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A systematic review of waterborne infections from nontuberculous mycobacteria in health care facility water systems

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ABSTRACT

Healthcare-acquired infections are an increasing problem 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, and particularly problematic in health care facility water systems, and cause a variety of diseases. The purpose of this review is to assess health care associated NTM infections from health care facility water systems. We documented susceptible populations, modes of transmission, and the median attack rate (e.g. patients infected per patients exposed). We aimed to identify transmission risk factors and inform evidence-based policies for infection control and prevention. 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. 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 were extracted by one investigator, and a second confirmed accuracy for 10% of results. We included 22 observational studies. Immunocompromised, post-surgical, and hemodialysis patients were commonly affected populations. 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). 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.

1. Introduction

Nosocomial infections result in a high disease burden, both in the United States (U.S.) (Scott, 2009) and globally (Bartram et al., 2015; WHO and UNICEF, 2015). Well-known water related bacteria are *Pseudomonas* spp. *Acinetobacter* spp. and others, many species are well known for emerging antibiotic resistance (Leiblein et al., 2016). Overuse and misuse of antibiotics has led to the rise of antimicrobial resistance, which has made preventing and combating nosocomial infections difficult (Boucher et al., 2009; Cohen, 1992) In the U.S., as health systems attempt to reduce cost and prevent waste, nosocomial infection prevention has become a focus for health care providers and policy makers (McHugh et al., 2011; Scott, 2009). 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 source of infection which is preventable through simple and cost-effective strategies (Beggs, 2015). Operations and maintenance of health care facility water systems generally fall under the purview of engineers and environmental health specialists, and providers may not include water in infection prevention considerations (Beggs, 2015). However, exposure to non-sterile water can lead to a variety of infections especially among patients in health care facilities (Anaissie et al., 2002a).

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Nontuberculous mycobacteria (NTM), cause water-borne infections, and the health care facility water system can be a reservoir for these microorganisms (Cervia et al., 2008; Donohue et al., 2015). A study of the U.S. 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 et al., 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 et al., 1988; Peters et al., 1995).

Several variables promote NTM growth. Water stagnation and the limiting of hot water temperatures for scald prevention may contribute to biofilm production and provide conditions suitable for mycobacterial growth (Mandel et al., 1993; Wallace, 1998). Biofilms provide nutrition and protection for microorganisms, partly accounting for the challenge of mycobacterial eradication from water systems (Torvinen et al., 2007; Vaerewijck et al., 2005). Additionally, mycobacteria have strong intrinsic resistance to common disinfectants, such as, chlorine due to their hardy cell wall (Falkinham, 1996; Russell, 1999; Wallace, 1998) and are also resistant to high water temperatures (Miyamoto et al., 2000). These factors contribute to the persistence of NTM in health care water systems.

1.1. Clinical disease and pseudo-outbreaks

For the general population, mycobacterial exposure through tap water rarely results in clinical disease (Johnson and Odell, 2014). However, among patients in health care facilities, this exposure is more likely to result in symptomatic disease. Clinical symptoms range widely, but most commonly include respiratory disease, skin and soft tissue infection, and disseminated disease (Phillips and von Reyn, 2001). A number of pseudo-outbreaks have 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 rather than disease (Griffith et al., 2007).

1.1.1. Microbiological classification and identification

Given the ubiquity of mycobacteria, genotypic methods are especially important to accurately confirm an outbreak's environmental source. Pathogenicity of NTM varies 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 species that take longer (more than seven days) to exhibit growth under optimal laboratory conditions (Phillips and 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 and 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 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 understanding of the sources of NTM disease.

1.1.2. Nosocomial waterborne infections of NTM

Prior reviews have described nosocomial mycobacterial outbreaks and pseudo-outbreaks, but no systematic reviews has 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. The use of genotypic molecular techniques have advanced since that time, changing understanding of mycobacterial outbreaks (Sabat et al., 2013). Phillips et al. similarly summarized studies relating to nosocomial infection by mycobacteria (Phillips and von Reyn, 2001), discussing the literature on prevention and control strategies but do not describe how included studies were identified.

More recently, Halstrom (2015) 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 but did not distinguish studies involving colonization versus infection and, 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 document 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 among patients in health care facilities 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 scope of the problem, 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.

2. Methods

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

2.1. Eligibility

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

2.2. Inclusion and exclusion criteria

We restricted this review to water-related mycobacterial infections in health care facilities. No restrictions were placed on the date of publication, patient age, or immune status. Infections included

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	Patients in health care facilities (inpatient and outpatient)		
Exposure	Waterborne mycobacteria		
Comparator	No exposure		
Outcomes	Primary: Attack rate Secondary: Mortality	No limitations	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.		

Table 2
Common Phenotypic & Genotypic Methods of Determining NTM Strain Relatedness (Halstrom, 2015; Phillips and von Reyn, 2001; Wallace, 1998).

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

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 (patients infected per exposed) of nosocomial waterborne NTM infections.

2.3. Definitions

Health care facilities include hospitals, outpatient clinics, dental offices, hemodialysis facilities, nursing facilities, and physical rehabilitation facilities. Health care facility terms were selected from PubMed MeSH terms. 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 exposure of the patient to the infectious source, such as inadequate water quality or inappropriate use of non-sterile water. The attack rate is defined as the number of patients with disease divided by the number exposed to the infectious agent. Common phenotypic and genotypic methods of determining relatedness are summarized in Table 2.

2.4. Search strategy

Studies were identified from the peer-reviewed literature. Database searches consisted of 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 ou r searches may have missed. Searches were updated on March 17, 2016.

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 reviewers independently screened the search results' titles and abstracts for articles reporting water-related infections in health care settings. If two of three reviewers independently endorsed an article, then it was included in the full-text stage of screening. Conflicts in inclusion decisions were determined by a third reviewer. Full texts were reviewed, 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 reviewer.

2.5. Data extraction

Previous reviews were consulted to identify appropriate metadata to be extracted for this review (Anaissie et al., 2002b; Bain et al., 2014; Shields et al., 2015). For each eligible study, the following descriptive data and characteristics were extracted: basic reference information, health care facility type, service received, water source type, 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.

2.6. 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 latter value, the composite median attack rate was calculated. The methodological and clinical heterogeneity of the studies were qualitatively analyzed. Due to this heterogeneity, no *meta*-analysis was performed.

3. 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

Table 3
Abbreviated Results of Data extracted from studies on waterborne infections from nontuberculous mycobacteria in health care facility water systems.

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 et al. (1994)	case series	41	hospital	hospital hot water system,		DNA probe	PFGE	bloodstream	HIV/AIDS	5	5	–	–	–
Tobin-D'Angelo et al. (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 (2010)	retrospective cohort	3	clinic (mesotherapy)	tap water	rinsing multiple injection device w/tap water		PFGE	subQ	None	16	11	105	15	–
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 (blepharo-plasty)	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, 16 s 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
Cooksey (2008)	case-control	3	hematology-oncology unit	shower		stain, HPLC	PFGE, RAPD, rep-PCR, partial sequencing	bloodstream	malignancy, CVC	5	1	–	–	–
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

"–" indicates information was not reported.
*Samples.

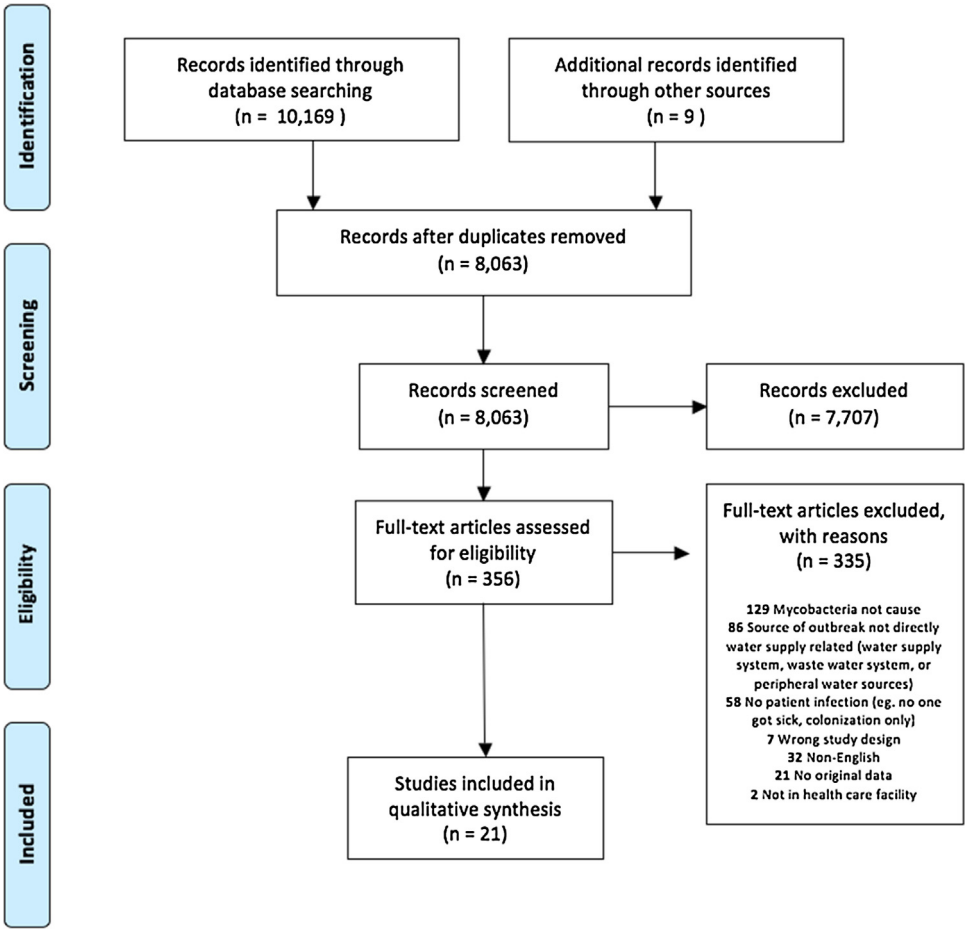

Fig. 1. Flow chart for areview of waterborne infections from nontuberculous mycobacteria in health care facility water systems.

are summarized in Fig. 1. The results of data extraction are summarized in Table 3, and full evidence tables are included in Appendix Table 2.

3.1. 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; Lowry et al., 1990; Lowry et al., 1988; Soto et al., 1991), two case reports (Jaubert et al., 2015; Kauppinen et al., 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 and Deresinski, 2011; Livni et al., 2008; Tagashira et al., 2015; Tobin-D'Angelo et al., 2004; von Reyn et al., 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 an outbreak of 49 patients (Astagneau et al., 2001). There was only one study from a low- or middle-income country (Mexico) (Soto et al., 1991).

3.2. Health care setting

The outbreaks of mycobacterial infection occurred in a range of settings including inpatient hospital units (9), outpatient procedure clinics (4), hemodialysis centers (3), inpatient hospital units (9), and operating rooms (4), and hemodialysis centers (3). 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 and 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; Lowry et al., 1988; Meyers et al., 2002; Wenger et al., 1990).

3.3. 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 the patients in the studies 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 (when sterile water should have been used for the procedure instead). For example, 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 (Lowry et al., 1990; 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).

3.4. 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; Lowry et al., 1990), and respiratory symptoms (von Reyn et al., 1994). Five studies reported soft tissue infection (Carbonne et al., 2009; Flesner and 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 sites 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 (Lowry et al., 1988).

3.5. Water infrastructure deficiencies

Five studies identified water system-related problems that contributed to the growth and spread of mycobacteria to patients. Two studies noted low concentrations 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 health care facility water system deficiencies.

3.6. 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; 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 (Lowry et al., 1988).

3.7. 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 and 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 and 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).

3.8. Heterogeneity

The included studies demonstrated both clinical and methodological heterogeneity. Methodologically, study designs ranged from single case reports to case-control and cohort studies. 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.

3.9. 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 and 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; Lowry et al., 1990), and one study, which reported 14 deaths, did not specify the causes of death (Bolan et al., 1985). The one 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.

3.10. Strategies for control and prevention

Twelve studies reported the strategies adopted 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 and 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 central venous catheter (CVC) and wound sterility, implementing removal or adequate sterilization of infected equipment, caregiver education, and improving 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 and 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).

4. 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. 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.

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 by Wallace et al. 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 and 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 our review and limitations of studies included in the review. As previously mentioned, our research questions were descriptive. Another limitation of this review is the heterogeneous results. The included patients had a variety of risk factors, representing differing vulnerabilities. This review also combined different NTM species, with differing pathogenicity (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 the predilection of NTMs for biofilms, differences in environmental sampling techniques may significantly affect test 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 stronger evidence of association. Therefore, the conclusion that environmental samples represent the source of an outbreak requires assumption about their temporality.

NTM infections are not considered a reportable infection (Adams et al., 2012), and the occurrence 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 and 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 included in studies by investigators. 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 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. The studies that used genotypic methods 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.

As the exposure routes in these studies suggest, 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.

This review revealed that there have been few studies of nosocomial waterborne NTM in low- and middle-income countries (LMICs). Exposure routes and infrastructural deficiencies may be very different in LMICs, rural areas, and low-resource settings (Bartram et al., 2015; WHO and UNICEF, 2015). In order to understand the true burden of disease and exposure mechanisms in these circumstances, additional studies in LMICs are needed. Improving health care facility monitoring initiatives in LMICs may increase data for surveillance of waterborne infections (Cronk et al., 2015).

5. Conclusion

This review demonstrates the common exposures, susceptible populations, and attack rate of waterborne NTM infections in health care settings. Improving detection methods and surveillance systems and using data to improve conditions may contribute to a reduction in morbidity and mortality. Additional high quality studies that examine nosocomial infections from health care facility water supplies may be useful for informing global burden of disease estimates, especially in low- and middle-income countries.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2016.12.002.

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