Unlocking of the secrets of *Mycobacterium ulcerans* disease transmission

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Mycobacterium ulcerans is a bacterial infection causing necrotising lesions of skin and subcutaneous tissue. Widely known as Buruli ulcer, it is classified as a neglected tropical disease by WHO. If diagnosed and treated early, outcomes are good,[1] but if left untreated it can progress to a severe disease resulting in high levels of morbidity and permanent disability.[2] Occurring in 33 countries worldwide, the largest burden of disease is found in children living in rural and resource-limited areas of central and western Africa where limited access to health care and community beliefs and stigma—in Ghana, witchcraft and curses are among the explanations for this disease—lead to delays in diagnosis and treatment, with devastating outcomes.[3] As a result, since its first description in Australia in 1948,[4] affected communities, clinicians, and researchers have been searching for ways to prevent this disease. This search has been thwarted by the fact that the exact environmental reservoir and method of transmission have not been established.

Prevailing opinion is that human beings are infected from the environment: in endemic regions, the disease is highly focal and usually associated with wetlands or coastal regions,[5] and PCR testing of environmental samples, such as water, aquatic plants, soil, and detritus from swamps, can find evidence of the organism.[6–8] Insects such as mosquitoes[7] and water-residing biting arthropods[9] have been associated with *M ulcerans* epidemiologically and via PCR testing and therefore proposed as vectors for transmission. In Victoria, Australia, evidence suggests that native possums might be involved in transmission.[6]

The Article in *The Lancet Planetary Health* by Maylis Douine and colleagues[10] provides an important epidemiological and clinical description of *M ulcerans* infection diagnosed and managed in French Guiana from 1969 to 2013. The great strength of the study is the long time period over which cases have been prospectively followed—to my knowledge, the longest known longitudinal recording of cases worldwide. It covers a period of substantial population expansion and increasing wealth. The long time period of this study represents a unique opportunity to study disease epidemiology over time and could provide insights into the environmental reservoirs and disease transmission in both this region and globally.

Some of the study observations are worth highlighting. First, as described in many African regions, the number of cases reported yearly has decreased, from 6·07 infections per 100 000 person-years (95% CI 4·46–7·67) in 1969–83 to 3·49 infections per 100 000 person-years (2·83–4·16) in 1999–2013. Reasons are unknown, but perhaps relate to changing environmental conditions in the era of climate change, the change in population dynamics and land use, or possibly some success with prevention methods such as mosquito net use. Some have even speculated that increasing antibiotic use against *M ulcerans* could be responsible if human beings represent the disease reservoir, although the situation in Victoria, Australia, where antibiotic treatment is widely used and cases of disease are rapidly increasing,[11] argues against this explanation. An alternative explanation could be improvements in the accuracy of diagnosis. For example, in the study of Douine and colleagues, an increased proportion of cases were classified as suspected in the early period (1969–98) before PCR confirmation testing for *M Ulcerans* became available in the year 2000.[12] Thus, the reduced incidence worldwide[13] could reflect the increased accuracy of diagnosis since PCR confirmation was introduced.

Second, despite an increasing proportion of children in the general population, a decrease was found in the incidence and proportion of cases diagnosed in children over the study period. Once again, the reasons are unclear, but the authors have postulated that this decrease could reflect improved living conditions and hygiene, presumably related to improved population wealth or possibly a change in clothing or children's activities. Alternatively, as the periods in which most cases in children were reported coincided with a much higher proportion of non PCR-confirmed cases, overdiagnosis of disease could be responsible.

Third, sex differences were noted with respect to location of lesions, with men more often affected on the chest and upper limbs than women and women more likely to be affected on the lower limbs than men. Sex differences in disease presentation have also been noted

in Africa[2] and Australia.[14] These differences provide some clues about disease transmission—for example, they might argue against insect vectors, whose biting patterns are unlikely to be sex specific (unless the disease patterns represent differences in use of protective clothing, bed nets, or sleeping patterns), but perhaps point to trauma as a method of infection, as body areas prone to trauma might differ by gender.

Finally, various observations were similar to those from other world regions, suggesting a common link between world regions in environmental reservoirs and disease transmission. These observations include the fact that cases were limited to coastal regions, the number of cases varied from year to year and region to region, and the number of cases was sex balanced.[2,14] No information was provided on seasonality of disease presentation—observations that have been noted elsewhere.[14,15]

This study raises many interesting questions about *M ulcerans* disease epidemiology, which require intensive research into factors such as climate, local flora and fauna, and population characteristics, building on the clues from this and other studies. Answers to these and other questions are urgently required[16] as the world desperately requires concrete public health interventions based on solid evidence to truly hope that we can consign the devastating health consequences of this infection to history.

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I declare no competing interests.

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