Bangladesh J Med Microbiol 2018; 12 (1): 1-3
Bangladesh Society of Medical Microbiologists

Editorial

Mysteries of Melioidosis: Unearthing the Enigma

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One of the most fascinating aspects of medical microbiology is the periodic discovery of emerging and reemerging organisms. In recent years, the SARS-CoV-2, Human Immunodeficiency Virus (HIV), Nipah virus, Ebola virus, *Legionella* species, *Helicobacter pylori* and other new pathogens have been discovered. Although *Burkholderia pseudomallei*, the causative agent of melioidosis has been described almost a century ago and considerable progress in terms of diagnosis and treatment was achieved, *B. pseudomallei* is still "the unbeatable foe", for several reasons like under-recognition, high case-fatality rate, unacceptable relapse rate and a "time-bomb" effect for sero-positive individuals.[1] There is a growing body of evidence that, once considered an obscurity, melioidosis is now recognised as an emerging disease of global significance. It represents an excellent example of an emerging disease in two respects: it is being reported increasingly in many countries; and it is being recognised for the first time in countries where it has not previously been described. This frequently fatal infection of man and numerous other animal species is a facultative intracellular Gram-negative ß-proteobacterium. The world wide distribution of this organism is still unknown and our understanding of the environmental factors determining the presence of *B. pseudomallei* is rudimentary. It is believed that the organism is a ubiquitous soil and water dwelling saprophyte of tropical and subtropical regions worldwide; a relationship in the high incidence of disease among people sharing a close association with the environment. Just like *Mycobacterium tuberculosis*, the organism can remain latent for decades before the onset of clinical signs and symptoms.[2] Infection follows aspiration of contaminated water, inoculation of bacteria through traumatic skin breaches or inhalation of contaminated dusts and aerosols.[3,4] There is a substantial number of factors that have driven melioidosis research, most importantly: increasing awareness and discovery of *B. pseudomallei* in areas outside the previously recognised regions of endemicity, the recent surge in disease associated with survivors of the December 2004 tsunami in Indonesia and the accelaration of bioterrorism research in light of the *Bacillus anthacis* mailing in United States of America which has raised public awareness of health security, and in particular the threat of bioterrorism.[3]

The pioneering work of Indian bacteriologist C. S. Krishnaswami and British pathologist Alfred Whitmore first identified the organism *Burkholderia pseudomallei*, among Burmese morphine addicts in 1911.[5,6] Since then, it took a century to determine its source in the environment of Indian sub-continent. The organism was recovered for the first time in 2011 from soil of Gazipur district of Bangladesh.[7] However, the first case of melioidosis from Bangladesh was reported in 1964 in a 29 year old British sailor who was travelling through Bangladesh and stayed in Chittagong for 3 months.[8] Since then, melioidosis has been sporadically detected in Bangladesh over last several decades. But first melioidosis case in a native Bangladeshi child was diagnosed in 1988.[9] Subsequently, five more cases were detected in U.K among Bangladeshi immigrants from Sylhet region from 1991 to 1999.[10,11,12] Later on, at least 35 culture-confirmed melioidosis cases were detected among the diabetic patients in Bangladesh and most of these cases were diagnosed at Ibrahim Medical College and BIRDEM Hospital in Dhaka from 2001 to 2016.[13] Analysis of the reported cases strongly indicate that the disease is potentially endemic in at least ten districts of Bangladesh particularly in north eastern regions (Gazipur, Mymensingh, Sylhet) of the country.[7] So far, 51 culture positive melioidosis cases have been diagnosed in Bangladesh.[14]

Many challenges exist for the control and prevention of melioidosis. At present, cellular and molecular

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mechanisms associated with these diverse clinical manifestations are not fully understood. Vaccine development and better therapeutics are necessary to prevent and treat melioidosis. However, knowledge of the relationship between hosts and pathogen is still limited. This has hindered improved vaccine and therapeutic developments, which require a full understanding of genomics and bacterial pathogenesis. After the first genome of *B. pseudomallei* K96243 was released in 2004, subsequent studies capitalized upon this foundation, which lead to enhanced genetic and genomic analyses that have facilitated a better understanding of this organism. As additional genomic sequences have been generated, striking differences have been observed. For example, two mutually exclusive gene cassettes, termed "BTFC and YLF", have been described that are dissimilar in their geographical distribution[15] as well as in terms of pathogenicity. A study conducted in Bangladesh showed all *B. pseudomallei* isolated in Bangladesh posses YLF gene, which confirms their Asian origin. As YLF strains are more virulent than BTFC strains, so people in this region are at higher risk of severe form of infection. Multi-locus sequence typing (MLST) has revealed that a number of novel sequence types of *B. pseudomallei* exist in Bangladesh environment and these same sequence types are present in soil as well as in melioidosis patients from same geographic area.[7]

It is noticed that this killer disease has been raising its ugly head in recent times and it is high time the microbiologists engaged in tackling this disease come together to face the challenge. Recently, the global environmental distribution of *B. pseudomallei* and the world-wide incidence and mortality of melioidosis was estimated using a modeling approach. It was predicted that 165,000 melioidosis cases occur per year worldwide, in which 89,000 die.[16] Unfortunately, this infectious disease has still remained in the shadows for far too long. It is still considered a rare and esoteric disease in many countries, and consequently it does not feature highly on the syllabus of Medical Colleges or even postgraduate courses. If clinicians are not aware of the disease, they will be unable to make the diagnosis. Perhaps the best example of this problem is Myanmar, where melioidosis was first discovered and where, in 1913, Krisnaswami reported that approximately 5% of the autopsies he performed in Rangoon were cases of the disease.[5,6] Yet in 1990s, few Burmese doctors had ever heard of melioidosis.[17] The most striking reason for this unawareness is that, melioidosis is still considered as one of the most neglected tropical diseases (NTDs), so much so that it is not even included in the WHO list of NTDs. Yet the modeling suggests that it kills more people worldwide every year than diseases that are much known, such as leptospirosis and dengue.

Whilst specific details regarding the immunopathogenesis of melioidosis are accumulating, comparatively little is known concerning the organism's niche and reservoir of infection. *Burkholderia* are key microbial consituents of the rhizosphere and have significant roles including the provision of nutrients to the growing plant nodule, fixation of atmospheric nitrogen, inhibition of plant pathogens including fungi, and degradatrion of complex compounds. They are versatile and inhabit ecological niches as varied as rice paddy water, and water holes and sea water. This versatility has led to use of a number of *Burkholderia* species, for biocontrol, bioremediation, and plant growth promotion. The introduction of a biocontrol strain with the planting material reesults in the colonization of the rhizosphere and the suppression of the pathogenic competing bacteria and fungi with proven economic benefits. Other *Burkholderia* strains have been widely used for the bioremediation of soils and agricultural environments due to their ability to degrade complex hydrocarbons and herbicides. Such information not only has the potential to expose new therapeutic avenue, bio-active compounds and mechanisms of bioremediation[18], but also to predict regions of hyperendemicity in which the disease is frequently misdiagnosed.[19] The identification of such high risk areas may aid in advising traditional inhabitants of high risk areas in which bathing, washing and playing should be avoided.

In recent unpublished analyses, it has been found that when compared to existing genomic sequences, new *B. pseudomallei* genome sequences can contain as much as 500 kb of additional genomic material in the form of blocks of novel DNA known as genomic islands. It is hypothesized that the primary differences among *B. pseudomallei* genomes are horizontal gene transfer events from diverse bacterial or phage origins. Horizontal gene transfer involves the incorporation of genetic elements, perhaps directly into the genome where they form genomic islands.[20] Currently, very little is known about the adaptability or fitness of *B. pseudomallei*. It seems likely that the genes contained in genomic islands may generate unique phenotypes and affect bacterial fitness, such as the interaction of bacterial cells with their surrounding environment. Fitness phenotypes could range from the ability to survive under extreme environmental conditions to the ability to defeat host immune system defenses.

This bacterium still has many secrets left to be revealed. So, currently we need to perform whole genome sequencing of both clinical and environmental isolates of *B. pseudomallei* hailing from a particular region of the country and present a comparative analysis to identify

essential genes involved in their pathogenicity, adaptability and drug resistance mechanisms. Such study will also help us to understand the phylogenetic relationship among strains persisting in Bangladesh with foreign strains. Deep analysis of the complete genome will be helpful for us in understanding the evolution of the bacterium and its adaptation to the environment, such as high temperatures and antibiotics.

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