Curr Envir Health Rpt (2016) 3:161–167
DOI 10.1007/s40572-016-0086-z

WATER AND HEALTH (T WADE, SECTION EDITOR)

Current Epidemiologic Trends of the Nontuberculous Mycobacteria (NTM)

Joseph O. Falkinham III[1]

Published online: 28 March 2016

Abstract The nontuberculous mycobacteria (NTM) are waterborne opportunistic pathogens of humans. They are normal inhabitants of premise plumbing, found, for example, in household and hospital shower heads, water taps, aerators, and hot tubs. The hydrophobic NTM are readily aerosolized, and pulmonary infections and hypersensitivity pneumonitis have been traced to the presence of NTM in shower heads. Hypersensitivity pneumonitis in automotive workers was traced to the presence of NTM in metal recovery fluid used in grinding operations. Recently, NTM bacteremia in heart transplant patients has been traced to the presence of NTM in water reservoirs of instruments employed in operating rooms to heat and cool patient blood during periods of mechanical circulation. Although NTM are difficult to eradicate from premise plumbing as a consequence of their disinfectant-resistance and formation of biofilms, measures such as reduction of turbidity and reduction in carbon and nitrogen for growth and the installation of microbiological filters can reduce exposure of NTM to susceptible individuals.

Keywords Nontuberculous mycobacteria · Drinking water · Ecology · Aerosol transmission

This article is part of the Topical Collection on *Water and Health*

✉ Joseph O. Falkinham, III
jofiii@vt.edu

[1] Department of Biological Sciences, Virginia Tech, Blacksburg, VA 24061, USA

Introduction

The nontuberculous mycobacteria (NTM) include almost 200 distinct species of the genus *Mycobacterium* that are opportunistic pathogens of humans [1•]. Medically important species include *Mycobacterium avium*, *M. intracellulare*, *M. chimaera, M. abscessus* [1•], and others (Table 1). Unlike their relatives, the members of the *M. tuberculosis* complex, the NTM are free-living bacteria and not obligate parasites of humans. NTM are in soils and natural waters and thereby enter drinking water treatment plants. As the NTM are disinfectant-resistant [2], NTM survive water treatment and then enter distribution systems and eventually households, hospitals, long-term care facilities, and office buildings. NTM persistence in pipes containing flowing water is due to their adherence to pipe surfaces, driven by their hydrophobicity [3]. Humans are surrounded by NTM, and, fortunately, only a small proportion of individuals are at increased risk for NTM disease.

Risk Factors for NTM Disease

Risk factors for NTM disease fall into several categories. There are two groups of older men that are at heightened risk for NTM pulmonary infection. First are smokers and heavy alcohol drinkers [4]. The second category includes older men who suffer lung damage due to occupational exposure to dusts: farmers, miners (black lung), and workers exposed to industrial dusts [4]. The recent reappearance of black lung in miners [5] suggests that a parallel rise in NTM cases associated with black lung will increase in the future as black lung is a risk factor for NTM pulmonary disease [4]. Historically, it was men who made up the major portion of the NTM-infected [4]—however, that is not the case now; women currently

Table 1 Medically important nontuberculous mycobacteria (NTM) species

Mycobacterium avium
Mycobacterium intracellulare
Mycobacterium chimaera
Mycobacterium kansasii
Mycobacterium malmoense
Mycobacterium abscessus
Mycobacterium chelonae
Mycobacterium fortuitum

make up the largest proportion of the NTM-infected [6]. Older women (>60 years) who are slender (BMI < 20) and taller (average height = 5′ 8 ″) are at elevated risk for NTM pulmonary disease [7]. Currently, this group makes up the greatest proportion of current NTM patients, estimated at over 80,000 in the United States alone [8•]. Although there have been no studies of this observation, there are several possible reasons for this shift from predominantly men to women that occurred over the period of 1970–1990 [4]. First, workers (primarily men) are now protected from dusts and other industrial pollutants. Second, both women and men are living longer to the point where they become susceptible, although that age-associated increased susceptibility is clearly more evident in women. Third, the Clean Water Acts first enacted in 1970 have led to widespread improvement in water quality, particularly through disinfection, that possibly has resulted in selection of the disinfectant-resistant NTM in drinking water. Cervical lymphadenitis due to NTM infection is seen in young children (<6 years) with erupting teeth [9•]. Unfortunately, NTM-associated cervical lymphadenitis is not required to be reported, but estimates from published studies in the United States suggest that the numbers are low (ten per month) [9•]. Interestingly, until approximately 1980, all cases in young children with erupting teeth were caused by *M. scrofulaceum*, whereas after that time all are caused by *M. avium* [9•]. The last group of individuals at heightened risk for NTM infection is those who are immunodeficient. Inherited mutations, cancer, cancer chemotherapy, transplantation, and HIV infection can all result in reduced immune function [6]. In fact, reports of *M. avium* infection in HIV-infected men in the United States in 1982 heralded the beginning of the AIDS epidemic. The advent of highly active anti-retroviral treatment (HAART) has led to a dramatic reduction in AIDS-associated NTM infections, and consequently, those make up a small proportion of current number of NTM-infected today [6, 8•]. However, it is anticipated that as many developed countries continue to age and the number of cancer and chemotherapy-treated patients to increase, the number of individuals that are immunosuppressed due to organ transplantation will increase, and thus also the number of NTM infections.

Continued Increase in NTM Pulmonary Disease

Although NTM bacteremia due to HIV infection and AIDS has been dramatically reduced with the advent of HAART, the prevalence and incidence of NTM pulmonary disease and the number of clinical samples yielding NTM have risen at an annual percentage of 5–10 % for the past 20 years [6, 8•]. Current estimates range from 5 to 15 NTM pulmonary disease cases per 100,000 and estimates the number of NTM pulmonary disease patients at 84,000 [8•]. These estimates are based on hospital records and would necessarily miss those NTM patients treated outside hospitals and, thus, likely underestimates of the true burden of NTM disease. Further, as NTM disease is not required to be reported, as is *Legionella pneumophila* disease, many NTM-infected individuals are simply missed by any attempt at gathering data.

Ecology of NTM

The NTM are normal inhabitants of natural soils and water (Table 2). Numbers are particularly high in the pine, boreal forests of northern Europe and the United States [10] and the coastal, acidic, brown-water swamps of the Atlantic and Gulf coastal states of the US [11]. From surface waters, the particulate-attached NTM enter water treatment plants. NTM numbers are reduced by particulate reductions [12], but are resistant to disinfection. The NTM are approximately 10–100-times more resistant to chlorine, chloramine, chlorine dioxide, and ozone compared to *Escherichia coli* [2]. As a result, the NTM pass into the distribution system where they can grow on the available nutrients in the absence of competitors [12]. In the distribution system, the hydrophobic NTM attach to pipe surfaces and form biofilms [3], thus preventing these slowly growing (one-generation per day) bacteria from being washed out of the system. The major determinant of NTM growth and persistence in distribution systems is the presence

Table 2 Environmental sources of nontuberculous mycobacteria (NTM)

Peat-rich soils
Drainage water from peat-rich soils
U.S. coastal swamp soils, waters, and sediments
Natural streams, rivers, ponds, and lakes
Drinking water distribution systems
Premise (hospitals, homes, apartments) plumbing
Instruments with water reservoirs (humidifiers, heater-coolers)
Refrigerator water, taps, and ice
Shower aerosols
Spas and hot tubs
Biofilms in all the above

of disinfectant and reduced organic carbon, but NTM are disinfectant-resistant, and in the absence of competitors, the NTM can utilize all the available organic carbon [12]. From the distribution system, NTM enter the plumbing of homes, hospitals, long-term care facilities, and office buildings. NTM numbers increase appreciably in water heating systems, and thereby, higher numbers enter premise plumbing. Premise plumbing is an ideal habitat for NTM: the water is warm, there are plenty of surfaces for biofilm formation, and there are few competitors for the limited nutrients. Although NTM can be recovered from premise plumbing water samples in the range of 100–1000 colony-forming units (CFU)/mL, many more NTM cells are in biofilms (10,000 CFU/cm^2) [12]. Opening a tap or showering both generate aerosols containing droplets with NTM. *M. avium* cells in a showerhead were shown to be identical by DNA fingerprinting to *M. avium* cells isolated from the patient using the shower [13]. Although individuals are infected by NTM in aerosols generated by splashing water in showers or sinks, it is the NTM in biofilms that ensure the persistence of NTM in premise plumbing. Further, NTM in biofilms, as is the case with other bacteria, are even more resistant to disinfectants than those in water [14]. In another study, half of 30 households of NTM-infected patients had NTM species that were identical by DNA fingerprinting to the NTM species infecting them [15]. The high prevalence of NTM in premise plumbing was confirmed in a study of showerheads across the United States; 70 % of showerheads (likely none were from NTM patients) had NTM [16]. Thus, NTM-infected individuals are not the only persons with NTM in their showerheads and premise plumbing; NTM are present in almost every plumbing system.

Although not as emphasized as waterborne NTM infection, NTM in soil have also been linked to pulmonary disease. Comparison of NTM isolates from patients and dusts generated by soil samples that the patients used in gardening showed that 5 of 11 patients were infected with genetically the same isolate that was found in the soils [17]. In light of the fact that gardening can be a hobby of older Americans and potting soils purchased from home and garden stores are rich in NTM (i.e., 1 million per gram of soil) [17], individuals with risk factors for NTM disease ought to consider foregoing gardening. I suspect that the high numbers of NTM in potting soils is due to inclusion of peat in such commercial soils, and peat is a habitat rich in NTM [10, 17].

Impact on NTM of Switching from Chlorine to Chloramine for Disinfection

A current trend in the drinking water industry is a shift in disinfectant from chlorine to chloramine. The two reasons have driven this shift: (1) chloramine does not produce the halogenated carcinogens to as great an extent as does chlorine and (2) chloramine was reported to be superior at killing microbial cells in biofilms. Monitoring of a municipal water system before and after the shift from chlorine to chloramine led to the disturbing discovery that although *L. pneumoniae* disappeared from building water samples, the frequency of recovery of nontuberculous mycobacteria increased [18•]. As that result has been found in other, independent studies, it raises the question that the disinfectant shift has unexpected consequences that may have an impact on public health.

Mycobacterium spp. and Cervical Lymphadenitis in Children

Over the period 1975–1985, there was a shift in the species of *Mycobacterium* responsible for cervical lymphadenitis in children [9•]. Before 1975, almost all the cases of cervical lymphadenitis in children were caused by *M. scrofulaceum*, whose colonies appear quickly (for a mycobacterium) and are a distinctive bright yellow color [9•]. Currently, and after the period 1975–1980, *M. scrofulaceum* is not isolated from children with cervical lymphadenitis at all; it is the unpigmented, more slowly growing *M. avium* that is isolated [9•]. Although the species causing cervical lymphadenitis has changed, there have been no changes in the prevalence of cervical lymphadenitis in children and its presentation [9•]. This is not a simple mutation to loss of pigmentation and slower growth; the species are distinct. A possible hypothesis to explain this switch is that improvement in water quality in the U.S. led to the disappearance of *M. scrofulaceum* and its replacement by *M. avium* as a result of widespread chlorine disinfection of drinking water. In 1970, the U.S. Congress passed the first of the Clean Water Acts, designed to improve the water quality of U.S. rivers, by distribution of funds to improve water treatment. Relevant to my hypothesis, over the period of 1975–1985, the quality of U.S. rivers improved [19]. Second, *M. scrofulaceum* is considerably more sensitive to chlorine, chloramine, chloride dioxide, and ozone than *M. avium* [2]. Although there are other possible explanations, the fact remains that *M. scrofulaceum* has disappeared as a causative agent of cervical lymphadenitis in children and has been replaced entirely by *M. avium* without any change in the frequency of this manifestation of NTM infection [9•].

Hypersensitivity Pneumonitis in Automobile Workers

In 2000, the Centers for Disease Control reported an outbreak of cases of hypersensitivity pneumonitis (HP) among workers in the automotive industry [20]. HP requires that the auto worker be released from work; avoidance of the workplace leads to remission of symptoms. That costs the auto manufacturer

money and the loss of a skilled worker and a great deal of hardship for the employee. Studies showed that the afflicted workers were exposed to aerosols generated by grinding and finishing metal castings [20]. Metal castings are ground and polished and sprayed with metal recovery fluid (metal working fluid) to reduce heat and carry away particulate matter. The metal recovery fluid (MRF) is an oil-water emulsion that is recovered and reused during grinding and polishing activities. Unfortunately, the oil-water emulsion is a substrate for the growth of microorganisms, and the growth of microbes in the MRF emulsion leads to loss of its ability to carry away particulates. When contamination is discovered, disinfectants are used to inhibit the growth of microorganisms, leading to recovery of MRF activity. As a consequence of disinfectant use, there is a shift in the composition of the MRF and NTM predominate [20, 21]. In fact, a novel species, *M. mucogenicum*, was found in the MRF [21]. Workers suffering from HP can be excused from work, and HP symptoms disappear, linking the MRF-mycobacterial exposure to HP.

The appearance of HP is consistent with exposure to mycobacteria. Mycobacterial cells or cellular fractions can elicit hypersensitivity reactions [22]. Exposure to aerosols from hot tubs from which *Mycobacterium* spp. have been isolated is associated with HP and even mycobacterial pulmonary disease [23]. In addition to identifying an occupational risk, a review of the HP cases illustrates that HP only occurred following disinfectant use to inhibit and eradicate microorganisms growing in the MRF emulsion [20]. Thus, as is shown in drinking water treatment plants, disinfectants are selective agents and result in the selection of disinfectant-resistant mycobacteria introduced into the MRF by mixing the oil fraction with tap water.

NTM Infections in Cardiac Surgery Patients Linked to Heater-Coolers

An October 2015 publication described an outbreak of *M. chimaera* infections with high mortality (50 %) in patients who had undergone cardiac surgery (e.g., heart transplant) [24]. The source of the infecting *M. chimaera* was traced to the water reservoir of an instrument used to heat and cool patients' blood during the periods of time when the patient's circulation is mechanical [24]. Although the number of NTM-infected, cardiac surgery patients is low, the high mortality of the infection and the high number of heart transplants or other operations involving mechanical circulation throughout the world, this outbreak has received a great deal of attention. Patients undergoing heart transplantation are more susceptible to NTM infection, as a result of their transplant-associated immunosuppression. Protection against mycobacterial infection involves the same graft-rejection system that is suppressed for transplantation. The infections have been reported from Europe and the United States, and the U.S. Food and Drug Administration [25] and the European Center for Disease Control [26] have issued alerts. At present, the hospitals involved in the different outbreaks have been carrying out retrospective medical record surveys of all prior cardiac patients to assess their infection status. In addition, blood samples have been obtained to determine whether any have subclinical infections.

One approach to preventing these infections is to thoroughly disinfect the water reservoirs in the heater-coolers. As the NTM involved in these infections are likely to have formed biofilms throughout all surfaces in the instruments, disinfection will be difficult. As NTM are disinfectant-resistant [2] and biofilm-grown cells in biofilms are 5–10-fold more resistant [14], dosages (i.e., disinfectant concentration and time) must be made higher to ensure suitable disinfection. As there is no data on infectious dose of NTM, the end-point for disinfection is unknown. One possible end-point could be the number of NTM found in drinking water, namely between 10 and 1000 colony-forming units/mL and 10,000 CFU/cm^2 of biofilm [12]. One important focus will be to determine whether the heater-coolers amplify NTM numbers, as happens in premise plumbing. As some NTM are expected to survive any disinfection regimen, repeated cycles of disinfection would be expected to be performed regularly. The choice of disinfectant is limited by the tolerance of the tubing, piping, pumps, and other materials that come in contact with the water in the heater-coolers; some disinfectants will rapidly corrode and damage the components. At present, it is unknown how long it takes for NTM numbers to rise after disinfection, even using sterile water in the reservoirs. Finally, it might be possible to continue to use heater-coolers, but move them out of the operating room to prevent the formation of NTM-laden aerosols in the operating room. Alternatively, the heater-cooler could be encased in an isolation chamber with the air and aerosols removed by HEPA filtration.

Recommendations and Their Rationales to Reduce NTM Numbers in Premise Plumbing

What follows is a list of measures that can be taken to reduce NTM numbers in premise plumbing or reduce exposure and the generation of NTM-laden aerosols (Table 3). None have been tested thoroughly but are based on observations of factors influencing the presence and absence of NTM. The rationale for each measure is included.

(1) Drain the hot water heater. Hot water heaters have a resident population of NTM [15]. The highest numbers are in the sediment that collects in the bottom [15]. Attach a hose to the drain and let the water, sediment, and bacteria nourish the garden.

Table 3 Measures to reduce NTM exposure

Drain water heater
Increase water heater temperature to 55 °C (130 °F)
Switch from piped to well water
Install microbiological filters (≤0.2-μm pore size)
Do not use granular activated carbon filters
Replace showerhead with one having large holes
Disinfect showerhead monthly
Reduce bathroom aerosols
Remove aerators from all taps
Get rid of all humidifiers
Avoid dusts from potting soils
Boiling water for 10 min kills NTM

(2) Raise hot water heater temperatures. Turn up the water heater to 130 °F (55 °C). NTM patient household plumbing that did not have NTM had higher hot water temperatures (130 °F or 55 °C or higher), compared to households whose hot water heater temperature was 125 °F (50 °C) or lower [15].

(3) Use a well, not a public or private piped water system source. NTM patient household plumbing from wells were less likely to have NTM compared to households with a public or private water system source [15]. NTM are abundant in water systems; they grow in chlorine without any competition, as other bacteria are killed. Caution must be taken in using well water, as wells may have other contaminants, such as heavy metals, pollutants, and pathogens. Test well water first before switching.

(4) Install filters that remove bacteria. Water filters whose pore sizes are less than 0.2 μm will prevent the passage of NTM. A number of manufacturers produce and sell such filters, primarily for the hospital market. For example, Pall Medical makes such filters for taps and showerhead replacements. My own research has shown that they prevent passage of NTM. One drawback is that the filters are recommended for use for only 30 days, so they need to be replaced and are expensive (e.g., $ 50–100/month).

(5) Beware of granular activated carbon (GAC) water filters. GAC filters are widely marketed and sold directly to consumers to reduce the bad taste of drinking water. GAC binds chlorine and other disinfectants, metals, and organics that impart a bad taste to water. However, they promote the growth of NTM without preventing their passage [27]. The pores of GAC filters are not small enough to prevent bacterial passage; the tortuous path of movement merely delays passage for a while. NTM grow well in GAC filters; they attach and grow on the carbon-bound organics and metals as they are resistant to the disinfectant [27]. The manufacturer's recommendation for replacement of the filters is based on the capacity to remove disinfectants, metals, and organics, not on preventing passage of bacteria. In our hands, the recommended time to replace a GAC filter is longer than the time when high NTM numbers pass the filter.

(6) Replace showerhead with one that produces streams and not a fine mist. NTM cells are concentrated in aerosol droplets. Many "low-flow" showerheads produce a fine mist that contains droplets with high numbers of NTM, small enough to enter the alveoli. Replace such a "low flow" or misting showerhead with one that has large holes (1-mm diameter).

(7) Remove and clean showerheads. Showerheads harbor high numbers of NTM. One way to disinfect a showerhead would be to remove it and place it in undiluted household bleach (right out of the Clorox bottle) for 30 min, then rinse. If possible, clean the inside surfaces (biofilms) before disinfection. It has been recommended to wash a showerhead in a dishwasher. That probably helps, especially as the drying cycle would expose any NTM in the showerhead to high temperature (160 °F).

(8) Reduce shower aerosols by opening the bathroom window. A likely spot where NTM infection occurs is a bathroom shower or sink. Make sure that the bathroom fan actually removes mists (most just make noise and cannot even hold a Kleenex against their surface). Make your showering experience as short as possible and dry off in another room.

(9) Get rid of any and all humidifiers. Humidifiers generate aerosols with high numbers of NTM, even from reservoir water containing relatively low numbers of NTM (30–100 colony-forming units/mL) [Falkinham, unpublished]. The new style humidifiers ("ultrasonic") generate a higher density aerosol (visible as a thick fog coming out of the machine) and thus are better than previous humidifiers at transferring water to air and unfortunately NTM. From a low density suspension of NTM (30–100 colony-forming units/mL) in an ultrasonic humidifier, in 10 min, the room air contained 200 colony-forming units of NTM per cubic meter [Falkinham, unpublished].

(10) Turn off the humidifier attached to the heating/cooling system. In an ongoing study of NTM patients in Philadelphia (the same hospital and area where the elderly, slender women were first identified at risk for NTM pulmonary disease), our colleagues at the Lankenau Medical Research Institute (led by Dr. Leah Lande) discovered that all the NTM-infected women have humidifiers that are simple fabric filters with a channel above with holes for tap water (and NTM) to drip through (like "swamp coolers" in the desert southwest). It may be that NTM attach to the filter material (maybe grow) and are transferred the household air that

is drawn through the filter. Humidity helps breathing, but it exposes one to NTM-laden aerosols.

(11) Boiling water (10 min) will kill mycobacteria.

(12) Avoid dusts from potting soil. Commercial potting soil is rich in peat and peat harbors very high numbers of NTM (1 million per gram) [17]. As peat or potting soil dries, the dust generated has high numbers of NTM. In a study of pulmonary NTM patients, we found that a proportion (who were gardeners) had been infected from their potting soil [17].

Conclusions

One of the questions that has yet to be answered is whether or not the numbers of NTM in drinking water are increasing or not. Clearly, the number of NTM cases is increasing [8•]. Over the period 1970–2000, a major factor contributing to the increased numbers of NTM cases was wider recognition of NTM disease and improved methods of culturing sputum and other samples for NTM. However, that period is behind us, and possibly, the increased number of cases reflects two changes: one common knowledge and one hypothetical. First, the U.S. population is aging, with percentage of individuals over 60 years estimated to reach 25 % by 2020 [28]. That includes the slender, taller women who for some reason, as of yet unidentified, are more susceptible to NTM pulmonary disease [7] as their homes have no more NTM than those of non-NTM-infected [15]. In addition, the proportion of individuals with cancer, undergoing cancer chemotherapy or transplantation, will also increase. The second, and speculative, explanation for the increased number of NTM cases is that the number of NTM in drinking water is increasing. Increased numbers of NTM would have the effect of raising numbers of NTM to those that could trigger infection and disease, thus raising the number of cases. One possible change in drinking water might be responsible for an increase in NTM numbers. It is well established that nitrate levels are increasing in drinking waters, due to runoff from fertilized agricultural fields and industries [29]. NTM, in particular the major mycobacterial pathogen by numbers in the United States, *M. avium*, can utilize nitrate as a sole source of nitrogen [30]. If drinking water is nitrogen-limited for microbial growth, it follows that increased nitrogen in drinking water will benefit those disinfectant-resistant, nitrate-utilizing microorganisms.

Recommendations

Currently, NTM infections are not required to be reported, so every one of the figures for number of cases is estimate, primarily based on hospital records. As a substantial proportion of NTM-infected patients do not require hospitalization, the number of NTM-infected individuals is low. NTM disease should be reported, as is disease caused by *Legionella pneumophila*, another waterborne opportunistic pathogen.

Research needs for NTM are enormous. First, it will be necessary to develop a robust knowledge of dose-response for NTM disease caused by the major infecting species: *M. avium, M. intracellulare, M. chimaera,* and *M. abscessus*. Once that is known, surveillance can identify sources that are of higher and lower risk. Second, as antibiotic therapy for NTM disease requires combinations of antibiotics that carry with it debilitating side effects, efforts must be taken to rigorously test the efficacy of any measures for exposure reduction. Finally, for protocols for reduction in numbers of NTM in premise plumbing and instruments, this will require identification of anti-mycobacterial disinfectants and methods to kill NTM cells in biofilms. NTM in biofilms are more resistant than those in the water suspension and can serve to repopulate premise plumbing and instruments after disinfection. Finally, efforts must continue to discover and develop novel anti-NTM antibiotics. These antibiotics may not be hand-me-downs from anti-*M. tuberculosis* drugs as they are at present. The NTM are free-living bacteria, not obligate parasites of higher organisms, and thus present a more complex metabolism and structure than that of *M. tuberculosis*.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent The article does not contain any studies with human or animal subjects performed by the author.

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