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REVIEW

The looming tide of nontuberculous mycobacterial infections in Portugal and Brazil

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SUMMARY

Nontuberculous mycobacteria (NTM) are widely disseminated in the environment and an emerging cause of infectious diseases worldwide. Their remarkable natural resistance to disinfectants and antibiotics and an ability to survive under low-nutrient conditions allows NTM to colonize and persist in man-made environments such as household and hospital water distribution systems. This overlap between human and NTM environments afforded new opportunities for human exposure, and for expression of their often neglected and underestimated pathogenic potential. Some risk factors predisposing to NTM disease have been identified and are mainly associated with immune fragilities of the human host. However, infections in apparently immunocompetent persons are also increasingly reported. The purpose of this review is to bring attention to this emerging health problem in Portugal and Brazil and to emphasize the urgent need for increased surveillance and more comprehensive epidemiological data in both countries, where such information is scarce and seriously thwarts the adoption of proper preventive strategies and therapeutic options.

Contents

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1. Introduction

The genus *Mycobacterium* is notorious for including the pathogens accountable for two of the most ancient diseases known to humankind, leprosy and tuberculosis (TB), responsible for countless deaths and affliction through human history [1,2]. However, since Hansen's discovery of *Mycobacterium leprae* in 1873 and Koch's discovery of *Mycobacterium tuberculosis* nine years later, the list of described mycobacterial species has grown and currently counts with 170 species and subspecies (www.bacterio.net/mycobacterium.html) (Figure 1). These less known and often neglected mycobacteria, collectively called nontuberculous mycobacteria (NTM), are ubiquitous environmental saprophytes and increasingly regarded as opportunistic human pathogens [6]. Although only a few NTM species are familiar to clinicians and commonly associated with human infection, many of the species described over the last two decades are regarded as potentially pathogenic (Figure 1) [7,8]. The success of NTM both as ubiquitous saprophytes and as opportunistic pathogens can in part be explained by their natural resilience to stress conditions such as desiccation, nutrient starvation, extreme temperatures and pH, and antimicrobials resistance [9,10]. Along with their biofilm-forming capabilities, these characteristics render NTM particularly well-suited for the colonization of artificial environments such as chlorinated water supply networks, where they can proliferate and gain advantage over their chlorine-sensitive competitors [9,11,12].

Mycobacteria are traditionally divided into slowly-growing mycobacteria (SGM) and rapidly-growing mycobacteria (RGM) based on growth rate and although historically the species within the SGM group are the ones that have almost always been associated with disease, the significant numbers of nosocomial infections caused by RGM have changed this perception [13]. In fact, convincing evidence indicates that the numbers of NTM infections caused by both SGM and RGM species are rising worldwide although the lack of systematic reporting in most countries still renders it difficult to establish definitive conclusions concerning their true global incidence [14–17]. Several hypotheses have been proposed to explain this rising trend, notably the increasing overlap of human and mycobacterial habitats (e.g., water distribution systems), increased numbers of NTM in drinking water due to changes in water quality and wider adoption of disinfection regimens that promote selection for these organisms, greater physician awareness of NTM as a possible cause of infections leading to more cases being diagnosed and reported, and the greater prevalence of some predisposing factors in the human population [18]. Risk factors for NTM disease that have been identified so far include: (i) lowered immunocompetence due to HIV infection, cancer, chemotherapy, use of immunosuppressive drugs following transplants or ageing-dependent immunosenescence; (ii) underlying lung conditions such as chronic obstructive pulmonary disease, cystic fibrosis, lung damage due to occupational exposure, to smoking, to prior tuberculosis or other lung disease; (iii) genetic factors, namely mutations in the cystic fibrosis transmembrane conductance regulator gene or in the α-1-antitrypsin gene [19].

In this review, we will focus on the information available about the current status of NTM infections in Portugal and Brazil, two countries for which epidemiological data is still scarce and whose historically high TB burdens [20] have for many years overshadowed the role of NTM in human disease. In 2013, Portugal had a tuberculosis incidence rate of 26 cases per 100,000 population while in Brazil the incidence rate was 46 per 100,000 population [20]. In order to shed light into this emerging health problem, we conducted a survey of the available literature on NTM infections in Portugal and Brazil by searching PubMed, Web of Science, Google Scholar, SciELO and Lilacs databases between December 2014 and February 2015. The keywords mycobacter*, atypical or non-tuberculous or non-tuberculous, Portugal or Brazil, infection or outbreak or disease or isolation were used and the search was repeated in Portuguese. Reports in languages other than English or Portuguese and with ambiguous or absent geographical information were excluded, no other exclusion criteria were employed.

2. Pulmonary NTM infections

Pulmonary disease is a common manifestation of NTM infection and has been the focus of many recent reviews [21–24]. However, only a few studies have investigated the epidemiology of pulmonary NTM (PNTM) infections in Portugal and Brazil (Table 1) [25–44]. In addition many of these studies have important limitations as will be discussed later in this section. Two of these surveys, conducted in the Greater Lisbon Area, covering the period between 2005 and 2009, independently found NTM to account for approximately 12% of all isolates from patients diagnosed with mycobacterial disease, leaving the remaining 88% of the cases to species of the *Mycobacterium tuberculosis* complex [25,26]. In Brazil, the reported incidence rates differ significantly between different states, periods, and population samples. In the states of Bahia, Pará and Piauí, 8% of patients presenting symptoms compatible with pulmonary TB were actually found to be infected with NTM [39,43,44]. In the state of São Paulo, where most Brazilian studies have been conducted, the percentage of NTM infection among patients suspected of mycobacteriosis has been reported to be around 20% [32,33,37,34] and in the state of Rondônia one study also found a similar result [41]. Agertt and coworkers reported 33% of NTM in Rio Grande do Sul but the inclusion of non-clinically relevant samples of both pulmonary and extrapulmonary origin probably led to an overestimation and does not reflect the true incidence of PNTM disease [42].

These results illustrate the relevance of PNTM infections as a public health problem in Portugal and Brazil, but because PNTM disease cases are not of mandatory notification, the true incidence in both countries remains indeterminate due to lack of more comprehensive data. Even in countries with a high incidence of TB, it is important to be aware that a significant proportion of mycobacterial pulmonary disease cases are in fact caused by NTM,