Is BCG vaccination of possums the solution to the Buruli ulcer epidemic in south-eastern Australia?

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Buruli ulcer (BU) is a flesh-eating infection caused by *Mycobacterium ulcerans* that leads to significant community morbidity, with an estimated cost to Victoria in 2016 of more than $2.5 million.[1] It was first recognised in Victoria, Australia, in 1948.[2] Until the turn of the century, it was only reported in low numbers and a few localised regions, but the BU epidemic in Victoria has shown a consistent upward trend in recent years. In 2022, reported case numbers increased to 340, the equal highest annual case load recorded and more than five times the number reported 10 years previously. Alarmingly, the disease is also moving into new areas — in the past 5 years it has moved into a coastal region south of Geelong (Surf Coast), with urban outbreaks in the regional city of Geelong and in the inner north-western suburbs of Melbourne. The proportion of severe cases at diagnosis is also on the rise — since 2010, the proportion of people with infection presenting with World Health Organization category 2 or 3 lesions has increased from 20% to about 30%.[3] Efforts to implement public health interventions to address this have been hindered by the lack of a clear understanding of the environmental reservoir and transmission mechanisms of *M. ulcerans*.[1]

Possums and Buruli ulcer transmission

An important discovery in the mid-2000s identified that possum faecal specimens (both common ringtail [*Pseudocheirus peregrinus*] and common brushtail [*Trichosurus vulpecula*] possums) were *M. ulcerans* DNA positive in the newly endemic area of Point Lonsdale, Victoria.[4] On further assessment, 33% of captured possums either had evidence of clinical disease or were asymptomatic but had positive excreta. The rate of BU lesions or positive excreta was higher in ringtail (38%) than in brushtails (24%) possums. Interestingly, *M. ulcerans* isolates from possums were genetically indistinguishable from those from Victorian BU patients.[5] More comprehensive One Health surveillance has found that the presence of *M. ulcerans* positive possum faecal samples correlates geographically with the occurrence of human BU cases, and the detection of positive samples in a new area can herald the onset of human cases in the next one to two years.[6]

Further evidence for the role of possums in BU transmission comes from a large comprehensive case–control study across Victoria's endemic regions from 2018 to 2020.[7] This showed a greatly increased risk of BU among people reporting the presence of possums on their property, with a dose–response effect suggested by more possums reported correlating with a higher risk of BU. Additionally, when environmental samples were collected from case and control properties, a high proportion of possum faeces (mainly ringtail) was found to be *M. ulcerans* DNA positive, and a large percentage was shown to contain viable *M. ulcerans* that suggests transmissibility.[8] Other environmental features associated with possums, such as known food sources, habitat and mobility, were also associated with detection of *M. ulcerans* at the property. Finally, to support possums carrying viable *M. ulcerans* organisms that can be transmitted to humans, a case was recently reported where a man bitten while helping a sick ringtail possum developed a BU lesion at the bite site within 6 months.[9]

The case for possums being a zoonotic reservoir and being involved in the transmission of *M. ulcerans* is now strong in Victorian endemic areas. Considering the urgent need to deal with the worsening Victorian BU epidemic, the challenge is how we can utilise this knowledge to reduce *M. ulcerans* transmission. Preventing contact between possums and humans via public education campaigns to increase awareness of potential risks, especially if possums are sick or unwell, may help. However, possums have adapted well to suburban settings, including gardens where their faeces can cover much of the ground, making limiting contact (direct or indirect) very difficult. Culling is not an appropriate solution as they are a protected species in Victoria and form an important part of the natural ecosystem, with unintended consequences likely to result if their social structure is disrupted. Culling would also likely result in significant public anger.

Innovative solutions that do not involve possum culling are required

We propose that research be undertaken to explore the effectiveness and feasibility of vaccinating ringtail possums with an oral bait bacille Calmette–Guérin (BCG) vaccine in the wild. If effective in reducing BU disease in possums, it should hopefully simultaneously reduce the occurrence in humans. Furthermore, it would benefit possums, as BU can lead to death, and this would be a safe intervention that could reduce both morbidity and mortality in possums. The aim would be to manage this zoonotic pathogen in its reservoir possum host with benefits for human and animal health, without damaging the local ecosystem.

Oral bait vaccines have been used to control other diseases in wildlife such as rabies in Europe and North America and classical swine flu virus in Europe.[10] Specifically, the use of oral bait BCG vaccine has been successfully employed to control bovine tuberculosis in wildlife such as badgers in Ireland and the United Kingdom, deer in North America, and wild boars in Spain.[11] Most importantly, researchers

in New Zealand, where bovine tuberculosis is a major problem in non-native Australian brushtail possums, have shown that they can successfully vaccinate possums with oral bait BCG and induce immunity to bovine tuberculosis lasting more than two years.[10] This was effective both in laboratory studies and in wide-scale field trials, with up to a 95% reduction in the prevalence of bovine tuberculosis in vaccinated wild possum populations.[12] It is reasonable to expect that the intervention would be equally effective in both ringtail and brushtail possums. Furthermore, BCG vaccine has been shown to be safe for numerous livestock and wildlife species.

Whether BCG vaccination of ringtail possums could protect them against *M. ulcerans* infection has not been evaluated, but mice vaccinated with BCG are protected against BU.[13] Two large randomised controlled trials of BCG vaccination in humans for the prevention of BU conducted in Uganda during the late 1960s and early 1970s found significant but short-lasting protection against BU.[14,15] In a recent case–control study in Victoria, a history of BCG vaccine was associated with a 40% reduction in the risk of BU (odds ratio, 0.6; 95% CI, 0.4–0.9).[7]

Although BCG vaccination of humans in endemic areas could also be considered, vaccinating possums would have the added benefits of protecting everyone in endemic areas regardless of vaccine status, protecting visitors living outside the area (Victorian endemic regions are high tourism areas), and providing health benefits for possums. Additionally, as possums likely play a role in introducing the disease into new areas, it may stop disease spread. Furthermore, the uptake of oral bait BCG by non-target species could be beneficial as *M. ulcerans* infection has been detected in a wide range of mammalian species in Australia.[1] The accidental vaccination of these animals could therefore contribute to overall host immunity within the endemic ecosystem and subsequently reduce the risk to humans.

The proposed research would involve several stages. The first would be to establish housing and husbandry conditions for ringtail possums in a research facility. Once established, this would be followed by attempts to develop a *M. ulcerans* infection model using both high dose (~ 10^3 colony-forming units) and low dose (~ 20–30 colony-forming units) *M. ulcerans* inocula, with monitoring of excreta and clinical signs of disease to determine infective dose and susceptibility to infection, incubation periods, immunological responses, and the routes and magnitude of *M. ulcerans* shedding. If successful, possums would then be vaccinated with BCG before *M. ulcerans* challenge, to assess the level and durability of BU protection by comparing vaccine with control groups. Blood samples would be collected to measure the immune responses to BCG vaccination, which would be correlated with immune protection. If shown to be effective, attempts would be made to optimise the palatability and feasibility of oral bait BCG delivery. Finally, testing the effectiveness of oral bait BCG vaccine against *M. ulcerans* in ringtail possums would be performed in laboratory and real-life field settings. Data obtained from these studies could be used to assess whether possum vaccination would be cost-effective in controlling BU, provide information on the epidemiology of infection in possums, and help develop disease transmission models. Studies could also be extended to brushtail possums.

Although mosquitoes are considered to play a role in transmission,[1] and mosquito prevention measures might have an impact on human case numbers, evidence for their effectiveness is lacking. It is therefore important to explore other interventions that may reduce transmission, such as possum vaccination.[7]

Conclusion

In south-eastern Australia, BU is a One Health challenge involving a complex interaction between the environment, insects, wildlife and humans, with many knowledge gaps remaining. However, there are currently no proven public health interventions to address the worsening epidemic of BU in this region. A proposal to vaccinate possums in the wild with oral bait BCG provides hope that an acceptable, safe, feasible and cost-effective intervention can be found that would benefit both human and possum populations by reducing the transmission of *M. ulcerans* and the incidence of BU in the region.

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