 2013, with an incidence of about 5.2 per 100,000 person-years depending on the districts. However, *M ulcerans* infection mean incidence significantly decreased in French Guiana over time, as also reported throughout the world over the last 5 years. This finding could potentially be related to environmental changes, such as an increase in deforestation and the building of dams and irrigation systems that deeply modify the structure of floodplains and changes in climatic patterns, particularly rainfall. In French Guiana, *M ulcerans* was found to be correlated with short-term (6 months) and long-term (a decade) rainfall patterns and the El Niño-Southern Oscillation. Similar correlations with rainfall have been identified in Cameroon and Australia.

Some specific local land use changes could potentially explain the rise or disappearance of some *M ulcerans* infection clusters. For example, the first cluster of

![Figure 2: Annual number of Mycobacterium ulcerans infections and population size in French Guiana, 1969–2013](image-url)
*M. ulcerans* infections occurred in Sinnamary between 1969 and 1978, with 23 *M. ulcerans* infection cases. In 1994, a reservoir (the Petit-Saut Dam) was built on the Sinnamary river and the number of *M. ulcerans* infections declined substantially to only three *M. ulcerans* infections in the Sinnamary district after the dam construction compared with 36 infections between 1969 and 1994. The dam has thus been hypothesised to have led to a substantial modification in the ecological functioning of the floodplain (eg, reduction of flooding, changes in aquatic communities, and change in land use), with a potential knock-on effect of *M. ulcerans* abundance or its host reservoirs and spread in the environment.²⁵ The second cluster of cases observed in Mana between 1984 and 1988 occurred just after the development of rice fields located on previous marshy mangrove forests in this region. Although we cannot be certain that this change in land use facilitated the development or transmission of *M. ulcerans* in the environment, the mean incidence during that period increased up to 101 per 100 000 person-years and decreased after 1988 to about 34 per 100 000 person-years between 1999 and 2003 and to about 4 per 100 000 person-years between 2004 and 2008, while still remaining higher than in the rest of French Guiana. In Africa, most people infected by *M. ulcerans* are children.¹,²⁶–²⁸ By contrast, in Australia, only 8% of patients diagnosed between 1998 and 2011 were children.²⁹ Few studies have been done in South America; however, in Peru, eight cases were reported from 1996 to 2005, and all of them were in adults, with a mean age of 37.3 years (SD 14.6).²⁵ These results are in line with our observations in the last two decades, with a mean age of 34.9 years between 1999 and 2013. In French Guiana, the proportion of children diagnosed with *M. ulcerans* infection before 1984 was similar to that in Africa (more than 70%),¹,²⁶–²⁸ but decreased with time, reaching around 21% in 1999–2013, which is closer to that observed in Australia (8% of children). At the same time, the proportion of children in the French Guiana population increased (from 49.3% in 1969 to 55.8% in 2013; β=0.12; p=0.005 [Insee]). The mean incidence of *M. ulcerans* infection in French Guiana is generally higher in people older than 50 years of age than in those aged younger than 50 years. Although still controversial, the improvement of BCG immunisation coverage in French Guiana (92.4% in 2009)²⁹ could have played a role in the decrease of *M. ulcerans* infection incidence in children.²¹,³⁰,³¹ The decline in the immune system with age could also explain the incidence peak observed among those aged older than 50 years, as also reported in Africa.³⁰,³¹ Changes in clothing, improved hygiene, and wound care with soap linked to improving living conditions in French Guiana over the last few decades presumably explains these epidemiological changes.³²,³³ The reduction of children coming into contact with fresh water habitats because of education and protection of water points are other possible explanations for the observed change in age profile of patients with *M. ulcerans* infections in French Guiana. Additionally, with 49% of women affected by *M. ulcerans* infection in French Guiana (with the proportion remaining stable over time), men and women were similarly affected, as observed in other countries (eg, 49% of patients were women in Ghana,³⁴ 52% were in Benin,²⁶ and 51% were in Australia).³⁴

In our study, traumatised skin at the site where the ulcer subsequently developed was reported for only 20% of patients with *M. ulcerans* infection. Findings from some studies²¹,³⁵ show that many patients have a history of penetrating trauma at the site of the initial lesion, leading to the hypothesis that traumatised skin recently contaminated with *M. ulcerans* could be a plausible route of transmission. However, this variable is not precise enough as patients might not have remembered previous traumas. They could also have wrongly inferred the ulcer as a trauma. Given the time span of this study, observations in medical files could not be scrutinised or verified.
Additionally, we also found that 66% of *M ulcerans* infection lesions occurred on the lower limbs and 24% on the upper limbs, which is similar to Africa and Australia. In a cohort of 1511 patients in Benin, 17% of those with osteomyelitis had no skin lesions described. In Australia, extension to bone occurred in 1% of patients. A possible explanation could be that in French Guiana, a higher GDP per person and access to the French universal health system led to individual patients having earlier access to care than in poorer countries. Also, patients in French Guiana are less likely to harbour intestinal parasites than are those in poorer countries, which are known to dampen type 1 helper cell responses and could thus reduce cellular immunity against mycobacteria. This hypothesis has not yet been studied. Finally, a difference in *M ulcerans* clinical strains in French Guiana could also potentially explain the absence of bone lesions.

A study of the genetic diversity of *M ulcerans* from DNA extracts of 25 *M ulcerans* infection biopsies in French Guiana based on six genetic markers identified three genotypes. Genotypes I and III were very close to the French Guiana genotype described in the literature, but genotype II had never been described before and appeared completely different. On the basis of multi-locus variable number tandem repeat analyses or whole-genome sequencing, mycobacterial isolates from French Guiana appear more related to the mycolactone-producing mycobacteria of ectotherms (fishes and frogs) than to classic *M ulcerans* causing *M ulcerans* infection in human beings. This cluster could constitute a transitional step in the reductive evolution process between the *Mycobacterium marinum* progenitor and *M ulcerans* as found in western and central Africa. Genetic specificities of *M ulcerans* from French Guiana should be further explored with whole-genome sequencing.

Environmental risk factors for *M ulcerans* infection in French Guiana were studied in a case-control study between June, 2002, and August, 2004. 30 patients with *M ulcerans* infections and 60 controls were enrolled over a 3 year period and were asked to precisely describe their access to and contact with several kinds of water bodies. Findings from the study showed that the risk of *M ulcerans* infection increased with proximity of marshes, rivers, floodable areas, and farmland near the respondent’s home or workplace and with recreational use of this environment for activities such as hunting and fishing. A review has further highlighted that human infections could result from the interaction of multiple factors, such as socioeconomic factors driving behaviours and practices that favour suitable environmental conditions for *M ulcerans* and exposure of humans, differences in the pathogenicity of *M ulcerans* strains, genetic factors, and local exposure influencing immune responses in people.

This study has several limitations because of the 45 year time span, but this time span might have helped understanding of medium-term and long-term processes responsible for causing *M ulcerans* infection in French Guiana. Diagnostic methods changed over this time, so many cases were not bacteriologically confirmed; before the arrival of PCR testing in 2000, some cases might not have actually been *M ulcerans* infections, thus leading to overestimations of the disease incidence. The first positive *M ulcerans* culture was obtained in 1974. Since then, apart from *M ulcerans*, very few other species of mycobacteria have been cultured, with three *Mycobacterium chelonei*, one *Mycobacterium fortuitum*, and one *Mycobacterium tuberculosis* mycobacteria cultured between 1969 and 1990 in French Guiana (Couppié P, unpublished). Therefore, the risk of misdiagnosis of other cutaneous mycobacterioses as...
M *ulcerans* infection was fairly low. Additionally, the clinical and epidemiological features of *M. ulcerans* infection are often evocative, especially when the dermatologists are *M. ulcerans* infection experts; therefore, this bias is likely to be small. Data collection started in 1969, when knowledge of *M. ulcerans* infection was different from today, which led to variations in the collection of medical information. Thus, data for risk factors or detailed descriptions of reported trauma are not available for the whole time period. Finally, the all patient numbers might have led to so-called noisy random fluctuations in the background of the data presented. However, despite these limitations, this study represents a unique historical long-term series documenting an epidemiological transition in a continent for which few data are available.

French Guiana has the highest number of *M. ulcerans* infections reported in the Americas.\(^9\) Although transmission methods remain unknown, coastal marshy savannah, dam construction, and rice fields appear to be important factors in the local epidemiology. During the 45 years of the study, the population of French Guiana has increased by seven times to reach a population of 240,000 inhabitants, GDP has doubled—specifically following the development of the European Space Center in 1968, which represents 15% of the GDP of French Guiana—and the infant mortality rate has decreased by almost ten times, from 50 deaths per 1000 newborns to 5·5 deaths per 1000 newborns (Insee). Improving living conditions with better hygiene, gradual elimination of intestinal nematodes, and easier access to health care could explain the transition between a so-called African-like epidemiology—with *M. ulcerans* infecting mostly children during the 1970s and 1980s—to the more so-called Australian-like epidemiology, with mostly adults infected. Whether the incidence of *M. ulcerans* infection will continue to decline or will increase in line with the historically expected periodic incidence peak remains to be seen. That so few cases of this clinically recognisable disease are reported in other parts of southern and Central America is remarkable.\(^9\) Either the disease is overlooked in most Central and South American countries or French Guiana and possibly the whole Guiana Shield represents a unique ecological niche favourable to *M. ulcerans* establishment and development.

**Contributors**

PC and RP designed data collection and collected most data, with JD and DS-M collecting some data. YR, SL, and AB-A did diagnostic tests. PC and RP designed data collection and collected most data, with JD

**Declaration of interests**

We declare no competing interests.

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**References**


