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Unprecedented Melioidosis Cases in Northern Australia Caused by an Asian *Burkholderia pseudomallei* Strain Identified by Using Large-Scale Comparative Genomics

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Melioidosis is a disease of humans and animals that is caused by the saprophytic bacterium *Burkholderia pseudomallei*. Once thought to be confined to certain locations, the known presence of *B. pseudomallei* is expanding as more regions of endemicity are uncovered. There is no vaccine for melioidosis, and even with antibiotic administration, the mortality rate is as high as 40% in some regions that are endemic for the infection. Despite high levels of recombination, phylogenetic reconstruction of *B. pseudomallei* populations using whole-genome sequencing (WGS) has revealed surprisingly robust biogeographic separation between isolates from Australia and Asia. To date, there have been no confirmed autochthonous melioidosis cases in Australia caused by an Asian isolate; likewise, no autochthonous cases in Asia have been identified as Australian in origin. Here, we used comparative genomic analysis of 455 *B. pseudomallei* genomes to confirm the unprecedented presence of an Asian clone, sequence type 562 (ST-562), in Darwin, northern Australia. First observed in Darwin in 2005, the incidence of melioidosis cases attributable to ST-562 infection has steadily risen, and it is now a common strain in Darwin. Intriguingly, the Australian ST-562 appears to be geographically restricted to a single locale and is genetically less diverse than other common STs from this region, indicating a recent introduction of this clone into northern Australia. Detailed genomic and epidemiological investigations of new clinical and environmental *B. pseudomallei* isolates in the Darwin region and ST-562 isolates from Asia will be critical for understanding the origin, distribution, and dissemination of this emerging clone in northern Australia.

The Gram-negative soil-dwelling bacterium *Burkholderia pseudomallei* is the etiologic agent of melioidosis, an often deadly tropical disease that can be difficult to diagnose, particularly in nonendemic or resource-poor regions where cases are not expected and appropriate microbiological diagnostic tools are not readily available (1). Diabetics are particularly susceptible to melioidosis. *B. pseudomallei* infection can be acquired from contaminated soil or water by percutaneous inoculation, inhalation, aspiration, or ingestion, and no vaccine targeting this organism is available (2). In 2012, *B. pseudomallei* was reclassified by U.S. federal agencies as a tier 1 select agent, the highest risk category for a biological entity, due to concerns that this bacterium would pose a severe threat to humans and animals in the event of its deliberate misuse (3).

The *B. pseudomallei* genome exhibits high homologous recombination rates. On a per-allele basis, recombination is estimated to occur between 18 and 30 times more frequently than mutation (4). This extensive lateral gene transfer can confound population analyses, particularly those that are based on studying limited geographic regions (e.g., the Northern Territory, Australia [5]) due to high rates of homoplasy observed among genetic variants. In contrast, genomic analyses of *B. pseudomallei* populations on a continental scale have revealed a clear separation of *B. pseudomallei* isolates between Asia and Australia (4, 6, 7). Bayesian analysis of *B. pseudomallei* genome variation points to an ancient separation, with migration out of Australia into Asia occurring tens of thousands of years ago during the Pleistocene (4). The rarity of pathogen movement is due largely to one factor: new melioidosis cases almost always result from bacterial infection acquired from the local environment, with human-to-human and zoonotic transmission of this pathogen being exceedingly rare (8). In support of the rarity of *B. pseudomallei* movement across major biogeographic boundaries, the definitive transmission of *B. pseudomallei* from Asia into Australia has not yet been observed. Nevertheless, melioidosis cases imported into nonendemic locations via travelers are being increasingly reported, as is recognition of locations that are endemic for melioidosis outside the classical regions of Southeast Asia and Australia (9). With modern global travel and

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