

Melioidosis, diabetes and chronic kidney disease

Essay Summary

The importance of combatting both non-communicable diseases and neglected tropical diseases is recognised in the United Nations' Sustainable Development Goals (SDGs) of 2015. However, the limitations of the Sustainable Development Goals agenda are highlighted by the interaction between non-communicable diseases (NCD) and neglected tropical diseases (NTD), which are often considered in isolation from one another. This is demonstrated by the increased risk of developing the serious tropical infection melioidosis among patients living with diabetes mellitus and chronic kidney disease. The rise in all three conditions demonstrates that separate approaches to tackling non-communicable diseases and neglected tropical diseases will not address the double burden of NCD-NTD comorbidities. This is compounded by the fact that melioidosis and chronic kidney disease are further neglected by the current global health agenda through their exclusion from the approach to NTD eradication and the Sustainable Development Goals respectively.

Strategies to counteract melioidosis and other neglected tropical diseases must not ignore the interplay with NCDs. Interventions can include greater health policy coordination between programmes addressing infectious and non-infectious disease, targeted vaccinations where available, and improvements to public health and infrastructure.

Essay

Introduction

The importance of combatting both non-communicable diseases and neglected tropical diseases is recognised in the United Nations' Sustainable Development Goals (SDGs) of 2015. However, the SDGs focus on these as isolated categories of disease, ignoring the interactions between them, despite the multiple comorbidities between non-communicable diseases and many tropical diseases.

These connections are clearly shown by the relationship between diabetes mellitus, chronic kidney disease (CKD) and melioidosis, a serious bacterial infection endemic to much of the tropics. Both diabetes and CKD increase the risk and severity of melioidosis (Cheng & Currie 2005; Jabbar & Currie 2013). Similar interactions are seen for other neglected tropical diseases such as dengue (Mehta & Hotez 2016) and leishmaniasis (Dunachie & Chamnan 2018).

These links are pertinent to examine as diabetes and CKD are on the rise in low- and middle-income countries (van Crevel et al. 2017; George et al. 2017), and melioidosis itself is already thought to be grossly under-reported (Limmathurotsakul et al. 2016), which all contributes to predictions that the incidence of melioidosis will increase further.

Sustainable Development Goals

The Sustainable Development Goals were announced by the United Nations (2016b) as targets for ending all forms of poverty by 2030. Health is covered in goal 3 – Ensure healthy lives and promote well-being for all at all ages – which has a number of targets, including reducing mortality from non-communicable diseases and from neglected tropical diseases (UN 2016).

In terms of non-communicable diseases (NCD), the SDGs specifically mention mortality attributed to cardiovascular disease, cancer, diabetes and chronic respiratory disease. Chronic kidney disease is not included, despite huge increases in mortality over the past 25 years, some of which is linked to the global rise in diabetes (Wang et al. 2016).

The SDG target of ending the epidemics of various communicable diseases focuses on the 'big three' – tuberculosis, malaria and HIV – alongside so-called neglected tropical diseases (NTD). The World Health Organization (2017a) classes a group of 20 diverse communicable diseases as NTDs, which affect more than one billion people around the world, particularly those “living in poverty, without adequate sanitation and in close contact with infectious vectors and domestic animals and livestock”.

The wider social determinants of health are covered by other Sustainable Development Goals, including targets for hunger, inequality, and water and sanitation

The SDGs provide a focus for research, investment and policy initiatives from governments and non-governmental organisations; the focus on neglected tropical disease has enabled progress to be made in addressing them (WHO 2017b).

However, NTD-NCD comorbidities highlight shortcomings in the SDG agenda, demonstrating that these disease categories must not be considered in isolation, but in fact seen as a double burden for patients, especially in often resource-poor settings.

Melioidosis

Melioidosis is a disease so neglected it does not make the WHO list of neglected tropical diseases (Dance & Limmathurotsakul 2018). Caused by *Burkholderia pseudomallei*, a gram-negative saprophytic bacterium first identified in Burma in 1911, it is endemic in soil in south-east Asia and the tropical north of Australia. Transmission to humans is through skin inoculation, inhalation or ingestion (Wiersinga et al. 2012).

The clinical presentation is highly variable, ranging from localised infection to sepsis. It is hard to diagnose and can present similarly to many other conditions, including pulmonary tuberculosis (Dance 2013). Although the commonest outcome of infection is asymptomatic seroconversion, more serious disease is characterised by pneumonia and multiple visceral abscesses (Dance 2013). Melioidosis can deteriorate rapidly into sepsis and has a reported case fatality rate of 40% (Limmathurotsakul et al. 2016).

Previously thought rare, today melioidosis is considered to be vastly under-reported. A recent estimate of the true global burden suggests that there are 165,000 cases in humans each year, with a mortality of 89,000 (Limmathurotsakul et al. 2016). This global mortality estimate is similar to that for measles and exceeds mortality from both leptospirosis and dengue, a more-recognised neglected tropical disease (Limmathurotsakul et al. 2016).

Even at current reporting levels, melioidosis is a serious burden in endemic areas; in Ubon Ratchanari in Thailand, melioidosis causes 20% of hospital admissions for community-acquired bacteraemia (Cheng & Currie 2005), while it is the most common cause of severe community-acquired pneumonia in tropical northern Australia during the wet season (Chalmers et al. 2014).

It is predicted to be ubiquitous across the tropics, with surveillance hindered by a lack of microbiology facilities and expertise, and poor reporting (Limmathurotsakul et al. 2016; Dance & Limmathurotsakul 2018).

As diagnosis and reporting mechanisms improve, its incidence is only likely to increase, compounded by expansion into new areas by both people and the bacterium, and also the increased prevalence of diabetes (Limmathurotsakul et al. 2016). Increasing travel (Ismail et al. 2013) and importation of animals (Limmathurotsakul et al. 2016) raise the chances of infections being detected outside recognised endemic areas.

Melioidosis exposes the complex interplay between NTDs and NCDs, seen in the increased risk of contracting melioidosis among those with underlying diseases, most frequently patients with diabetes mellitus and chronic kidney disease (Limmathurotsakul et al. 2016; Dance 2013). Like many other neglected tropical diseases, melioidosis disproportionately affects poorer populations, such as rice farmers in Thailand or the indigenous population in Australia (Chalmers et al. 2014), who are already more likely to bear the burden of many NCDs.

Prevention

Work is ongoing to develop a vaccine against *B. pseudomallei* (Cheng & Currie 2005). Recommendations from Limmathurotsakul et al. (2013) for preventing transmission include avoiding direct contact with soil and water, for instance using protective gloves and boots. In common with many tropical diseases, and the focus of SDG 6, improvements to water and sanitation are an important area of focus. Advice is to not consume untreated water, to wash raw food using treated water, and to improve public water infrastructure.

Management

Management options are limited by *B. pseudomallei*'s intrinsic resistance to numerous antibiotics, including third-generation cephalosporins, penicillins, rifamycins, and aminoglycosides (Cheng & Currie 2005). It is also relatively resistant to quinolones and macrolides (Cheng & Currie 2005). Therefore delays in diagnosis can be fatal, as empirical treatment for bacterial sepsis will not cover melioidosis (Wiersinga et al. 2012). Septicaemic melioidosis requires aggressive antibiotic treatment; current recommended options are ceftazidime, carbapenems and amoxicillin-clavulanate (Cheng & Currie 2005). Trimethoprim/sulfamethoxazole or co-amoxiclav are recommended for post-exposure prophylaxis (Lipsitz et al. 2012).

Diabetes

The global epidemic of type 2 diabetes mellitus is well recognised. Deaths attributed to diabetes increased by 32.1% (95% UI 27.7-36.3), to 1.5 million between 2005 and 2015 (Wang et al. 2016).

An overlooked aspect of this global increase is the implication for tropical diseases. Diabetes is known to increase the incidence and severity of *B. pseudomallei*. The mechanisms for this are unclear but a number have been suggested. A recent review summarises these clearly, and notes that as an intracellular pathogen *B. pseudomallei* may be particularly well suited to take advantage of impairments in phagocyte function and adaptive T cell immunity (Dunachie & Chamnan 2018). Diabetes is a chronic

immunocompromised state, with “decreased functioning of immune cells, including neutrophils, macrophages, T cells and antibody-producing B cells” (van Crevel et al. 2017). In addition, diabetic complications lead to increased rates of skin damage and reduced wound healing. Diabetic foot wounds may provide a route of transmission for melioidosis, particularly for people working in fields or in contact with soil or water. For other infections, such as TB, a correlation between hyperglycaemia and infection risk and outcome has been noted (van Crevel et al. 2017).

In resource-poor settings such as much of the tropics, diabetes is more likely to be undiagnosed and, even where recognised, is associated with poor glycaemic control (van Crevel et al. 2017). In addition, there is some evidence that diabetes medication itself affects the risk and severity of melioidosis, with a suggestion that sulfonylurea use decreased proinflammatory cytokine responses (van Crevel et al. 2017).

Chronic kidney disease

While diabetes is the focus of enormous worldwide attention, chronic kidney disease has been described as the “neglected of neglected” in the Lancet (Horton 2017). CKD affects around 500 million people worldwide, 78% of whom are in low- and middle-income countries (George et al. 2017). In the Global Burden of Disease 2016 study, CKD ranked 11th as the cause of death (GBD 2017). Deaths increased by 31.7% (95% UI 27.7 to 35.6) between 2005 and 2015 (Wang et al. 2016), even as mortality from cardiovascular disease and cancer fell.

Given this, its exclusion from the SDG agenda underscores the limitations of this approach to global health (GBD 2017), although analysts have mapped a multisectoral SDG approach to addressing kidney disease (Luyckx et al. 2018). Failure to address CKD will undermine efforts to reduce NCD mortality; indeed the figures above exclude CKD’s contribution to deaths from cardiovascular disease, the primary cause of death for CKD patients (Luyckx et al. 2018).

Infectious disease is a known cause of chronic kidney disease in the tropics, but there has been less research into how pre-existing CKD complicates infectious tropical diseases such as melioidosis. Chronic kidney disease is a risk factor in itself for melioidosis, independent of the relationship between diabetes and CKD. An Australian study found an adjusted relative risk of 13.1 (9.4 to 18.1) for diabetics and 3.2 (2.2 to 4.8) for chronic kidney disease (Cheng & Currie 2005).

Again, the mechanism by which CKD increases risk is not well understood. As with diabetes, impaired neutrophil and macrophage function is implicated (Jabbar & Currie 2013). End-stage renal disease reduces neutrophil ability to kill phagocytosed bacteria (Chalmers et al. 2014; Currie et al. 2000). An increased risk of melioidosis has also been observed in immunosuppressed patients, including renal transplant patients (Jabbar & Currie 2013).

Discussion

The SDG and NTD approaches to combating disease fail to take into account the burden of NCD-NTD comorbidities. This is particularly striking with regard to chronic kidney disease, which is excluded from the Sustainable Development Goals entirely, while

melioidosis does not garner the attention it perhaps should do based on the estimates of its likely prevalence.

The worsening global epidemic of diabetes and rise in chronic kidney disease in low- and middle-income countries makes it all the more important to understand the interaction between *B. pseudomallei* infection and these diseases. Reducing the burden of diabetes and improving diabetic control is likely to reduce the development of both chronic kidney disease and melioidosis.

Strategies for eliminating neglected tropical diseases include greater access to medicine and stronger, more efficient health systems (WHO 2017a). More attention must be directed at improving microbiology facilities to enable countries to quickly identify and therefore treat melioidosis (Limmathurotsakul et al. 2016). As important are improvements in infrastructure and water and sanitation, which would help prevent transmission of *B. pseudomallei* and other NTD vectors.

An understanding of the interaction between melioidosis and non-communicable disease will enable more focused public health interventions, such as work towards universal health coverage, and coordination between programmes addressing infectious and non-infectious disease. Any future vaccines can be targeted at more vulnerable patient groups such as those with diabetes or CKD. Screening for melioidosis should be undertaken for patients in endemic areas who are to receive immunosuppressive treatment, such as renal transplant patients (Jabbar & Currie 2013).

Further research is required into many aspects of melioidosis and its associations. This includes the mechanisms by which CKD and diabetes predispose individuals to disease, and whether drugs used to combat these diseases have any effect on the risk and course of infection.

Conclusion

A broader approach to healthy lives in the tropics is needed. The current global health agenda neglects melioidosis and CKD through their exclusion from the NTD and SDG strategies, although both are likely to increase as long as the diabetes epidemic continues. Approaches to counteract melioidosis must not ignore the interaction with NCDs and requires coordinated public health interventions.

This work has relevance beyond melioidosis. For instance, other neglected tropical diseases will also be reduced through improved water and sanitation, and efforts to reduce the burden of non-communicable disease will also make patients more resistant to infection.

Biography

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