Water Research 109 (2017) 310–326

Contents lists available at ScienceDirect

Water Research

journal homepage: www.elsevier.com/locate/watres

Review

Dose response models and a quantitative microbial risk assessment framework for the *Mycobacterium avium* complex that account for recent developments in molecular biology, taxonomy, and epidemiology

Kerry A. Hamilton [a, *], Mark H. Weir [b], Charles N. Haas [a]

[a] Department of Civil, Architectural, and Environmental Engineering, Drexel University, 3141 Chestnut Street, Philadelphia, PA 19104, USA
[b] Division of Environmental Health Sciences and Department of Civil Environmental and Geodetic Engineering, The Ohio State University, USA

ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form
20 November 2016
Accepted 22 November 2016
Available online 24 November 2016

Keywords:
Mycobacterium avium complex
Mycobacterium intracellulare
Mycobacterium chimaera
MAC
Quantitative microbial risk assessment
QMRA
Dose response
Opportunistic pathogen
Biofilm
Engineered water system
Aerosol

ABSTRACT

Mycobacterium avium complex (MAC) is a group of environmentally-transmitted pathogens of great public health importance. This group is known to be harbored, amplified, and selected for more human-virulent characteristics by amoeba species in aquatic biofilms. However, a quantitative microbial risk assessment (QMRA) has not been performed due to the lack of dose response models resulting from significant heterogeneity within even a single species or subspecies of MAC, as well as the range of human susceptibilities to mycobacterial disease. The primary human-relevant species and subspecies responsible for the majority of the human disease burden and present in drinking water, biofilms, and soil are *M. avium* subsp. *hominissuis, M. intracellulare,* and *M. chimaera*. A critical review of the published literature identified important health endpoints, exposure routes, and susceptible populations for MAC risk assessment. In addition, data sets for quantitative dose-response functions were extracted from published *in vivo* animal dosing experiments. As a result, seven new exponential dose response models for human-relevant species of MAC with endpoints of lung lesions, death, disseminated infection, liver infection, and lymph node lesions are proposed. Although current physical and biochemical tests used in clinical settings do not differentiate between *M. avium* and *M. intracellulare*, differentiating between environmental species and subspecies of the MAC can aid in the assessment of health risks and control of MAC sources. A framework is proposed for incorporating the proposed dose response models into susceptible population- and exposure route-specific QMRA models.

Contents

* Corresponding author.
E-mail address: kh495@drexel.edu (K.A. Hamilton).

http://dx.doi.org/10.1016/j.watres.2016.11.053
0043-1354/

1. Introduction

In recent years, improvements in disinfection practices have reduced the health burden of diarrheal pathogens in drinking water systems in developed and some developing countries. As a result, the focus for waterborne disease burden mitigation in these regions has shifted to opportunistic pathogens that live in biofilms growing on the inner surfaces of distribution system and premise plumbing pipes such as *Legionella* spp., *Mycobacterium* spp., and *Pseudmonas aeruginosa*, among others (Falkinham et al., 2015a, Pruden et al., 2013). For example, *Legionella* spp., a known inhabitant of these systems, now represents the most common cause of drinking water outbreaks in the United States (Beer et al., 2015). Opportunistic premise plumbing pathogen-related illness is likely to represent a lesser portion of the waterborne disease burden in developing countries compared to developed ones, however, outbreaks and isolations from environmental media in developing countries have been reported (Bartram et al., 2007; Pavlik et al., 2009a; von Reyn et al., 1993b). While significant attention has been devoted to the study of health risks from exposure to *Legionella* spp. in engineered water systems (Armstrong and Haas, 2007a,b; Schoen and Ashbolt, 2011), a framework has not yet been developed for quantifying health risks due to *Mycobacterium* spp., an increasingly important cause of opportunistic infections (Falkinham et al., 2015b; Pavlik et al., 2009d).

The genus *Mycobacteria* contains over 150 species (Tortoli, 2003) and is divided into human/animal obligate pathogens including tuberculosis-causing mycobacteria, and non-tuberculosis mycobacteria (NTM[1]) (Portaels, 1995; Vaerewijck et al., 2005). Most mycobacteria are 2–5 μm long and 0.2–2.0 μ thick (Pavlik et al., 2009a). *Mycobacterium avium* complex (MAC) is a group of related species of non-tuberculosis mycobacteria (Portaels, 1995; Vaerewijck et al., 2005) listed on the United States Environmental Protection Agency contaminant candidate list (CCL3 and Draft CCL4) (USEPA, 2009, 2015). MAC is the most frequently identified cause of the 4.2–7.2 per 100,000 annual pulmonary infections due to NTM in the United States in the general population and 15–47 per 100,000 in elderly (>65 years of age) populations, but is not a United States Centers for Disease Control and Prevention (CDC) reportable illness (Adjemian et al., 2012b; Cassidy et al., 2009; CDC, 2011; Kasperbauer and Daley, 2008; O'Brien et al., 1987; Winthrop et al., 2011). Additionally, MAC has been associated with several hospital acquired infections and healthcare outbreaks (Aronson et al., 1999; Tobin-D'Angelo et al., 2004). It is environmentally transmitted, and person-to-person transmission is not believed to occur. In addition to pulmonary disease, various disease outcomes are associated with MAC including soft tissue infections and cervical lymphadenitis in immune-competent patients, and disseminated infections in immunocompromised patients (Falkinham, 1996). MAC pulmonary disease is rare in children and usually related to other immune deficiencies, however, MAC cervical lymphadenitis is the most common form of NTM disease in children (Lai et al., 1984; Lincoln and Gilbert, 1972). Few epidemiologic studies of NTM in children have been conducted, but those from developed countries indicate an annual incidence ranging up to 5.7 NTM infections per 100,000 children under 5 years from Sweden (Lopez-Varela et al., 2015; Romanus et al., 1995).

The public health importance of MAC is increasing; it is suggested that the disease prevalence and laboratory isolation is increasing even after considering its evolving taxonomy, increased awareness, improved laboratory analytical methods (Supplementary Table S1), and improved clinical diagnostic tools (Johnson and Odell, 2014; Kasperbauer and Daley, 2008; Khan et al., 2007). Some of this increase may be due to recognition of the role of MAC in cystic fibrosis and bronchiectasis, increased use of showers compared to baths, and ageing of the population (Angrill et al., 2001; Barker, 2002; Field et al., 2004; Kilby et al., 1992; Oliver et al., 2001; Prince et al., 1989). In addition, increased prevalence of diseases which decrease immunocompetence (HIV/AIDS and cancer), increased use of chemotherapeutic drugs for cancer treatment resulting in immunosuppression, lifestyle changes that bring humans into contact with habitats where NTM naturally occurs, improved water treatment that plays a role in selecting for pathogenic NTM, and changes to the climate and environment may also play a role (Pavlik et al., 2009b). MAC is widespread in waterborne environments and soil (especially those containing peat or sphagnum vegetation) (Falkinham et al., 2001, Rusin et al., 1997; Tuffley, 1980; Vaerewijck et al., 2005; von Reyn et al., 1993b), as well as animal-derived foods (Klanicova et al., 2011) and produce (Cerna-Cortes et al., 2015). It is associated with engineered water systems and biofilms, contributing to its resistance to disinfectants and behavior as an intracellular parasite of free-living protozoans such as *Acanthamoeba* spp. in a similar manner to *Legionella* spp. (Berry et al., 2010; Cirillo et al., 1997; Drancourt, 2014; Falkinham, 2013; Steinert et al., 1998; Wang et al., 2012; Whiley et al., 2012).

The number of species classified as MAC are increasing with advances in genetic sequencing, but currently include *M. avium, M. intracellulare, M. arosiense, M. chimaera, M. colombiense, M.*

[1] NTM is often also referred to as atypical mycobacteria, environmental mycobacteria, potentially pathogenic environmental mycobacteria, or mycobacteria other than tuberculosis.