Systematic Review of Nosocomial Waterborne Infections caused by Nontuberculous Mycobacteria

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Abstract

Background: Healthcare-acquired infections are an increasing priority for health care providers and policy makers. Water is an overlooked source of infectious microorganisms in health care facilities. Waterborne nontuberculous mycobacteria (NTM) are ubiquitous, especially in health care facility water systems, and are known to result in a variety of clinical diseases.

Purpose: To contribute to an understanding of prevalence and disease burden, we conducted a systematic review to assess health care associated NTM infections from health care facility water systems. We document susceptible populations, modes of transmission, and the median attack rate. We aim to identify transmission risk factors and inform evidence-based policies for infection control and prevention.

Methods: We searched Embase, Pubmed, Web of Science and clinicaltrials.gov without date restrictions. English language articles with original data on NTM waterborne infections in health care settings were included.

Study Selection & Data Extraction: Randomized controlled trials, descriptive studies (case reports, case series), case-control studies, cohort studies, cross-sectional surveys, and quasi-experimental studies on nosocomial waterborne infections were included. Three investigators independently screened titles and abstracts for relevant articles, and one screened full-text articles. Data was extracted by one investigator, and a second confirmed accuracy for 10% of results.

Results: We included 22 observational studies. Immunocompromised, post-surgical, and hemodialysis patients were commonly affected populations, and a range of exposure routes such as uncovered central venous catheters (CVCs), wound exposure, and contamination during surgical procedures was reported. The median attack rate was 12.1% (interquartile range, 11-27.2).

Conclusion: Waterborne NTM infection affects susceptible patients through common, preventable exposure routes. Effective prevention strategies will require both medical and environmental health expertise, and inter-professional cooperation will optimize these efforts. Additional high-quality studies using genotypic methods are also needed, especially in low- and middle-income countries.

Background

Health care acquired infections (HAIs) result in a high disease burden, both in the United States (U.S.) (Scott, 2009) and globally (WHO & UNICEF, 2015). In the U.S., as health systems attempt to reduce cost and prevent waste, HAI prevention has become a focus for health care providers and policy makers (McHugh, Van Dyke, Osei-Anto, & Haque, 2011). Value-based policies have reduced reimbursement for post-surgical and catheter-related infections, drawing particular attention to these problems (Federal Register, 2008). As health systems pursue new infection control strategies, safe health care facility water systems are often overlooked as a preventable infection source (Beggs, 2015). Hospital water systems fall under the purview of engineers and environmental specialists, and as a result, providers may not include water in infection prevention considerations (Beggs, 2015). However, inappropriate exposure to non-sterile water can lead to a variety of infections in the vulnerable hospitalized population (Anaissie, Penzak, & Dignani, 2002).

NTM in Health Care Water Systems

Nontuberculous mycobacteria (NTM), is a known cause of water-borne infections, and the hospital water system can be a reservoir for these microorganisms (Cervia, Ortolano, & Canonica, 2008). A study found that 61% of hospital water systems from 21 states were positive for mycobacteria and that hospital water had the highest rates of contamination compared to other buildings such as offices, hotels, and private residences (Covert, Rodgers, Reyes, & Stelma, 1999). Other investigations of hospital water in the absence of disease outbreaks have

also reported high mycobacterial concentrations in health care facility water systems (du Moulin, Stottmeier, Pelletier, Tsang, & Hedley-Whyte, 1988; Peters et al., 1995).

In these settings, several variables promote NTM growth. Water stagnation and the limiting of hot water temperatures for burn prevention may contribute to biofilm production and provide ideal conditions for mycobacterial growth (Mandel, Sprauer, Sniadack, & Ostroff, 1993; Wallace, 1998). Biofilms provide nutrition and protection for microorganisms, partly accounting for the challenge of mycobacterial eradication from water systems (Torvinen, Lehtola, Martikainen, & Miettinen, 2007; Vaerewijck, Huys, Palomino, Swings, & Portaels, 2005). Additionally, mycobacteria have strong intrinsic resistance to common disinfectants such as chlorine and glutaraldehyde due to its hardy cell wall (Falkinham, 1996; Russell, 1999; Wallace, 1998) and are also resistant to high water temperatures (Miyamoto, Yamaguchi, & Sasatsu, 2000). These factors contribute to the singular persistence of NTM in health care water systems.

Clinical Disease and Pseudo-outbreaks

For the general population, mycobacterial exposure through tap water rarely results in clinical disease (Johnson & Odell, 2014). However, in the immunologically vulnerable hospital population, this exposure is more likely to result in symptomatic disease. Clinical symptoms can range widely, but most commonly include respiratory disease, skin and soft tissue infection, and disseminated disease (Phillips & von Reyn, 2001). A number of pseudo-outbreaks have also been reported, in which contaminated positive samples simulate disease outbreak without evidence of patient colonization or infection, sometimes resulting in inappropriate treatment

(Scorzolini et al., 2016; Zlojtro et al., 2015). Therefore, correlation of positive cultures with clinical symptoms is essential, as contamination of samples is common and positive samples are more likely to indicate contamination than disease (Griffith et al., 2007).

Microbiological Classification and Identification

Pathogenicity of NTM vary by species, and the identification of mycobacterial species has changed with technological advances. NTM species are traditionally classified by their rate of growth. Rapidly growing mycobacteria (RGM), including *M. fortuitum*, *M. abscessus*, and *M. chelonae*, grow in less than seven days, while slow growing varieties include other species that take longer to exhibit growth under ideal conditions (Phillips & von Reyn, 2001).

The identification of NTM and characterization of species has progressed from phenotypic to genotypic techniques. Traditional phenotypic methods include a battery of biochemical tests for species identification, growth rate, and antimicrobial susceptibility profiles (Griffith et al., 2007; Phillips & von Reyn, 2001). However, since the early 1990s, genotypic techniques have allowed for greater strain discrimination and increased accuracy in determining molecular relatedness. Pulsed field gel electrophoresis (PFGE) is most commonly used for strain identification, but other techniques such as random amplified polymorphic DNA (RAPD) and multilocus enzyme electrophoresis (MEE) are available.

Pulsed field gel electrophoresis results are interpreted by the Tenover Criteria, which provides the standard threshold to identify indistinguishable clones (Tenover et al., 1995). These criteria define genetic relatedness by similarity of electrophoretic banding that allow for characterization of random genetic events. Tenover et al. defines a single genetic event (two to

three band difference) as “closely related,” while two genetic events (four to six band difference) as “possibly related.” These criteria are best for samples from discrete outbreaks of one to three months (Tenover et al., 1995). This landmark paper continues to be the standard for PFGE interpretation to determine molecular relatedness.

Genotypic techniques for determining molecular relatedness have provided more definitive and rigorous ways to investigate disease outbreaks, thereby strengthening researchers’ understanding of the sources of NTM disease. Given the ubiquity of mycobacteria, genotypic methods are especially important to accurately confirm an outbreak’s environmental source.

Nosocomial Waterborne Infections of NTM

Prior reviews have described studies of nosocomial mycobacterial outbreaks and pseudo-outbreaks, but no systematic reviews have been conducted. Wallace et al. summarized studies of nosocomial mycobacteria outbreaks and pseudo-outbreaks as well as then-current molecular techniques (Wallace, 1998). However, the method for identifying studies was not described and a systematic search was not reported. In addition, as previously mentioned, the use of genotypic molecular techniques has proliferated since this review, changing investigators’ understanding of mycobacterial outbreaks (Sabat et al., 2013). Phillips et al. similarly summarized studies relating to nosocomial infection of mycobacteria (Phillips & von Reyn, 2001). In addition, this review article discusses prevention and control strategies in the literature. This review also does not describe how included studies were identified.

More recently, Halstrom et al. reviewed mycobacterial infections linked to environmental sources, including samples ranging from hospital and residential water sources to community produce (Halstrom, 2015). This review included studies of patient colonization and pseudo-outbreaks and did not clearly delineate which studies involved colonization versus infection. Halstrom et al. briefly described a search of databases, but like prior reviews, did not include a systematic process of screening results.

Since NTM are prevalent in health care facility water systems, and no prior systematic reviews of nosocomial waterborne mycobacterial infections have been published, we aim to systematically review the literature to better understand the effect of waterborne NTM infection in health care settings. The primary objectives of this systematic review were to answer the following questions:

- How commonly does mycobacterial water exposure result in clinical disease and what are their outcomes, i.e. the attack rate?
- What routes of exposure most commonly cause waterborne NTM disease in health care settings?
- What patient populations are most affected by nosocomial waterborne NTM disease?

By understanding the problem's scope, populations affected, and routes of exposure, health care providers can better understand who is at risk of nosocomial NTM disease and develop strategies for control and prevention. This systematic review aims to describe the causes and consequences of waterborne mycobacteria in health care settings and contribute to an understanding of burden of disease.

Methods

We conducted a systematic review of the literature for studies reporting waterborne infections of NTM in the health care setting.

Eligibility

The research questions and criteria for inclusion and exclusion of studies are summarized in Table 1.

Table 1. Research Question and Inclusion and Exclusion Criteria

	How common is clinical disease from mycobacterial water exposure?	What patient populations are most affected by nosocomial waterborne NTM disease?	What routes of exposure are most commonly associated with waterborne NTM disease in health care settings?
Population	No limitations		
Exposure	Waterborne mycobacteria		
Comparator	No exposure		
Outcomes	Primary: Attack rate Secondary: Mortality	Adult, pediatric, immunocompromised, immunocompetent, post-surgical	Routes of contaminated water exposure leading to infection
Timing	No limitations		
Setting	Health care facilities		
Included Study Designs	Randomized controlled trials, descriptive studies (case reports, case series), case-control studies, cohort studies, cross-sectional surveys, quasi-experimental designs		
Excluded Study Designs	Studies not reporting original data, such as non-systematic reviews and editorials.		

We restricted this review to water-related mycobacterial infections in health care facilities. To comprehensively measure the burden of disease, no restrictions were placed on the date of publication, patient age, or immune status. Infections included patients with

symptomatic clinical disease and studies of colonization without clinical disease were excluded. The primary summary measure of this review was the attack rate (people infected per exposed) of nosocomial waterborne NTM infections.

Definitions

The definition of health care facilities included hospitals, outpatient clinics, dental offices, hemodialysis facilities, nursing facilities, and physical rehabilitation facilities. Water supplies and sources included pipes, peripherals (e.g. faucets, sinks, shower heads), ice machines, distilled water reservoirs, hemodialysis equipment, and dental unit waterlines. Process deficiencies were defined as any action during the administration of care that resulted in the undue exposure of the patient to the infectious source, such as inadequate disinfection or inappropriate use of non-sterile water. The attack rate is defined as the number of patients with disease divided by number exposed to the infectious agent. Common phenotypic and genotypic methods of determining relatedness are summarized in Table 2.

Table 2. Common Phenotypic & Genotypic Methods of Determining NTM Strain Relatedness

Phenotypic	Genotypic
• Antimicrobial susceptibility • Colony morphology • Time for growth • Biochemical tests • High-performance liquid chromatography (HPLC) • Multilocus enzyme electrophoresis(MEE)	• Pulse field gel electrophoresis (PFGE) • Random amplified polymorphic DNA (RAPD) • Restriction fragment length polymorphism (RFLP) • Repetitive sequence PCR (rep-PCR) • Partial sequencing

(Halstrom, 2015; Phillips & von Reyn, 2001; Wallace, 1998)

Search Strategy

Studies were identified from the peer-reviewed literature. Database searches included PubMed, Web of Science, and Embase. We searched *clinicaltrials.gov* for unpublished studies. The bibliographies of included studies were reviewed to identify any relevant studies that our searches may have missed. Searches were last updated on March 17, 2016. The systematic review was conducted with adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist is included in the appendix.

The statement used in the database searches was as follows:

(waterborne OR water) AND (health facilities OR "health care facilities, manpower, and services" OR hospitals OR hospital OR "Hospital Design and Construction" OR hospital-acquired OR nosocomial) AND (disease outbreaks OR infection control OR "Cross Infection" OR "Disease Reservoirs"). As reflected by the broad search statement, this review was originally designed to include all nosocomial waterborne infections and was subsequently narrowed to NTM-specific results due to literature volume.

We used Cochrane's Covidence online software for the process of screening search results. Three authors (TL, SF, MM) independently screened the search results' titles and abstracts for articles reporting water-related infections in health care settings. If two of three authors independently endorsed an article, then it was included in the full-text stage of screening. Conflicts in inclusion decisions were determined by TL. Full texts were reviewed by TL, and articles were chosen for data extraction. Reasons for full-text exclusion were noted. Data from eligible studies were extracted to a standardized spreadsheet. After extraction, ten percent of texts were subject to independent quality control by a second author (SF).

Data Extraction

For each eligible study, available descriptive data and characteristics were extracted: basic reference information, facility type, service received, water source, microorganism, process deficiencies, phenotypic and genotypic methods for determining relatedness of water and human samples, type of human sample, patient infection site, attack rate, mortality, length of outbreak (in months), outbreak control and prevention strategies, and patient risk factors for infection.

Synthesis of Results

Relevant results were tabulated and described to summarize participant characteristics, common sources of contamination, modes of transmission and rates of clinical disease. For those studies that reported this value, the composite median attack rate was calculated. Sensitivity analysis was performed by recalculating the median attack rate with only the studies with a low risk of bias. The methodological and clinical heterogeneity of the studies were qualitatively analyzed. Due to this heterogeneity, no meta-analysis was performed.

Risk of Bias

We assessed the risk of bias using criteria for observational studies designed by the CLARITY group at McMaster University (CLARITY group). This tool assesses study designs for case-control and cohort studies and was adapted for descriptive studies. Studies were rated for quality based on the criteria in Table 3. Each individual criterion question was rated on a scale of zero to three, with zero assigned for a response of definitely no and three assigned for a

response of definitely yes. One was assigned for probably no and two for probably yes. A quality score between 0 and 18 was determined by these criteria. Studies with any zeroes or multiple ones were rated low quality.

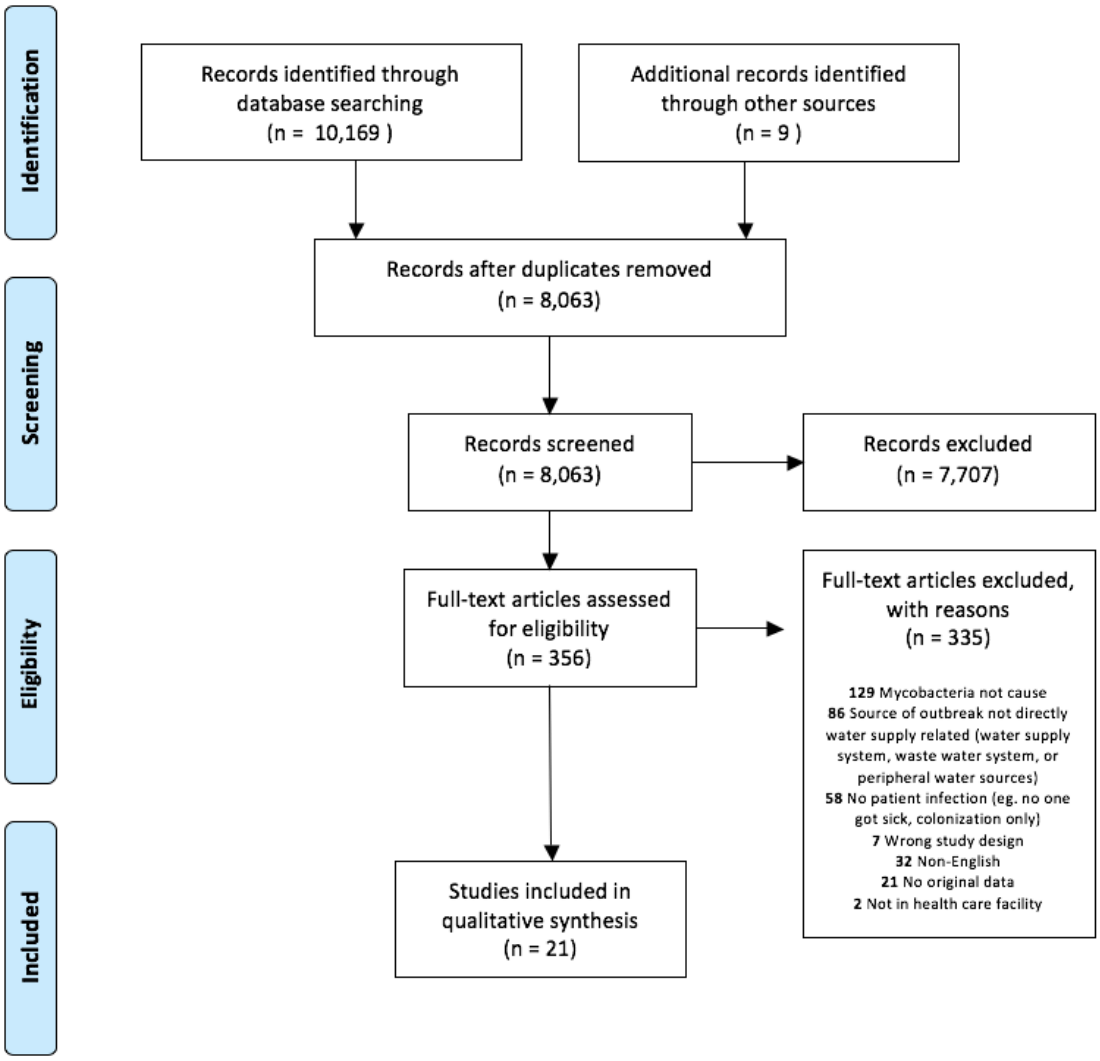
Table 3. Risk of Bias Criteria

Criteria	**Score**
1. Were exposed and nonexposed cohorts drawn from the same population? - Was the sample representative of the target population?	
2. Was the exposure assessment certain? - Is it consistent across groups?	
3. Are we certain that the outcome was not present at the start of the study?	
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? - Associated variables to match on include patient age, time of hospitalization/clinic visit/procedure, location (clinic, hospital unit) and procedure (if applicable).	
5. Is the outcome assessment certain? - The strength of relationship between water and human sample? - The certainty of clinical disease - Is it consistent across groups? - Objective?	
6. Was follow-up adequate?	
Total	

Results

A total of 10,178 articles were identified, including 10,169 from databases and 9 from other sources. After removing duplicates, 8,063 titles and abstracts were screened, resulting in 356 articles for full-text review. After full-text review, 21 articles were included for data extraction and synthesis. The screening process and results are summarized in Figure 1. The results of data extraction are summarized in Table 4, and full evidence tables are included in Appendix Table 2.

Figure 1. PRISMA Flow Diagram



Study Design and Location

The 21 studies included eight case-control studies (Band et al., 1982; Bolan et al., 1985; Cooksey et al., 2008; Kline et al., 2004; Kuritsky et al., 1983; P W Lowry et al., 1990; Philip W Lowry et al., 1988; Soto et al., 1991), two case reports (Jaubert et al., 2015; Kauppinen, Nousiainen, Jantunen, Mattila, & Katila, 1999), three retrospective cohort studies (Carbonne et al., 2009; Meyers et al., 2002; Wenger et al., 1990), and eight case series (Ashraf et al., 2012; Astagneau et al., 2001; Baird et al., 2011; Flesner & Deresinski, 2011; Livni et al., 2008; Tagashira et al., 2015; Tobin-D'Angelo et al., 2004; von Reyn, Maslow, Barber, Falkinham, & Arbeit, 1994). These studies aimed to report and analyze the causes of outbreaks retrospectively. Though most studies included time periods of less than one year, included studies spanned from three months to four years. Numbers of infected patients ranged from single cases to a single outbreak of 49 patients (Astagneau et al., 2001). Most studies were from high-income countries, with one exception of a study from Mexico (Soto et al., 1991).

Health Care Setting

The outbreaks of mycobacterial infection occurred in a range of settings including outpatient procedure clinics (4), hemodialysis centers (3), inpatient hospital units (9), and operating rooms (4). Of the 13 studies occurring in the hospital, five were in hematology-oncology units (Baird et al., 2011; Cooksey et al., 2008; Kline et al., 2004; Livni et al., 2008; Tagashira et al., 2015) and four involved infections in the operating room (Astagneau et al., 2001; Flesner & Deresinski, 2011; Kuritsky et al., 1983; Soto et al., 1991). Of the eight studies in the outpatient setting, three were in dialysis centers (Band et al., 1982; Bolan et al., 1985; P W

Lowry et al., 1990), and four involved outpatient procedures (Carbonne et al., 2009; Philip W Lowry et al., 1988; Meyers et al., 2002; Wenger et al., 1990).

Infectious Causes and Routes of Exposure

Of the 21 studies included in this review, 11 involved rapidly growing mycobacteria (*M. fortuitum*, *M. abscessus*, and *M. chelonae*). Six studies involved *M. mucogenicum* as the infectious agent, and the remaining studies included *M. avium* (2), *M. immunogenum* (1), and *M. xenopi* (1).

All of the included studies had the water system identified as the ultimate source of NTM microorganisms, but different routes of patient exposure were reported. The most common source of these microorganisms was tap water from showers and sinks. Most of these patients were susceptible to infection through central venous catheters (Ashraf et al., 2012; Baird et al., 2011; Cooksey et al., 2008; Kline et al., 2004; Livni et al., 2008; Tagashira et al., 2015) or post-surgical wounds (Jaubert et al., 2015; Kauppinen et al., 1999). Another common route was through non-sterile water exposure during procedures. Two studies reported the use of tap water for rinsing equipment (Astagneau et al., 2001; Carbonne et al., 2009), and two reported contamination of suction and spray devices with tap water (P W Lowry et al., 1990; Philip W Lowry et al., 1988). Other procedure-related exposures included contamination of water reservoirs, such as distilled water for injections (Wenger et al., 1990) and water baths (Kuritsky et al., 1983). One study noted strain-specific NTM contamination of water pipes and multiple possible procedure-related routes of exposure, without establishing which route was the specific outbreak cause (Meyers et al., 2002).

Clinical Disease Manifestations

The manifestations of mycobacterial disease varied based on the route of exposure. Nine studies reported symptomatic bloodstream infection with fevers, largely related to central venous catheters (Ashraf et al., 2012; Baird et al., 2011; Bolan et al., 1985; Cooksey et al., 2008; Kauppinen et al., 1999; Kline et al., 2004; Livni et al., 2008; P W Lowry et al., 1990; Tagashira et al., 2015; von Reyn et al., 1994). Some of these studies also noted other clinical signs of infection such as abscesses (Bolan et al., 1985; Kauppinen et al., 1999), graft infections (Bolan et al., 1985; P W Lowry et al., 1990), and respiratory symptoms (von Reyn et al., 1994). Five studies reported soft tissue infection (Carbonne et al., 2009; Flesner & Deresinski, 2011; Kauppinen et al., 1999; Meyers et al., 2002; Wenger et al., 1990). One study noted respiratory symptoms only (Tobin-D'Angelo et al., 2004). Other specific areas of infection were related to procedures such as endocarditis after sternotomy (Kuritsky et al., 1983), spinal abscess after discovertebral surgery (Astagneau et al., 2001), and otorrhea and mastoiditis after tympanostomy (Philip W Lowry et al., 1988).

Water Infrastructure Deficiencies

Five studies included water system-related problems that contributed to the growth and spread of mycobacteria to patients. Two studies noted low levels of chlorination during outbreaks (Kline et al., 2004; Livni et al., 2008). Three studies reported water stagnation due to causes including generator failure during ongoing construction (Cooksey et al., 2008),

interrupted water supply (Baird et al., 2011), and water tank sediment (Astagneau et al., 2001). No other studies reported hospital water system deficiencies.

Patient Populations

Most of the patients involved in mycobacterial outbreaks belonged to a susceptible population. Six studies reported patients with malignancies. One study included a single patient with breast cancer (Kauppinen et al., 1999), while two included leukemia and lymphoma patients (Baird et al., 2011; Tagashira et al., 2015). Other studies included a variety of cancers (Livni et al., 2008) or did not specify the tumor type (Cooksey et al., 2008; Kline et al., 2004). Other immunocompromised populations included those with HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) (Tobin-D'Angelo et al., 2004; von Reyn et al., 1994) and chronic kidney disease (Band et al., 1982; Bolan et al., 1985; P W Lowry et al., 1990)

Two studies included pediatric populations. One reported an outbreak from a pediatric hematology-oncology unit (Livni et al., 2008), while another included a cluster of patients with infections after tympanostomy (Philip W Lowry et al., 1988).

Molecular Relatedness

All but one study (Carbonne et al., 2009) reported the phenotypic method of identifying environmental and clinical samples. Some studies employed methods other than the traditional stain and biochemical techniques to phenotypically identify strains. Five studies used antimicrobial susceptibility profiles to evidence strain relatedness (Bolan et al., 1985; P W

Lowry et al., 1990; Philip W Lowry et al., 1988; Meyers et al., 2002; Wenger et al., 1990), and five used HPLC to identify mycobacteria (Ashraf et al., 2012; Cooksey et al., 2008; Flesner & Deresinski, 2011; Kline et al., 2004; Meyers et al., 2002). More recent studies used gene sequencing (Jaubert et al., 2015; Livni et al., 2008; Meyers et al., 2002; Tagashira et al., 2015) and DNA probe technology to identify strains (Jaubert et al., 2015; Tobin-D'Angelo et al., 2004; von Reyn et al., 1994).

Twelve studies used genotypic methods of determining molecular relatedness. PFGE was the most common method used to determine molecular relatedness of strains (Carbonne et al., 2009; Cooksey et al., 2008; Flesner & Deresinski, 2011; Meyers et al., 2002; Tagashira et al., 2015; Tobin-D'Angelo et al., 2004; von Reyn et al., 1994), and the Tenover criteria was commonly used to interpret results. Less common genotypic methods included RAPD (Cooksey et al., 2008; Kline et al., 2004; Livni et al., 2008; Tagashira et al., 2015) and rep-PCR (Ashraf et al., 2012; Cooksey et al., 2008; Jaubert et al., 2015). The earliest study to use genotypic methods was in 1994 (von Reyn et al., 1994).

Heterogeneity

The included studies demonstrated both clinical and methodological heterogeneity. Methodologically, study designs ranged from single case reports to case-control and cohort studies. The risk of bias and study quality varied greatly based on design differences. Clinically, these studies included a range of patient populations, including adult and pediatric, immunocompromised, and immunocompetent, post-procedural patients. The studies reported different manifestations of disease depending on exposure route, from febrile bacteremia

through central venous catheters to soft tissue infection from direct wound exposures. In addition, the methods of determining the link between environmental and human samples varied. Water sampling and testing techniques were not standardized. Some studies swabbed the interior of peripherals, while others simply tested water from faucets and showers. More recent studies were more likely to use genotypic methods given its increased availability.

Attack Rate and Mortality

The attack rate quantifies how common exposure to mycobacteria results in clinical disease. Twelve studies reported attack rates, or reported the numbers of patients exposed and infected, such that attack rates could be calculated. The range of reported attack rates varied greatly among included studies, from 2% to 60%.

The definition of exposed population differed among studies, partially accounting for this discrepancy. Most studies defined exposure as those patients who received a given treatment in the time frame of the outbreak (Band et al., 1982; Bolan et al., 1985; Kline et al., 2004; Kuritsky et al., 1983; Philip W Lowry et al., 1988; Soto et al., 1991; Wenger et al., 1990). One study estimated this value based on general clinic trends but did not directly measure the number exposed (Astagneau et al., 2001). Two other studies defined exposure as those who received the treatment from a single practitioner in the outbreak period (Flesner & Deresinski, 2011; Meyers et al., 2002). One study did not describe its definition of exposure (Carbonne et al., 2009). To account for this heterogeneity, those studies that defined exposure by a single practitioner, and the one that did not define exposure were excluded from the summary measure calculation. The overall median attack rate was 12.1% (interquartile range, 11-27.2).

Mortality resulting from mycobacterial outbreaks was low. Eight of twenty-two studies did not report mortality rates. Of the studies that did report mortality, most reported no deaths as a result of NTM infection. Four studies reported deaths from underlying disease (Baird et al., 2011; Band et al., 1982; Livni et al., 2008; P W Lowry et al., 1990), and one study, which reported 14 deaths, did not specify the causes of death (Bolan et al., 1985). The only study that reported deaths directly related to mycobacterial infection reported two deaths out of six patients infected after cardiac surgery (Kuritsky et al., 1983). One patient suffered an embolic stroke after declining surgery for NTM infective endocarditis, while another died of unspecified complications of sternectomy and antibiotic therapy that the author attributed to the infection.

Strategies for Control and Prevention

Twelve studies reported their strategies for ending outbreaks and preventing future infections (Ashraf et al., 2012; Astagneau et al., 2001; Baird et al., 2011; Band et al., 1982; Bolan et al., 1985; Flesner & Deresinski, 2011; Jaubert et al., 2015; Kline et al., 2004; Kuritsky et al., 1983; Livni et al., 2008; Soto et al., 1991; Tagashira et al., 2015). Broadly, these strategies were related to ensuring CVC and wound sterility, implementing removal or adequate sterilization of infected equipment, caregiver education, and water supply disinfection. Four studies reported ending outbreaks after ensuring CVC coverage (Baird et al., 2011; Kline et al., 2004; Livni et al., 2008; Tagashira et al., 2015), and three after preventing wound contact with non-sterile water (Flesner & Deresinski, 2011; Jaubert et al., 2015; Kuritsky et al., 1983). Eight studies reported equipment disinfection or removal of disinfected equipment to end outbreaks (Ashraf et al., 2012; Astagneau et al., 2001; Baird et al., 2011; Band et al., 1982; Bolan et al., 1985; Kline et al.,

2004; Livni et al., 2008; Soto et al., 1991). Two studies included caregiver education about infection exposures (Ashraf et al., 2012; Kline et al., 2004), and three included water supply disinfection (Astagneau et al., 2001; Livni et al., 2008; Soto et al., 1991). Six of these studies included multiple control methods (Ashraf et al., 2012; Astagneau et al., 2001; Baird et al., 2011; Kline et al., 2004; Livni et al., 2008; Soto et al., 1991).

Risk of Bias

The tabulated results of the risk of bias assessment for individual studies are included in Appendix Table 1. This review included observational and descriptive studies, and risk of bias was, therefore, high in many included studies. Thirteen studies were considered high risk of bias and eight were a low risk of bias. All descriptive studies received at least one 0 due to the lack of a control group and were, therefore, all subject to high risk of bias. In addition, three case-control studies had a high risk of bias, all due to inadequately matching for the appropriate prognostic variables (risk of bias criteria 4) (Band et al., 1982; P W Lowry et al., 1990; Philip W Lowry et al., 1988).

In general, descriptive studies such as case reports and case series had the highest risk of bias because they report only on positive results, do not include a control group, and are inherently subject to selection and publication bias. Ten descriptive studies were included (Ashraf et al., 2012; Astagneau et al., 2001; Baird et al., 2011; Flesner & Deresinski, 2011; Jaubert et al., 2015; Kauppinen et al., 1999; Livni et al., 2008; Tagashira et al., 2015; Tobin-D'Angelo et al., 2004; von Reyn et al., 1994). All of these studies were assessed with low scores indicating a high risk of bias (Appendix Table 1). Conclusions about causation and

generalizability cannot be drawn from these descriptive studies. However, since this review focuses on qualitative and descriptive questions without questions of causation or intervention effectiveness, these descriptive studies were included.

The case series by Astagneau et al. exemplifies the weaknesses of these descriptive studies (Astagneau et al., 2001). This case series occurred after multiple NTM spinal infections were identified in surgical patients at a private French hospital. Given the lapse of years between onset and recognition of the outbreak, identification of exposed patients and case patients was nonspecific, and both definite and probable cases were included in the study. Additionally, though investigations pointed to the inappropriate use of tap water for rinsing equipment as the likely exposure, no genotypic studies were done to definitively link environmental and human samples.

Case-control studies include a non-infected control group matched on clinically relevant characteristics, and thus have a lower risk of bias. The control group allows for comparison of factors that may have contributed to the infection. However, those studies that use historical data from chart review and interviews are limited by the quality of information in charts and recall bias. Eight case-control studies were included in this review (Band et al., 1982; Bolan et al., 1985; Cooksey et al., 2008; Kline et al., 2004; Kuritsky et al., 1983; P W Lowry et al., 1990; Philip W Lowry et al., 1988; Soto et al., 1991).

Sensitivity Analysis and Quality Control

The attack rate was recalculated after excluding studies with a high risk of bias, resulting in an attack rate of 12.1% (interquartile range, 11.4-19). The inclusion of those studies that

defined exposure based on a single practitioner or did not clearly define exposure resulted in an overall attack rate of 17.1% (interquartile range, 11.3-29.3). The sensitivity analysis including only the low risk of bias studies demonstrated an unchanged attack rate with a narrower interquartile range.

Quality control on data extraction of two randomly selected studies was performed with 100% agreement.

Reference	Study Design	Time Period (mos)	Room Type (procedure)	Matched Water Sample	Process Deficiencies	Phenotypic methods	Genotypic methods	Infection Site	RFs for infection	Infected	Matched samples	Exposed	Attack Rate (%)	Mortality
M. avium														
von Reyn, 1994	case series	41	hospital	hospital hot water system,		DNA probe	PFGE	bloodstream	HIV/AIDS	5	5	-	-	-
Tobin-D'Angelo, 2004	case series	6	hospital	hospital hot water system	None	DNA probe	PFGE	pulmonary	HIV/AIDS	35	19*	-	-	-
M. chelonae														
Lowry, 1988	case-control	5	clinic (tympanostomy)	suction sink water & tubing	use of water bath with infrequent water change	stain, antimicrobial susceptibility, plasmid analysis	None	otorrhea, mastoiditis	post-surgical, peds	17	13	-	-	0
Meyers, 2002	retrospective cohort	7	exam room (liposuction)	water system pipes	inadequate sterilization, rising surgical equipment with tap water, reuse of tubing after rinsing in tap water	stain, HPLC, antimicrobial susceptibility testing, hsp65 gene sequencing, PCR	PFGE	cutaneous	post-surgical	34	12	82	42	-
Wenger, 1990	retrospective cohort	5	podiatry clinic (injection)	distilled water	jet injector inadequate disinfection	stain, biochemical methods, antimicrobial susceptibility	None	cutaneous	None	8	8	66	12	-
Lowry, 1990	case-control & retrospective cohort studies	12	dialysis center (hemodialysis)	tap water, water spray device	inadequate disinfection	stain, antimicrobial susceptibility	None	bloodstream, skin, breast tissue, graft	CKD	5	-	18	28	0
Soto, 1991	case-control	5	OR (rhinoplasty)	hospital water tank	inadequate disinfection	stain	None	nasal cellulitis	post-surgical	22	10	81	27	-
Kuritsky, 1983	case-control	6	OR (sternotomy)	water system, faucet, ice, cardioplegia fluid	use of nonsterile ice bath for cardioplegia solution	biochemical profile	-	incision site, endocardium	post-surgical	6	-	53	11	2
Carbonne,	retrospective cohort	3	clinic (mesothera	tap water	rinsing multiple injection device w/ tap water		PFGE	subQ	None	16	11	10	15	-

2010			py)									5		
Bolan, 1985	case-control, prospective surveillance	8	dialysis center (hemodialysis)	dialysis machine, water treatment system	low formaldehyde concentration, hemodialyzer design	stain, antimicrobial susceptibility	None	bloodstream	CKD	27	27	140	19	14
Band, 1982	case-control	30	dialysis center (chronic peritoneal dialysis)	dialysis machine	reverse osmosis membrane defects, inadequate disinfection	stain, culture morphology, biochemical tests	None	peritoneum	CKD	10	5	30	33	0
M. fortuitum														
Jaubert, 2015	case report	NA	hospital (breast reconstruction)	shower	None	probe hybridization, ribosomal sequences; partial sequencing of hsp65 gene	rep-PCR	breast	post-surgical	1	1	-	-	0
Kauppinen, 1999	case report	NA	hematology-oncology unit	shower		stain	AP-PCR	breast, bloodstream	malignancy	1	1	-	-	0
M. immunogenum														
Flesner, 2011	case series	5	OR (blepharoplasty)	ice	direct ice application to wounds	HPLC, rRNA analyses	PFGE	cutaneous	post-surgical	3	3	5	60	-
M. mucogenicum														
Kline, 2004	case-control	4	hematology-oncology unit	shower	showering w/ CVCs uncovered	standard methods, HPLC	MEE, RAPD	bloodstream	malignancy, CVC	6	1		11	-
Ashraf, 2012	case series	2	hematology clinic	faucet	improper preparation of saline flushes by the sink	HPLC	rep-PCR	bloodstream	sickle cell dz, CVC	4	4	101	4	0
Livni, 2008	case series	6	hematology-oncology unit	faucet	showering w/ CVCs uncovered	standard methods, hsp65 gene sequencing	RAPD	bloodstream	malignancy, aplastic anemia, CVC, peds	5	-	-	-	0
Tagashira, 2015	case series	5	hematology-oncology unit	shower		stain, 16s rRNA gene sequencing	RAPD, PFGE	bloodstream	malignancy, aplastic anemia, CVC	5	4	-	-	0
Baird, 2001	case series	10	hematology-oncology unit	shower, sink	None	stain	None	bloodstream	malignancy, CVC	5	-	-	-	0
Cooks	case-control	3	hematology	shower		stain, HPLC	PFGE,	bloodstrea	malignancy	5	1	-	-	-

ey, 2008			-oncology unit				RAPD, rep-PCR, partial sequencing	m	, CVC					
M. xenopi														
Astagneau, 2001	case series	4 yr	OR (discovertebral surgery)	tap water	use of tap water to rinse equipment	stain	None	spine	post-surgical	49	-	3244	2	0

Table 4. Abbreviated Results of Data Extraction
"-" indicates information was not reported
*samples

Discussion

This systematic review summarizes the common exposure routes, affected populations, and attack rate of waterborne nosocomial NTM infections. Most included studies involved immunocompromised and post-surgical patients. However, these studies' high risk of bias prevents conclusions about generalizable risk factors or susceptible populations. All included studies matched samples between the water system and patients, but reported a variety of exposure routes such as central venous catheters, hemodialysis, and wound exposures. The overall median attack rate was 12.1% (interquartile range, 11-27.2). This review described a variety of NTM disease presentations and revealed very low mortality rates. Clinical and methodological heterogeneity was high among the included studies, due to diverse patient populations and study designs. The risk of bias of most of the included studies, which were largely descriptive or observational, was also high.

Prior non-systematic reviews of nosocomial NTM infections have described similar findings on affected patients and exposures. Wallace et al. reported outbreaks in dialysis, HIV/AIDS, and post-surgical patients (Wallace, 1998). This review did not focus on waterborne infections, but did identify municipal and hospital water supplies as major NTM reservoirs among its included studies. Halstrom et al. included non-nosocomial and non-waterborne sources of NTM infection in their review, but also noted similar routes of water exposure in patients in health care settings (Halstrom, 2015). In another review article, Phillips et al. reported similar affected patients, but additionally noted that chronic lung disease patients were more susceptible to NTM infection (Phillips & von Reyn, 2001). Our review did not

demonstrate this finding in the health care setting. No prior review has reported an overall attack rate.

There were several limitations to this study. As previously mentioned, our research questions were descriptive, and most included studies were observational with high risks of bias. Sensitivity analysis without these lower quality studies resulted in a higher attack rate. Another limitation of this review is the heterogeneous results. The included patients had a variety of risk factors, representing differing susceptibilities. This review also combined different NTM species, with differing pathogenicities (Griffith et al., 2007). These varying studies were combined into a single summary measure and these factors should be considered when interpreting the summary measure.

Other limitations were related to the quality of evidence of included studies. Most studies relied on multiple water samples, but the detection of an outbreaks' environmental source is dependent on the sensitivity of this non-standardized testing. Given NTM's predilection for biofilms, differences in environmental sampling techniques may significantly affect this test's sensitivity. In many of the included studies, only a small fraction of environmental and human samples showed strain correlation (Appendix Table 2), and another review has noted similar results (Halstrom, 2015). This may demonstrate inconsistency or poor sensitivity in detecting microorganisms through environmental water sampling.

Another limitation of the evidence is the retrospective nature of all disease outbreak studies. These studies are initiated after an outbreak has been identified, and this limitation is largely unavoidable because storage of historical water samples for genetic testing in anticipation of an outbreak is impractical, and none of the studies reported such practices. No

studies reported testing for or identification of NTM in water supplies prior to outbreaks. In these studies, causation cannot be definitively established, and it is possible that microorganisms detected in water supplies did not predate the outbreak. However, the statistical increase in cases used to identify outbreaks and the use of PFGE testing to identify genetically related microorganisms in the incoming water supply provide strong causal evidence. Therefore, the conclusion that environmental samples represent the source of an outbreak requires assumption about their temporality.

Lastly, this review likely underestimates NTM disease due to unreported outbreaks as well as delayed disease presentation. NTM infections are not considered a reportable infection (Adams et al., 2014), and the incidence is likely underestimated. In addition, the indolent nature of NTM disease is a challenge for disease detection in outbreak studies. On average, NTM disease presents less than four weeks after initial exposure, but can take as long as nine months to present (Piersimoni & Scarparo, 2009). Therefore, those patients whose symptoms present after a significant delay or even after discharge may not attribute illness to nosocomial exposure. These patients may not be captured by investigators. One included study that attempted to notify exposed patients through mailed surveys demonstrated the challenge of identifying outbreak cases (Astagneau et al., 2001). This delayed presentation may also contribute to underestimation of NTM disease.

Reviewed studies uniformly demonstrated low mortality due to NTM disease. This high recovery rate is encouraging, but belies the extensive treatment regimens required to adequately treat NTM infections. Current guidelines recommend anywhere from four to twelve months of daily antimicrobial treatment for NTM infections, depending on the strain (Griffith et

al., 2007), and included studies reported similarly lengthy treatment courses and hospitalizations (Ashraf et al., 2012; Band et al., 1982; Jaubert et al., 2015; Kauppinen et al., 1999; Kuritsky et al., 1983). Though NTM infections rarely cause death, morbidity is high, and disease prevention should remain an important goal for health care providers.

Our results reveal great heterogeneity in the quality of nosocomial, waterborne NTM studies. A few studies also exemplify the potential of genotypic technology to more definitively identify an outbreak's origins and exposure risks. As genotypic technology is now widely available, the tools to conduct quality outbreak studies are more accessible. Additional high-quality studies demonstrating the molecular link between disease source and exposure as well as prevention control strategies would help to inform evidence base policies on NTM infection prevention.

This review revealed that there have been few studies of nosocomial waterborne NTM in low- and middle-income countries. As the exposure routes in these studies demonstrate, many nosocomial waterborne NTM cases are preventable through simple process changes such as covering CVCs and open wounds and ensuring appropriate equipment disinfection, if common exposure routes are identified and health care providers are aware. Many studies reported no recurrence of infection after caregiver education and procedural changes to prevent exposure. Exposure routes and infrastructural deficiencies may be very different in developing countries, rural areas, and low resource settings. In order to understand the true burden of disease and exposure mechanisms in these circumstances, additional studies in developing countries are needed.

Conclusion

This review demonstrates the common exposures, susceptible populations, and attack rate of waterborne NTM infections in health care settings. This high morbidity, low mortality infection is highly preventable through a combination of medical and environmental efforts. In order to understand the global burden of this infection, additional high-quality studies using genotypic methods are needed, especially in low- and middle-income countries.

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Appendix

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14-15
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	24-26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	23
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28-29
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27, 29-30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	32

Risk of Bias tables (appendix table 1)

Criteria	Ashraf	Astagneau	Baird	Band	Bolan	Carbonne	Cooksey	Flesner	Jaubert	Kauppinen	Kline	Kuritsky	Livni	Lowry'88	Lowry'90	Meyers	Soto	Tagashira	Tobin-D'Angelo	Von Reyn	Wenger
1. Were exposed and nonexposed cohorts drawn from the same population?	0	0	0	3	3	3	3	0	0	0	3	3	0	3	2	3	3	0	0	0	3
2. How certain and consistent is the exposure assessment?	2	2	1	2	2	2	2	3	0	2	2	2	1	2	1	3	2	2	2	2	2
3. How certain are we that the outcome was not present at the start of study?	2	2	2	2	2	3	3	3	3	3	3	3	3	3	2	3	3	3	2	2	2
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for	0	0	0	0	3	1	1	0	0	0	3	2	0	1	1	3	3	0	0	0	2

these prognostic variables?																						
5. How certain is the outcome assessment?	3	1	1	2	1	3	3	3	3	3	3	3	2	2	2	2	1	3	2		3	2
6. Was follow-up adequate?	0	1	2	2	3	2	2	2	2	3	2	2	2	1	1	3	2	2	1		1	1
Total	7	6	6	11	14	14	14	11	10	11	16	15	8	12	9	17	14	10	7		8	12

0 = definitely no, 1 = probably no, 2 = probably yes, 3 = definitely yes
Low risk of bias studies highlighted in yellow

Full evidence tables (Appendix Table 2)

Reference	**Study Design**	**location**	**Room Type (procedure)**	**Matched Water Sample**	**Environmental Sample (matched)**	**WaSH infrastructure deficiency**	**Process Deficiencies**	**Organism Name**	**Phenotypic methods**	**Genotypic methods**	**Infection Site**	**Pt RFs for infection**	**Symptoms**	**# Infected**	**Number matched samples**	**# Exposed**	**Attack Rate (%)**	**# Mortality 2/2 infection**	**Time Period (mos)**	**Control/Prevention Measures**
Ashraf, 2012	case series	USA	hematology clinic	faucet	faucet inner surface swab, hand swab, medication vials	Aerator	improper preparation of saline flushes by the sink	*M. mucogenicum*	HPLC	rep-PCR	bloodstream	sickle cell dz, CVC	fever, back pain, LE pain	4	4	101	4	0	2	education about IV medication prep (process change), removal of aerators
Astagneau, 2001	case series	France	OR (discovertebral surgery)	tap water	tap water	hot water tank sediment, stagnation prone	use of tap water to rinse equipment	*M. xenopi*	stain	None	spine	post-surgical	abscess	49	-	3244	1.5	0	48	multiple disinfection measures (3), decontamination of water supply
Baird,	case	Scot	hematol	show	shower	interru	None	*M.*	stain	None	bloods	malig	fever	5	-	-	-	0	10	clean cold

2001	series	land	ogy-oncology unit	er, sink	s, water tank	pted supply, stagnation		*mucogenicum, M. neoaurum*			tream	nancy, CVC							water storage tanks, ballcocks, water pumps; rebalancing to prevent stagnation, replace showerheads/hoses, program of periodic cleaning and maintenance implemented; changed dressing of CVC
Band, 1982	case-control	USA	dialysis center (chronic peritoneal dialysis)	dialysis machine	dialysis machine, dialyzate concentrate, tap water, solutions	None	reverse osmosis membrane defects, inadequate disinfection	*M. chelonei-like organism*	stain, culture morphology, biochemical tests	None	peritoneum	CKD	acute abdominal pain, peritonitis	10	5	30	33	0	30	removal of contaminated machine, adequate disinfection
Bolan, 1985	case-control, prospective surveillance	USA	dialysis center (hemodialysis)	dialysis machine, water treatment system	hemodialyzer, water treatment system	-	low formaldehyde concentration, hemodialyzer design	*M. chelonei ssp. Abscessus (25), M. chelonei-like organism (1)*	stain, antimicrobial susceptibility	None	bloodstream	CKD	fever, malaise, anorexia, disseminated dz, abscess, graft	27	27	140	19	14*	8	dialyzers reuse discontinued, water treatment systems disinfected

													infection						
Carbonne, 2010	retrospective cohort	France	clinic (mesotherapy)	tap water	tap water, injection device, topic creams	-	rinsing multiple injection device w/ tap water	*M. chelonae, M. fredericbergensen*	-	PFGE	subQ	None	subcutaneous lesion	16	11	105	15.2	-	3	-
Cooksey, 2008	case-control	USA	hematology-oncology unit	shower	hospital sink, faucet swab, shower, ice machine, municipal water tanks	generator failure, renovations -> water stagnation		*M. mucogenicum, M. phocaicum*	stain, HPLC	PFGE, RAPD, rep-PCR, partial sequencing	bloodstream	malignancy, CVC	fever, altered mental status***	5	1	-	-	-	3	-
Flesner, 2011	case series	USA	OR (blepharoplasty)	ice	ice	-	direct ice application to wounds	*M. immunogenum*	HPLC, rRNA analyses	PFGE	cutaneous	post-surgical	erythematous papules	3	3	5	60	-	5	apply sterile, gel cold pack to site
Jaubert, 2015	case report	France	hospital (breast reconstruction)	shower	tap, shower	none	None	*M. fortuitum*	probe hybridization, ribosomal sequences; partial sequencing of hsp65 gene	rep-PCR	breast	post-surgical	breast swelling, pain, F	1	1	-	-	0	NA	emphasize limiting exposure to water in first postoperative days
Kauppinen, 1999	case report	Finland	hematology-oncology unit	shower	shower	-	-	*M. fortuitum*	stain	AP-PCR	breast, bloodstream	malignancy	breast abscess, bacter	1	1	-	-	0	NA	-

												emia							
Kline, 2004	case-control	USA	hematology-oncology unit	shower	sink, shower, hot water source, city water supply to hospital	low chlorination	showering w/ CVCs uncovered	*M. mucogenicum*	standard methods, HPLC	MEE, RAPD	bloodstream	malignancy, CVC	fever***	6	1		11.4	-	4	replace showerheads & hoses, hang shower hoses straight, education, disconnect IV catheters for bathing or cover
Kuritsky, 1983	case-control	USA	OR (sternotomy)	water system, faucet, ice, cardioplegia fluid	water system, faucet in OR, water in cardioplegia solution, ice machines, settling plates, lamps oxygen tanks, suction apparatus	-	use of nonsterile ice bath for cardioplegia solution	*M. chelonae, M. fortuitum*	biochemical profile	-	incision site, endocardium	post-surgical	fever, incisional site pain, endocarditis, saphenous graft site infection	6	-	53	11	2	6	sterile ice bath used for cardioplegia solution
Livni, 2008	case series	Israel	hematology-oncology unit	faucet	auto faucet, manual faucet, ice machine	low chlorination	showering w/ CVCs uncovered	*M. mucogenicum*	standard methods, hsp65 gene sequencing	RAPD	bloodstream	malignancy, aplastic anemia, CVC,	fever, exit site infection	5	-	-	-	1	6	cover CVC during bathing, replace faucets, optimize water chlorinatio

											peds							n
Lowry, 1988	case-control	USA	clinic (tympanostomy)	suction sink water & tubing	suction tubing, suction sink water, disinfectants, otic drops, water, equipment, instruments	use of water bath with infrequent water change	*M. chelonae*	stain, antimicrobial susceptibility, plasmid analysis	None	otorrhea, mastoiditis	post-surgical, peds	ear drainage	17	13	-	-	0	5	-
Lowry, 1990	case-control & retrospective cohort studies	USA	dialysis center (hemodialysis)	tap water, water spray device	tap water, processed water, hose of water spray device, bicarbonate and acetate concentrates, dialysate, Renalin for disinfection	-	inadequate disinfection	*M. chelonae abscessus*	stain, antimicrobial susceptibility	None	bloodstream, skin, breast tissue, graft	CKD	graft drainage, mastitis, breast lesion, leg lesions, eosinophilia	5	-	18	28	0	12	-
Meyers, 2002	retrospective cohort	USA	exam room (liposuction)	water system pipes	faucet inner swab, pipes of water system, tap, irrigation water, liposuction equipment, disinfectants	inadequate sterilization, rising surgical equipment with tap water, reuse of	*M. chelonae*	stain, HPLC, antimicrobial susceptibility testing, hsp65 gene sequencing, PCR	PFGE	cutaneous	post-surgical	cutaneous abscess	34	12	82	42	-	7	-

							tubing after rinsing in tap water												
Soto, 1991	case-control	Mexico	OR (rhinoplasty)	hospital water tank	hospital water tank	water tank contamination	inadequate disinfection	*M. chelonae abscessus*	stain	None	nasal cellulitis	post-surgical	nasal swelling, abscess	22	10	81	27.2	-	5	instrument sterilization, cleasing & disinfecting of hospital water tanks
Tagashira, 2015	case series	Japan	hematology-oncology unit	shower	faucets, showers, bathtubs		-	*M. mucogenicum, M. canariasense*	stain, 16s rRNA gene sequencing	RAPD, PFGE	bloodstream	malignancy, aplastic anemia, CVC	fever	5	4	-	-	0	5	reinforce coverage of CVC during showering
Tobin-D'Angelo, 2004	case series	USA	hospital	hospital hot water system	hospital hot water system	-	None	*M. avium complex*	DNA probe	PFGE	pulmonary	HIV/AIDS	respiratory symptoms	35	19**	-	-	-	6	-
von Reyn, 1994	case series	USA	hospital	hospital hot water system,	hospital hot water system,		-	*M. avium*	DNA probe	PFGE	bloodstream	HIV/AIDS	respiratory symptoms	5	5	-	-	-	41	-
Wenger, 1990	retrospective cohort	USA	podiatry clinic (injection)	distilled water	distilled water, tap water, autoclave water	-	jet injector inadequate disinfection	*M. chelonae*	stain, biochemical methods, antimicrobial susceptiblity	None	cutaneous	None	skin infection	8	8	66	12.1	-	5	-

*unclear etiology

**isolates
***author correspondence