Dangerous bacteria in unexpected locations; *Burkholderia pseudomallei* and melioidosis in Australia

Bart J Currie

Tropical and Emerging Infectious Diseases Division
Menzies School of Health Research
PO Box 41096 Casuarina NT 0811
and Infectious Diseases Department, Northern Territory Clinical School, Royal Darwin Hospital Darwin NT 0811
PO Box 41096 Casuarina NT 0811
Tel (08) 8922 8196
Fax (08) 8927 5187
Email bart@menzies.edu.au

There are 25-50 human cases of melioidosis annually in Australia. While the vast majority occur in the tropical north, sporadic cases have been documented from unexpected temperate locations and, each year, several cases are diagnosed in southern hospitals in patients infected in and returned or travelling from northern Australia or southeast Asia.

Exposure to the soil and water bacterium *Burkholderia pseudomallei* often results in asymptomatic infection manifest only by seropositivity. Melioidosis is the clinical disease that can occur following infection and is usually an acute illness 1-3 weeks after exposure, with a spectrum from minor skin lesions to overwhelming systemic sepsis commonly with multiple abscesses in lungs and internal organs [1]. Around 10% of cases present with chronic melioidosis (sick for over 2 months) which often mimics pulmonary tuberculosis. Less than 5% of cases are from reactivation of latent *B. pseudomallei* infection. Overall mortality in Australia has now decreased to under 20%, but mortality remains over 50% in some locations in southeast Asia. Over the last 20 years the Darwin prospective melioidosis study has documented 538 culture-confirmed cases of melioidosis.

Melioidosis was first documented in Australia in 1949 in an outbreak in sheep in Winton, Queensland. It had been suggested that melioidosis was possibly recently introduced into Australia from southeast Asia. However, the enormous molecular diversity of *B. pseudomallei* strains from across northern Australia and comparisons with strains from southeast Asia confirm the long-standing presence of *B. pseudomallei* in the Australian environment [2]. Furthermore, recent analyses of a global dataset of *B. pseudomallei* strains actually support an Australian origin of the bacterium, with subsequent spread to southeast Asia and beyond [3].

Within Australia most cases of melioidosis have been sporadic, but outbreaks linked to water supplies contaminated with *B. pseudomallei* have been well documented [4], highlighting the need for ongoing epidemiological surveillance, robust molecular typing methodology and public health response preparedness and capability. Although melioidosis occurs in a wide range of animals and the potentially devastating impact on especially goats and sheep is well documented, zoonotic transmission is very rare [5], as are nosocomial transmission and laboratory-acquired infection [6].

The actual geographical extent of *B. pseudomallei* in the environment throughout the Australian continent (and indeed globally) remains unclear. In addition to widespread presence across the tropical north, a number of temperate locations well south of the tropics have been identified where melioidosis has occurred in humans and/or animals. These include hobby farms in an area of southwest Western Australia (31° South) [7] and the Brisbane river valley around Ipswich (27.5° South) in southeast Queensland [8]. Sporadic cases have even occurred in central Australia, with *B. pseudomallei* recovered from the local environment. Recent studies have also documented melioidosis and the presence of *B. pseudomallei* in Papua New Guinea [9]. What remains unclear is whether *B. pseudomallei* has recently been spreading within Australia (and overseas) and, if so, the nature and extent of that spread, or whether new cases are just unmasking a long-term presence of the bacterium in a larger geographical distribution than previously considered likely.

Ongoing environmental studies are unravelling the environmental correlates of the presence of *B. pseudomallei,* complementing the classical studies from Queensland, which identified the link between *B. pseudomallei,* seasonality, water table movements and clay layers [10]. A recent study from the Darwin region using multivariable, cluster logistic regression and principal component analysis found that at undisturbed sites, the occurrence of *B. pseudomallei* was found to be significantly associated with areas rich in grasses [11]. However, at environmentally disturbed sites, *B. pseudomallei* was associated with the presence of livestock animals, lower soil pH and different combinations of soil texture and colour. This raises concerns that *B. pseudomallei* may be spreading due to changes in land use and this is consistent with the well-recognised association of melioidosis with environmental perturbations, such as severe weather events, building and pipeline excavations and potentially mining activities [4, 12-14].

The clinical course of melioidosis following infection is likely to be determined by a combination of host risk factors for disease, mode of infection, infecting dose of bacteria and putative *B. pseudomallei* strain differences in virulence.

Diabetes, excessive alcohol consumption, renal impairment and chronic lung disease are the major risk factors for melioidosis, although the nature of susceptibility requires further study. The immune response to infection with *B. pseudomallei* has been elegantly studied in both humans and animal models in north Queensland [15, 16].

It has been proposed that aerosolisation of *B. pseudomallei* during severe weather events results in a shift from percutaneous inoculation to inhalation, thus accounting for more severe disease and higher mortality. Nevertheless, the occurrence, frequency and magnitude of such aerosolisation in endemic locations remain entirely unknown (Figure 1).

Despite the recognition that melioidosis can be such a dramatically overwhelming infection, the specific virulence factors responsible for severe disease remain surprisingly poorly elucidated. The genomes of an increasing number of strains of *B. pseudomallei* are being sequenced and this is enabling interrogation of the large global strain collection of *B. pseudomallei,* to assess bacterial diversity and geographical and clinical correlates of specific genomic islands and potential virulence genes of interest[3]. Studies from Queensland have identified novel possible virulence mechanisms, as well as a potentially critically important portal of bacterial entry and propagation of infection involving the nasal mucosa [17-19].

In conclusion, three important areas requiring further study are: (i) the geographical boundaries and determinants of the presence of *B. pseudomallei* in the Australian environment; (ii) the importance (or not) and implications of aerosolisation of *B. pseudomallei* during severe weather events; and (iii) the nature and importance (or not) of differential virulence amongst *B. pseudomallei* strains from the Australian environment and from human and animal cases of melioidosis.

Figure 1. Mark Mayo, Menzies Melioidosis Programs Manager, searching for *Burkholderia pseudomallei*.

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Bart Currie is an Infectious Diseases Physician at Royal Darwin Hospital and Professor in Medicine at the Northern Territory Clinical School, Flinders University. He is also Head of the Tropical and Emerging Infectious Diseases Division of the Menzies School of Health Research. Areas of interest include clinical and epidemiological aspects of tropical and emerging infections, development of treatment guidelines and clinical toxinology.