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Non-tuberculous mycobacteria in drinking water systems: A review of prevalence data and control means

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ABSTRACT

Non-tuberculous species of *Mycobacterium* are commonly found in a large diversity of water environments, and epidemiological studies suggest that natural or drinking waters are the principal sources of human contamination. Controlling non-tuberculous mycobacteria in water systems is therefore important to prevent infection with these micro-organisms. This review article summarizes the information and data published up to now on the factors favoring the presence of these bacteria in natural and artificial water systems, the effectiveness of water treatment means, and based on this information, identifies possible means to control the presence of non-tuberculous mycobacteria in drinking water.

1. Introduction

Unlike the tuberculous or "typical" species of *Mycobacterium* such as *M. tuberculosis* or *M. leprae*, which have only human or animal reservoirs, the non-tuberculous or "atypical" species of *Mycobacterium* are commonly found in a large diversity of water environments, including fresh, brackish, and sea waters (WHO, 2011). Exposure to these atypical *Mycobacterium* spp. through contact, inhalation, or ingestion of contaminated water can cause a range of diseases involving the skeleton, lymph nodes, skin and soft tissues, as well as the respiratory, gastro-intestinal and genito-urinary tracts.

Epidemiological studies suggest that natural or drinking waters are the principal sources of human contamination (Nishiuchi et al., 2017). Mycobacterial infections linked to contaminated hospital water, particularly hot water systems, have been recognized for many years (Li et al., 2017), but infections have also been linked to contaminated water in pools, spas, hot tubs, public baths, ice machines, irrigation waters, and the use of instruments contaminated by tap water in health care and cosmetic settings (Nichols et al., 2004). Infections are generally sporadic, and in the majority of cases, there is only circumstantial evidence of a causal relationship between the occurrence of bacteria in drinking-water and human disease (WHO, 2011). In some cases however, drinking water has been more evidently identified as the source of exposure to *M. avium* or *M. chelonae*, after comparing clinical isolates and strains isolated from point of use water taps, using biochemical tests (Regnier et al., 2009) or molecular methods (Von Reyn et al., 1994; Falkinham III et al., 2008; Hilborn et al., 2008; Falkinham III, 2015). Animals can also be exposed through drinking water. In a recent investigation of farms with cattle affected with Johne's disease, Samba-Louaka et al. found a same genotype of *Mycobacterium avium* subsp. *paratuberculosis* in the drinking troughs used by the cattle and in the infected animals (Samba-Louaka et al., 2018).

Controlling non-tuberculous mycobacteria (NTM) in drinking water is therefore important to prevent infection with these micro-organisms. Following already published reviews on this issue, the present article intends to summarize the results of the major studies published to date and to encompass all the aspects potentially manageable by drinking water operators to better control NTM in drinking water production and distribution systems.

2. Prevalence in water resources and in treated waters

Until recently, data on the occurrence of atypical mycobacteria were relatively limited because their isolation from water with culture-based methods was laborious and time consuming, since they grow very slowly and tend to be outgrown by other, more rapidly growing organisms. The application of PCR methods in the recent years has allowed the production of more important datasets. More recently, amoebal co-culture has also been described as an alternative means to efficiently isolate amoeba-resisting microorganisms from environmental samples, mycobacteria appearing as the most common bacteria retrieved by this technique (Greub and Raoult, 2004; Lienard and Greub, 2010).

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2.1. Water resources

Among the non-tuberculous mycobacteria, *M. avium* has been by far the most studied. Because of its ability to grow over a wide range of temperature, oxygen level, pH and salinity conditions, *M. avium* can be recovered from a large variety of raw source waters. Its preference for acidic pH, its resistance to reduced oxygen concentration and the stimulation of its growth by humic or fulvic acids especially favor its presence in high numbers in waters from peat-rich boreal forest soils and acid brown-water swamps (Falkinham et al., 2004).

Mycobacterial concentrations and frequency of recovery of *M. avium* in raw waters used for drinking water production in the USA have been associated with high turbidity levels, suggesting that *M. avium* cells may be bound to colloidal or suspended particles. In a study including two ground and six surface waters, important differences in the spectra of mycobacterial species and numbers appeared, but no seasonal effect was observed (Falkinham III et al., 2001). Among the 140 raw water samples collected over the 18-month period of this study, almost 28% of them (39/140) were positive for mycobacteria, slowly growing mycobacteria representing the majority of recovered isolates. All surface waters were positive for mycobacteria by culture method, and provided the largest number of species, some (*M. avium, M. gordonae, M. terrae*) being detected at higher frequency than others (*M. intracellulare, M. fortuitum, M. flavescens, M. marinum, M. smegmatis, M. abscessus, M. aurum, M. chelonae, M. shimoidei, M. szulgai*), whereas ground waters yielded no detection or only one species (*M. terrae*). The most contaminated resource was characterized by a frequency of detection of *M. avium* of 29%, and estimated concentrations up to 55,000 CFU/L for *Mycobacterium* spp. and 14,000 CFU/L for *M. avium*.

Several studies targeted especially *M. avium* subsp. *paratuberculosis* (Map) in water resources potentially impacted by the presence of livestock. In a 1-year survey of a river in South Wales, 32.3% of 96 samples were found positive by PCR method, and a significant association between rainfall, river flow, and detection of Map was found (Pickup et al., 2005). Similar studies conducted on another river in South Wales (70 samples) and lakes and water streams in the English Lake District region (67 samples) led to the same observations, with respectively 68.8% and 31% positive samples for Map. The presence of Map was also detected in the treated effluent from a domestic sewage treatment plant. Map was found to be particularly associated with suspended organic solids, and deep lake sediments were identified in this study as an environmental reservoir for Map (Pickup et al., 2006).

In a 1-year survey of raw waters supplying nine water treatment works in Northern Ireland Whan et al. analyzed 192 samples by immunomagnetic separation (IMS)-PCR assay and two culture-based methods (Whan et al., 2005). Overall, 8% of the samples tested positive for Map by one or more of the three detection methods, with at least one detection in eight out of the nine water treatment works, and no significant difference in detection rates observed between the seasons. A second 1-year sampling campaign was subsequently conducted on one lake used as raw water resource and the raw water intake of two of these water works (Aboagye and Rowe, 2011). The presence of Map was detected by PCR method in 29% of the 70 water and sediment lake samples and 56% of the 48 raw water intake samples collected.

In a survey of 13 surface waters in the Czech Republic, Makovcova et al. (Makovcova et al., 2014) confirmed the higher rate of recovery of NTM in sediments (35.1%), compared to water samples (11.1%). Out of 396 samples collected in this survey, 23.7% were found positive by conventional culture method. The most frequently detected isolates identified belonged to the *M. peregrinum/septicum* group (18.1%), and a wide range of other pathogenic mycobacteria were isolated in this study, including *M. asiaticum, M. chimaera, M. fortuitum, M. gordonae, M. interjectum, M. kumamotonense, M. lentiflavum, M. montefiorense, M. nebraskense, M. paraffinicum,* and *M. simiae*.

By using amoebal co-culture with *Acanthamoeba polyphaga*, followed by PCR amplification and sequencing of the 16S rRNA gene, Pagnier et al. investigated the amoeba-resisting population of a large series of environmental waters in the south of France, and isolated several mycobacterial species including *M. chelonae, M. abcessus, M. monacense,* and *M. neoparum* from fountains (Pagnier et al., 2008).

Table 1
Mycobacterial species recovered from a surface water treatment plant, by amoebal co-culture, or from infected amoebae. Adapted from (Loret et al., 2008; Thomas et al., 2008), and including non-published data.

Treatment step	Mycobacterial species
River water	*M. fluoranthenivorans* (from a non-identified protist)
	M. frederiksbergense
	M. frederiksbergense or *M. fluoranthenivorans*
	M. gadium
	M. gastri or *M. kansasii*
	M. gordonae
	M. insubricum
	M. neonaurum
	M. terrae
	M. vaccae
	M. vanbaalenii
Biofilm from sand filter	*M. gordonae*
	M. insubricum
	M. poriferae
	M. septicum or *M. peregrinum*
Sand-filtered water	*M. gordonae*
Ozonated water	*M. fluoranthenivorans*
	M. mucogenicum (from *Echinamoeba exudans)*
Biofilm from GAC filter	*M. fluoranthenivorans*
	M. gordonae
	M. neglectum
GAC-filtered water	*M. frederiksbergense*
	M. frederiksbergense or *M. fluoranthenivorans*
Distribution system	*M. anthracenicum*
	M. frederiksbergense or *M. fluoranthenivorans*
	M. gadium
	M. neglectum
	M. vanbaalenii

The same technique was applied with *Acanthamoeba castellanii* to raw waters supplying different drinking water treatment plants. Loret et al. and Thomas et al. looked for naturally infected amoebae and amoeba-resisting bacteria in the River Seine 30 Km upstream Paris, France (Loret et al., 2008; Thomas et al., 2008) and recovered a large spectrum of mycobacterial species (Table 1). With the same technique, Corsaro et al. analyzed 20 samples collected over one year from three surface and one ground waters supplying three drinking water treatment plants in Spain. Only non-identified species from the rapid-grower group of mycobacteria were detected in two of the surface waters. Interestingly, the diversity of mycobacteria in raw and treated waters was highest in the plant supplied with the surface water presenting the highest turbidity values (Corsaro et al., 2010).

Garcia et al. collected 68 samples from reservoirs and 15 samples from 3 water treatment plants to identify amoebae and intra-cellular bacteria within amoebae, in northeast Spain (Garcia et al., 2013). They detected a presence of amoebae in 77.1% of the samples, with 41.9% of them showing the presence of intra-cellular *Mycobacterium* spp. A significant association was found between the presence of mycobacteria and warm water temperature.

2.2. Drinking water production and distribution

In a study of six conventional treatment plants supplied with surface waters, and composed of clarification, filtration and disinfection stages, Falkinham et al. observed that the average reduction of slowly growing mycobacteria was about 2 log, except for the plant equipped with granular activated carbon (GAC) filtration, where numbers of mycobacteria at the plant outlet (220 000 CFU/L) exceeded those at the plant inlet (14 000 CFU/L). While no mycobacteria were detected in the finished water of the three plants applying chlorine for the final

disinfection, slowly growing mycobacteria (unknown species and *M. terrae*) were detected in the three other plants using monochloramine, with the highest frequency of occurrence (22%) in the water treated with GAC and monochloramine. Despite the presence of *M. avium* and *M. intracellulare* in all raw waters used by these plants, none of these species was detected in finished waters (Falkinham III et al., 2001; LeChevallier, 2004). An important regrowth was observed in all cases in the distribution systems, with mycobacterial numbers 25 000 fold higher on average in distributed water than at plant outlet, and concentrations of slowly growing mycobacteria up to 7×10^5 CFU/L. This increase was correlated with levels of assimilable (AOC) and biodegradable organic carbon (BDOC), for AOC levels ranging from 17 to 234 µg/L. Although *M. intracellulare* was seldom recovered from distributed water, it was frequently found in high numbers in biofilms (600 CFU/cm^2 on average) as well as slowly growing *Mycobacterium* spp. (820 CFU/cm^2 on average).

In as study aiming to investigate the effects of GAC filtration on the occurrence of opportunistic pathogens, Wang et al. confirmed, by using annular reactors, that the densities of *Mycobacterium* spp. in biofilms formed with GAC-filtered water were higher, compared to biofilms formed with unfiltered water, despite the significant reduction in total organic carbon (TOC) resulting from GAC filtration (Wang et al., 2013b).

Torvinen et al. studied 16 drinking water distribution systems supplied by 16 drinking water treatment plants in Finland (10 treating surface waters with conventional treatment, 4 treating ground waters, and 2 mixed surface and ground waters) (Torvinen et al., 2004). The isolation frequency of mycobacteria grown at 30 °C increased from 35% after the waterworks to 80% at most distal sites of the distribution system, and 100% in the deposits from the distribution system. Numbers in the positive samples increased from 1 to 30 cfu/L at the outlet of the waterworks to 10 to 3500 cfu/L in the distribution system. They observed that the mycobacterial numbers were higher in the systems using surface water and applying ozonation, where AOC concentrations were also highest (up to 350 µg/L), probably because ozone degrades organic matter and increases the fractions that can be assimilated by microbes. The numbers found in the sediments from the distribution system (up to 4.2×10^6 cfu/g) were several log units higher than those in the water samples. 64% of the mycobacteria recovered belonged to the species *M. lentiflavum, M. tusciae,* and *M. gordonae*.

An important regrowth was also observed in distribution systems supplied with unchlorinated water from 8 drinking water treatment plants in the Netherlands (Van der Wielen and Van der Kooij, 2013), with gene copy numbers in the distribution systems being on average 6 to 38 times higher than in the treated water. Numbers of NTM in the distribution system were significantly higher in summer than in winter. However, no influence of AOC on NTM regrowth was observed in this study, but AOC levels ranged only from 3.1 to 28.2 µgC/L, which demonstrates that mycobacteria can grow also at low levels of organic carbon in the water.

Pickup et al. observed the effective removal of Map from a raw surface water treated by flotation and filtration. The presence of Map was detected in the suspended solids from the flotation process, and no Map was detected by PCR in 100 L of finished water from the plant (Pickup et al., 2006). Aboagye and Rowe compared two plants treating the same resource (Aboagye and Rowe, 2011) and observed no difference in terms of Map removal between slow sand filtration (SSF) and dissolved air flotation (DAF). The micro-organism was detected both in the schmutzdecke from SSF and floccules from DAF, thus confirming its association with suspended solids. In this case however, despite the effective removal by these physical processes, the use of ozonation in one of the plants and final chlorination at both plants, the occurrence of Map as detected by PCR was still high in the finished waters (45 and 48%), compared to raw water intakes (54 and 58%). Cultivable Map was found after flotation and chlorination, thus confirming that at least some of the micro-organisms were alive.

Le Dantec et al. compared two conventional treatment plants fed by the River Seine and supplying Paris, France (Le Dantec et al., 2002a). The treatment lines included pre-ozonation, clarification, rapid sand filtration (RSF) for one of them and SSF for the other, ozonation, GAC filtration and final chlorination. The concentration and diversity of NTM decreased along the two treatment lines, with lower numbers observed after SSF, compared to RSF. Ozone effectively reduced the mycobacterial load by more than 3 log in the best cases, but low numbers of *M. gordonae* and *M. nonchromogenicum* (10 CFU/L) were still detectable after ozonation on some occasions. All samples were positive after GAC filtration, but regrowth in GAC filters was more important on the line equipped with SSF (1500 to > 3000 CFU/L of pathogenic mycobacteria, including *M. peregrinum* and *M. fortuitum*, in GAC-filtered water), than on the line equipped with RSF (10–20 CFU/L of unidentified mycobacteria in GAC-filtered water). Final chlorination again reduced the numbers to less than 60 CFU/L of *M. nonchromogenicum* and unidentified mycobacteria in the finished water. No correlation between water temperature and % of positive treated water samples or mycobacterial species was observed. Whereas only 27% of all finished water samples were positive for mycobacteria, this proportion increased to 72% in the distribution system. *M. gordonae* and *M. nonchromogenicum* were the most frequently identified species isolated from the distribution system, but pathogenic species including *M. fortuitum, M. peregrinum, M. chelonae* and *M. intracellulare* represented 16% of all positive samples.

In a subsequent study, Dubrou et al. compared again the treatment plant equipped with RSF to another plant supplying also Paris but receiving raw water from the River Marne, and composed of pre-ozonation, direct filtration, SSF, ozonation, GAC filtration and final chlorination (Dubrou et al., 2010). 10–16% of the samples were positive after ozonation in both plants, with higher concentrations and a more important biodiversity in the plant equipped with SSF. Again, a higher frequency of detection was observed after GAC filtration on the line equipped with SSF (68%), in comparison with the line equipped with RSF (30%). 63% of samples were still positive after final chlorination on the line with SSF (with 100–1000 CFU/L of *M. llatzerense, M. chelonae, M. septicum*), whereas only 10% were positive on the line with RSF (with 10–100 CFU/L of *M. llatzerense and Mycobacterium* spp.). These proportions increased to 95% in the distribution system. The increased occurrence in detection of mycobacteria in distributed water between these two studies was attributed to the injection of orthophosphoric acid in the distribution system, with the aim of reducing lead release from domestic water systems, but which could have favored biofilm production.

In a larger survey of the Paris drinking water production and distribution system, Dubrou et al. observed that mycobacteria were organized into communities correlating with water origin, some species (e.g. *M. llatzerense* and *M. salmoniphilum*) being more prevalent in parts of the distribution system fed with ground water, while others (e.g. *M. chelonae*) were more prevalent in parts of the distribution system fed with surface water (Dubrou et al., 2013).

In their investigation of the distribution system of Brisbane, Australia, Thomson et al. recovered mycobacteria from 61.5% of the samples and identified 34 different species, including potential pathogens such as *M. abscessus, M. avium* complex*, M. chelonae, M. flavescens, M. fortuitum* complex*, M. gordonae, M. interjectum, M. intracellulare, M. kansasii, M. lentiflavum, M. mucogenicum, M. simiae, M. szulgai,* and *M. terrae* (Thomson et al., 2013). They observed that the pathogenic species were more likely to be recovered from distal sites from the treatment plants, were pipes present smaller diameters.

In a study of the bacterial composition within the chlorinated drinking water distribution system of the Cincinnati metropolitan area, Gomez-Alvarez et al. showed by using 16SrRNA gene sequencing that NTM represented nearly 43% of the total sequences (Gomez-Alvarez et al., 2015). The main sequences were related to the species *M. tusciae, M. frederiksbergense, M. gadium, M. gordonae,* and *M. kyorinense*.

Gomez-Smith et al. applied a similar approach to investigate the chloraminated distribution system of the city of Saint Paul, Minnesota (Gomez-Smith et al., 2015). They observed that mycobacteria dominated the bacterial community in the biofilms (25–78% of the community). Out of the 72 mycobacterial species identified, the most common were the non-pathogenic *M. frederiksbergense* (85.7%) and *M. aurum* (6.5%), but opportunistic pathogens such as *M. hemophilum* (1.5%), *M. abscessus* and *M. xenopi* (both < 0.15%) were also detected.

Thomas et al. recovered different amoebal and mycobacterial species by amoebal co-culture at the different steps of a conventional treatment plant supplied with surface water (Table 1), except after final chlorination (Thomas et al., 2008). The largest number of isolates was found in the raw water and the biofilm extracted from the sand filters. One amoeba (*Echinamoeba exudans*) was found naturally infected with *M. mucogenicum* in ozonated water. Some strains were found to be identical in the raw, GAC filtered and distributed water, thus demonstrating that even a well operated full treatment chain composed of two filtration stages (sand and GAC) and two disinfection stages (ozonation and chlorination) does not constitute an absolute barrier against mycobacteria. An important population of amoebae isolated from the biofilm extracted from sand and GAC filters was found naturally infected with amoeba-resisting bacteria, especially in GAC filters. Intra-amoebal growth of mycobacteria could explain the important regrowth of these bacteria in GAC filters. With the same technique, Corsaro et al. also recovered different mycobacterial species at the different steps of three conventional treatment plants in Spain, except again after final chlorination. Mycobacteria were principally recovered from sand filters and from biofilms and sediments of distribution systems, and a significant correlation with the presence of amoebae was found.

Delafont et al. analyzed 251 water samples from 25 sites of the Paris (France) drinking water distribution system (Delafont et al., 2014). They observed the presence of cultivable free-living amoebae (FLA) in 69.3% of the analyzed samples, and 87.6% of them harbored mycobacteria. NTM appeared to be part of the most represented bacteria within the FLA microbiome. More than 90% of amoebal isolates were associated with *M. llatzerense*. Other species included *M. chelonae, M. aromaticivorans, M. phocaicum,* and *M. mucogenicum*.

2.3. Domestic water systems

The studies conducted on domestic water systems demonstrate that plumbing systems are generally colonized by mycobacteria, whatever the water source, the treatment applied or the water quality.

Pickup et al. investigated 54 houses supplied with treated surface water in a region of heavily grazed farmlands in South Wales (UK). Sediments from cold water header tanks or cisterns were collected and tested for Map by a PCR method. Although Map was not found at the treatment plant outlet, it was detected in one of the cisterns (Pickup et al., 2006).

Hilborn et al. compared the recovery of NTM in two unfiltered municipal drinking water systems supplied with chlorinated surface water in the western United States. Although NTM were seldom recovered from plant effluents and distribution systems, more than 50% of samples from cold water taps were positive, with a majority of samples yielding *M. avium* and some yielding *M. kansasii*, in concentrations ranging from 1 to > 500 CFU/500 mL (Hilborn et al., 2006). No significant reduction in NTM prevalence or enumeration was observed after introduction of ozonation and GAC filtration at one of the two plants, and molecular analysis demonstrated the persistence of the same *M. avium* strains at the points of use, despite the change in water treatment.

Beumer et al. investigated 33 homes or commercial buildings in two metropolitan areas of the Midwest in the USA, and found that 88% of cold water and 76% of biofilm samples were positive for Map by qPCR method (Beumer et al., 2010). In a subsequent study including the same sites and covering a larger geographical area however, they recovered no positive samples, thus showing that Map detection demonstrates important temporal differences.

In an investigation of tap and shower water at two homes supplied with non-treated ground water in the Netherlands, Van Ingen et al. found that all samples were positive for rapidly growing NTM including *M. peregrinum, M. salmoniphilum, M. llatzerense, M. septicum,* and some novel species (Van Ingen et al., 2010).

In a study including 29 houses in Virginia and 15 houses in Florida, Wang et al. detected a presence of *Mycobacterium* spp. by qPCR in 100% of the investigated sites, with concentrations up to 1.8×10^5 gene copies/mL, and *M. avium* detected in respectively 24.1% and 33.3% of sites (Wang et al., 2012). Application of a 3-min flushing led to significantly lower concentrations of mycobacteria, thus confirming the role of premise plumbing as an amplifier for these bacteria, especially after a long water stagnation time within the system.

Donohue et al. collected 272 samples at cold water taps from 40 sites geographically dispersed in the USA and detected cultivable mycobacteria at least once from 98% of the taps, with a median concentration of 110 CFU/500 mL (Donohue et al., 2015). They identified 24 species, 11 of them being of clinical relevance, the most frequently isolated being *M. mucogenicum* (25%), *M. avium* (30%), *M. gordonae* (25%), *M. intracellulare* (20%), and *M. kansasii* (18%).

Haig et al. applied a sequencing approach coupled with an improved DNA extraction method to investigate water samples from 15 households served by the same chloraminated distribution system in Ann Arbor, Michigan (Haig et al., 2018). They detected 13 different species, including the clinically relevant *M. abscessus, M. avium* subsp. *avium, M. chelonae, M. intracellulare,* and *M. mucogenicum*, with an average concentration of 6.47×10^6 gene copies/L, and 3.53×10^4 gene copies/L for *M. avium* subsp. *paratuberculosis*. They observed that *M. avium* subsp. *avium* largely dominated the mycobacterial community in samples with a water age of more than 24 h.

In the study of Van der Wielen and Van der Kooij, 2013, the sampling of cold tap water at 93 houses in the Netherlands, where water is distributed without chlorination, demonstrated the absence of detection of *M. avium* by PCR, which is in contrast with the studies conducted in the USA. This led the authors to suggest that the use of disinfectants in distribution systems might select for these bacteria, while selection for disinfectant-resistant bacteria does not occur in unchlorinated waters.

Thomas et al. studied the diversity of amoebae and amoeba-resisting bacteria in water and biofilm samples from a hospital water network in Switzerland (Thomas et al., 2006). By using amoebal co-culture, they observed the presence of *M. gordonae*, *M. kansasii* or *M. xenopi* in 20.5% of the samples, and found a strong association between the presence of amoebae and mycobacteria, thus confirming that free-living amoebae constitute a reservoir for mycobacteria. Ovrutsky et al. applied a similar approach to samples collected from multiple areas of a US medical center (Ovrutsky et al., 2013). By using amoebal co-culture, they observed that *M. gordonae* was the most frequently found isolate, followed by *M. peregrinum, M. chelonae, M. mucogenicum,* and *M. avium*. They also confirmed a statistically significant correlation between the presence of cultivable mycobacteria and the presence of cultivable FLA. In their investigation of domestic water systems in the USA and Europe, Gebert et al. also found a positive correlation between the abundances of mycobacteria and *Vermamoeba vermiformis* (Gebert et al., 2018).

3. Impact of biofilms and materials

Biofilms constitute an important ecological niche for NTM. The strong hydrophobic properties of mycobacterial cell walls favor their rapid attachment to the surfaces, and the ability of mycobacteria to grow even at low levels of assimilable organic carbon favors their proliferation in biofilms (Norton et al., 2004). High densities of mycobacteria, usually ranging from 10^2 to 10^4 and up to 10^6 CFU/cm^2 are generally observed in naturally or artificially grown biofilms (Schulze-Röbbecke and Fischeder, 1989; Schulze-Röbbecke et al., 1992; Dailloux

et al., 2003; September et al., 2004; Lehtola et al., 2006; Torvinen et al., 2007), and the application of gene sequencing approaches has shown that they can constitute the most abundant group of bacteria in biofilms from domestic water systems (Feazel et al., 2009; Gebert et al., 2018).

Studies considering the impact of materials have provided contradictory results. On a bench-scale distribution system operated for a few weeks, Norton et al. observed higher colonization rates with *M. avium* on iron and galvanized pipes, compared to copper or chlorinated polyvinyl chloride (Norton et al., 2004). In their investigation of domestic water systems in Europe and the USA, Gebert et al. also observed a higher relative abundance of mycobacteria in metallic showerheads, compared to plastic showerheads (Gebert et al., 2018). In contrast, Buse et al. observed a reduction in bacterial diversity together with a selection for pathogenic microorganisms such as *Legionella* and *Mycobacterium* species on copper surfaces, compared with unplasticized PVC (Buse et al., 2014). On real systems, the influence of materials is also not evident. In a study of 8 distribution systems in the USA, Falkinham et al. (Falkinham III et al., 2001) observed that the frequency of recovery of mycobacteria was not influenced by the material supporting the biofilm (brass, bronze, galvanized or plastic surfaces). In their study of the distribution system of the city of Saint Paul, Minnesota, Gomez-Smith et al. (Gomez-Smith et al., 2015) also observed that biofilm communities were similar whatever the type of pipe material (unlined cast-iron or cement-lined cast iron). In their investigation of the Brisbane (Australia) distribution system, Thomson et al. found no correlation between recovery of mycobacteria and main age or pipe material (Thomson et al., 2013). However, they observed that pathogenic species were more likely to be recovered from asbestos cement or modified PVC pipes, compared with other materials (cement or spun lined cast or ductile iron, cement lined or black unlined mild steel, unplasticized PVC).

4. Resistance to disinfection and temperature

4.1. Disinfection

With regards to disinfection, mycobacteria are among the most resistant waterborne pathogens. The hydrophobic properties of their cell wall and their ability to form aggregates in water make them very resistant to the disinfectants used in water treatment. Among the different species for which disinfection kinetics have been achieved, *M avium*, *M. fortuitum* and *M. chelonae* appear to be the most resistant. Necessary concentration x time (CT) values for a 3-log reduction of *M. avium* at pH7 and 25 °C range from 51 to 204 mg.min/L for chlorine, 91–1710 mg.min/L for monochloramine, 2–11 mg.min/L for chlorine dioxide, and 0.10–0.17 mg.min/L for ozone (Taylor et al., 2000; Vicuña-Reyes et al., 2008). Even higher values up to 13 mg.min/L have been found for a 2-log reduction of *M. fortuitum* with ozone (Farooq et al., 1977; Jacangelo et al., 2002). The poorer effectiveness of monochloramine, compared to other disinfectants is confirmed by the fact that mycobacterial occurrence in distribution systems increases when this disinfectant is used instead of chlorine (Pryor et al., 2004; Donohue et al., 2015).

Disinfection kinetics are usually conducted with culture-grown bacteria. However, it has been demonstrated that mycobacteria grown in low nutrient tap water are about ten times more resistant to chlorine than mycobacteria grown on culture medium (Taylor et al., 2000; Le Dantec et al., 2002b). Amoebae also provide protection against disinfectants, and it has been demonstrated that *M. avium* in co-culture with *Acanthamoeba castellanii* is much more resistant to monochloramine than the same strain cultured alone (Berry et al., 2010). Different species of mycobacteria have also been shown to survive inside *Acanthamoeba polyphaga* cysts after exposure 24 h to 15 mg/L free chlorine (Adékambi et al., 2006).

The UV dose applied in drinking water treatment, generally in the order of 40 mJ/cm^2, is able to achieve more than 3-log reduction of *M. avium* and of most mycobacterial species. No significant difference is observed between low pressure and medium pressure UV irradiation techniques (LeChevallier, 2004; Shin et al., 2008). In contrast, *M. fortuitum* demonstrates less susceptibility for UV and only a 2-log reduction is achieved with the same UV dose (Lee et al., 2010).

While some authors recommend an increased application of disinfectants to overcome mycobacterial resistance, some others in contrast support the concept of “protective biofilm” and “probiotic approach”, consisting in encouraging the growth of non-pathogenic bacteria over pathogens (Wang et al., 2013a). As NTM grow slowly, they are poor competitors for nutrients, and consequently letting other disinfectant-susceptible bacteria proliferate could constitute an effective strategy to limit NTM numbers in water systems (Falkinham III, 2015). The absence of *M. avium* observed in unchlorinated waters in the Netherlands by Van der Wielen et al. (Van der Wielen and Van der Kooij, 2013) supports this concept, as well as the results of the study conducted by Roeselers et al. to characterize the bacterial diversity in 32 distribution systems in the Netherlands, by using a high-throughput sequencing approach (Roeselers et al., 2015). In their comparison of the colonization of showerhead biofilms in US and European domestic water systems, Gebert et al. also found a 2.3 times higher abundance of mycobacteria in the USA (with *M. avium* being more abundant in the USA), compared with Europe, where chlorine concentrations were on average 11 times lower than in the USA (Gebert et al., 2018). The validity of this “protective biofilm” concept is also corroborated by the results of a recent experimentation conducted on the distribution systems of two French cities, where chlorination was stopped for 2 months. The metagenomics approach applied to characterize the bacterial diversity in the biofilms of these two distribution systems confirmed that reducing chlorination leads to an increased diversity of non-pathogenic environmental bacteria, and no increase in potential pathogens (Bertelli et al., 2018).

4.2. Temperature

Merkal and Crawford observed no loss of viability in five *M. avium – M. intracellulare* complex serotypes exposed 2 h at 50 or 55 °C in aqueous suspensions. These strains demonstrated an important increase in heat resistance when pH was decreased from 6.5 to 5.5 (Merkal and Crawford, 1979). Schulze-Röbbecke and Buchholtz compared the heat resistance of nine mycobacterial species, after removing the largest bacterial aggregates from the water suspensions. They found considerable differences in heat susceptibility, with decimal reduction times at 55 °C ranging from about 6 h for *M. xenopi*, to 1 h for *M. avium, M. phlei,* and *M. scrofulaceum*, 25 min for *M. fortuitum, M. intracellulare*, and *M. chelonae*, 15 min for *M. marinum*, and 6 min for *M. kansasii*. Resistance of *M. xenopi* was reduced to a few seconds at 70 °C. They assumed from these results that the minimum temperature of 50 °C recommended at any point of use for *Legionella* control in hot water systems (Bentham et al., 2007) was insufficient to control the most heat-resistant mycobacterial species (Schulze-Röbbecke and Buchholtz, 1992). Temperatures above 55 °C have been rather recommended (Falkinham III, 2015).

5. Conclusions and recommendations

Non-tuberculous mycobacteria are widespread in water environments, and natural as well as drinking waters constitute the main source of human infection with these bacteria. Their occurrence and diversity are generally lower in ground waters, compared to surface waters, where their concentrations are correlated with acidic pH, rainfall events, increased river flows, and high levels of turbidity and suspended solids. Their association with particles facilitates their accumulation in sediments and their elimination by physical processes used in drinking water treatment such as flotation, sedimentation and filtration. Therefore, conventional treatment lines composed of

clarification and rapid granular filtration efficiently reduce the numbers of these bacteria and usually demonstrate a reduction performance of about 2 log. Conversely, GAC filters favor mycobacterial re-growth, especially when they are preceded by slow sand filtration. The colonization of GAC filters by large quantities of biofilm and amoebae can explain this phenomenon. Non-tuberculous mycobacteria, and especially the pathogenic species such as *M. avium*, *M. fortuitum* and *M. chelonae,* are extremely resistant to disinfectants, and their ability to survive within amoebal cysts also contributes to this resistance. Consequently, even full treatment chains composed of two filtration and two disinfection stages (ozonation and chlorination) cannot constitute an absolute barrier against mycobacteria. Although UV can bring a significant additional reduction, the effect of UV irradiation on intra-amoebal mycobacteria still needs to be documented.

An important re-growth is generally observed in distribution systems, and to a larger extent in domestic water systems, where the prevalence and concentration of mycobacteria is correlated with the levels of organic matter, biofilms and amoebae. Temperatures encountered in domestic hot water systems are generally insufficient to avoid the colonization by the most heat-resistant mycobacterial species such as *M. xenopi* or *M. avium*.

The high resistance of mycobacteria to disinfection and temperature highlights the need to control these bacteria at the production steps, before they can enter the distribution systems. Removal processes including clarification techniques, granular or membrane filtration are key operations to reduce the presence of mycobacteria. Control strategies must also address the factors that favor their subsequent re-growth, i.e. organic matter, biofilms and sediments. Therefore, efficient elimination of organic matter by clarification, good management of sludge from clarifiers, adapted frequency of filter backwash, biofilm and sediment control in distribution systems, but also limitation of water retention time in distribution and domestic water systems are all essential measures to limit the re-growth of mycobacteria.

Last but not least, the results of applications of the “probiotic” or “protective biofilm” approach, consisting in promoting the growth of non-pathogenic bacteria, will deserve a close attention, since such approach may constitute an interesting alternative to current disinfection practices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.01.002.

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