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Review

A systematic review of nosocomial waterborne infections in neonates and mothers

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ABSTRACT

Background: Water is an important, overlooked, and controllable source of nosocomial infection. Hospitalized neonates and their mothers are particularly vulnerable to nosocomial waterborne infections. Our objectives through this systematic review were to: investigate water sources, reservoirs, and transmission routes that lead to nosocomial waterborne infections in neonates and their mothers; establish patient risk factors; compile measures for controlling outbreaks and recommended strategies for prevention; and identify information gaps to improve guidelines for reporting future outbreaks.
Methods: We searched PubMed, Web of Science, Embase, and clinicaltrials.gov. Peer-reviewed studies reporting contaminated water as a route of transmission to neonates and/or their mothers were included.
Results: Twenty-five studies were included. The most common contaminated water sources in healthcare facilities associated with infection transmission were tap water, sinks, and faucets. Low birthweights, preterm or premature birth, and underlying disease increased neonatal risk of infection. Effective control measures commonly included replacing or cleaning faucets and increased or alternative methods for hand disinfection, and recommendations for prevention of future infections highlighted the need for additional surveillance.
Discussion/conclusion: The implementation of control measures and recommended prevention strategies by healthcare workers and managing authorities of healthcare facilities and improved reporting of future outbreaks may contribute to a reduction in the incidence of nosocomial waterborne infections in neonates and their mothers.

1. Introduction

Nosocomial infections are a persistent challenge worldwide. In the United States, they affect up to 10% of all hospitalized patients (Anaissie et al., 2002). Nosocomial infections contribute to morbidity and mortality, and increase financial burdens and length of stay for patients in low-, middle-, and high-income countries (Anaissie et al., 2002; Ducel et al., 2002; Hassan et al., 2010). Water systems are significant and controllable sources of nosocomial infections that are often inadequately managed in healthcare facilities (HCFs) (Anaissie et al., 2002; Cunliffe et al., 2011; Exner et al., 2005). In large, urban HCFs such as hospitals, patients may be exposed to poorly designed or managed systems, leading to increased risks of disease outbreaks (Cunliffe et al., 2011). In smaller, rural facilities in low- and middle-income countries (LMICs), there may be limited access and availability of water or use of unsafe water sources and unsafe stored water (Bartram et al., 2015; Shields et al., 2015; World Health Organization and UNICEF, 2015).

Inadequate management of HCF water systems can lead to nosocomial infections in more vulnerable hospitalized populations, including those that are immune-compromised, are old, or have underlying diseases (Ducel et al., 2002). Neonates and their mothers are particularly vulnerable. Surveillance studies show 15–20% infection rates in neonatal intensive care units (NICU). Neonates with risk factors such as low birthweights are especially predisposed to infection due to poor immune defenses and intrusive life support systems (Baltimore, 1998). A point prevalence survey of 29 NICUs in the United States showed an infection rate of 11.4%, while individual NICU nosocomial infection rates ranged from 6% to 25%. Multicenter studies in Europe ranged from 8% to 10% (Sohn et al., 2001).

Postpartum sepsis is the leading cause of direct maternal death in the United Kingdom, and a growing source of morbidity and mortality

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in the United States (Bauer et al., 2013). Nulliparous women, women with multiple births, and women with chronic conditions are at a higher risk of developing infections after pregnancy (Knowles et al., 2015), though the large majority of the 6.0% observed postpartum infection rate manifest after hospital discharge (Yokoe et al., 2001). In 2013, estimates suggest 430,000 neonatal deaths were caused by sepsis or other infection (Oza et al., 2015).

Exposure to nosocomial pathogens can lead to a variety of adverse health outcomes in neonates and their mothers. Infections can occur in the bloodstream, lower respiratory tract, and urinary tract, and can increase mortality (Anaissie et al., 2002; Ducel et al., 2002; Sohn et al., 2001).

Prior systematic reviews have described studies of waterborne nosocomial infections, but there is a need for an up-to-date, comprehensive review that highlights the vulnerability of this population in particular. Experts and supporting actors call for improvements in water, sanitation, and hygiene (WaSH) in HCFs to improve maternal and neonatal health and reduce morbidity and mortality rates (Velleman et al., 2014). However, there is insufficient characterization of the impact of waterborne nosocomial infections on maternal and neonatal health.

We systematically reviewed the scientific literature to better understand the causes of and prevention strategies for waterborne nosocomial infections on neonatal and maternal health. The primary objectives were:

- What are the most common water sources, reservoirs, and transmission routes that lead to nosocomial infections in neonates and their mothers?
- What are the patient risk factors in nosocomial waterborne infections in neonates and their mothers?
- What measures and strategies are effective in controlling ongoing outbreaks or recommended for preventing future outbreaks of nosocomial waterborne infections in neonates and their mothers?
- What information gaps exist in the literature on nosocomial waterborne infections in neonates and their mothers?

In addition to addressing these topics, we propose a set of reporting guidelines for nosocomial waterborne infections to improve consistency and better inform practice and research.

2. Methods

A systematic review was conducted of studies reporting waterborne infections of neonates and their mothers in HCFs.

2.1. Eligibility

Studies were included based on the following criteria: reported symptomatic clinical disease; reported on HCFs where deliveries could occur; and contained primary data. Editorials, reviews, and studies exclusively reporting colonization of patients without infection were excluded. Studies exclusively reporting *Legionella pneumophila* species as the infectious microbe were also excluded due to recent literature review pertaining to *Legionella* (see Leiblein et al., 2016). There was no limit on the date of publication.

2.2. Definitions

Neonates are defined as children under 28 days old (World Health Organization, 2014). When age was not specified, patients referred to as “newborn” or “neonate” or treated in the neonatal or nursery unit of a hospital were characterized as neonates. Water sources, reservoirs and transmission routes included tap water, peripherals (e.g. faucets, sinks, shower heads), water baths, water used to prepare aqueous solutions, and water used in humidifiers, ventilators, and incubators. HCFs included hospitals, outpatient clinics, and nursery facilities.

2.3. Search strategy

We used the initial stages of a search strategy employed in a previous systematic review of nosocomial waterborne infections in patients of all ages (Li et al., 2016).

Peer-reviewed studies were identified through PubMed, Web of Science, Embase, and clinicaltrials.gov. The following search statements were used: (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”).

Three independent reviewers using Cochrane’s Covidence online software screened the titles and abstracts of studies obtained from searches. Studies independently approved by two of three reviewers were included in the next stage of screening. Conflicts between the three reviewers were resolved by one of these reviewers. Full texts of selected studies were screened in two stages: initially for the reasons for exclusion as described above, and subsequently to limit the review to neonates and/or mothers as an affected population. The references lists of included studies were searched for additional eligible studies. The search was updated on March 17, 2016.

2.4. Data extraction

The following data were extracted from included studies: setting (HCF type and country information), microbial testing (including temporality and antimicrobial susceptibility); water sources, reservoirs and transmission routes tested; non-water environmental reservoirs tested; conclusion about cause of infection; length of study; number of neonates and/or mothers affected; risk factors for infected patients; other populations affected (including staff and infants older than 28 days); outcomes for neonates, mothers, and other populations; implemented control measures; recommended prevention strategies.

2.5. Synthesis of results

Extracted data were tabulated to compare and summarize findings. Due to the heterogeneity of the results, meta-analysis was not performed.

3. Results

3.1. Search results and study characteristics

The screening process and results are summarized in Fig. 1. This resulted in 16 studies satisfying the inclusion criteria for nosocomial infections of neonates. No studies were found that reported exclusively on infection of mothers. A review of the references of included articles identified nine previously unidentified articles that were included after full text review. One additional study was excluded on the basis it reported on the same outbreak as another included study (Cabrera and Davis, 1961; George et al., 1961). Metadata for the 25 included studies are listed in Table 1 and a summary of the extracted data in Table 2. Based on the synthesized findings and the identified information gaps, a list of criteria for the reporting of waterborne nosocomial infections is proposed in Table 3.

The included articles were published between 1951 and 2016, with study lengths ranging from two weeks to six years. Most studies were case series (n = 17, 68%), followed by case-control studies (n = 3, 12%). All 25 studies took place in inpatient hospital settings, specifically in the neonatal unit, nursery, or neonatal intensive care unit. The hospitals had different managing authorities, most commonly university hospitals (n = 14, 56%). The studies were from 17 countries;

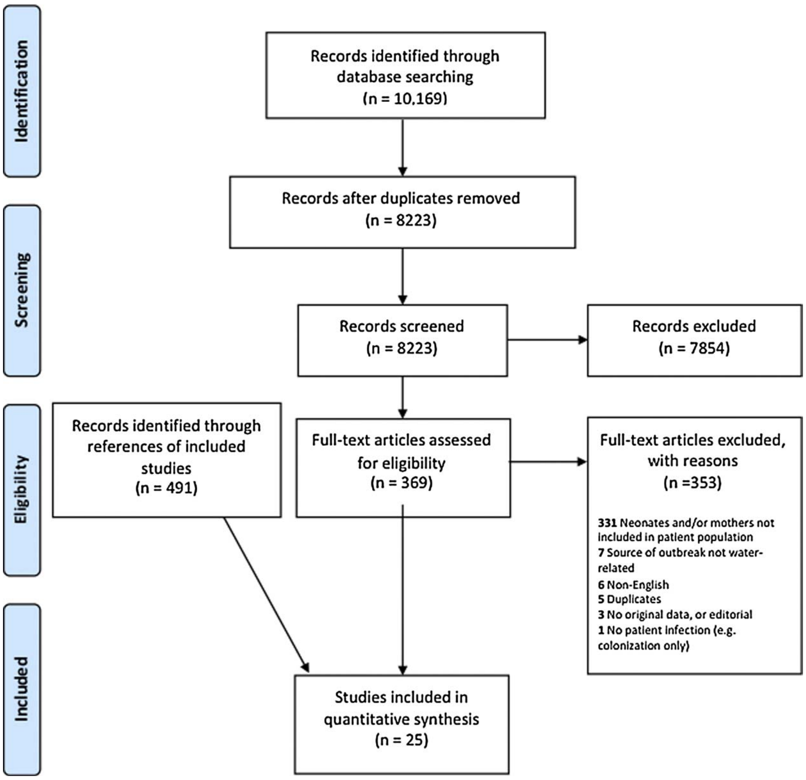

Fig. 1. Schematic of search strategy.

most studies took place in high income countries (n = 13, 52%), with fewer from upper middle income (n = 6, 24%) and lower middle income (n = 3, 12%), and one from a low income country (n = 1, 4%) according to the World Bank Income Classification (World Bank, 2016).

3.2. Patient populations

The number of neonates found to be infected or colonized by one or more waterborne pathogens ranged from one to 516.

Thirteen studies (52%) specified the age or age range of the infants affected, but all characterized patient(s) as "neonate(s)" and/or "newborn(s)" and/or took place in the neonatal or nursery unit of a hospital and thus satisfied the inclusion criteria. The majority of studies reported testing all other neonates in the unit after the initial infection was identified, and seven studies (28%) tested hospital staff or caregivers and/or postnatal mothers for colonization. Of the studies that tested hospital personnel, two found infections and/or colonization of one or more staff by the same species as the causal agent (Mendis et al., 1976; Randrianirina et al., 2009), and five noted a lack thereof (Abrahamsen et al., 1989; Antony and Prasad, 2011; Cabrera and Davis, 1961;

Table 1
Studies included in synthesis.

Study	Country	Income Classification	Managing Authority	Setting	Study design
Abrahamsen et al. (1989)	Norway	High income	Public university hospital	Urban	Case series
Antony and Prasad (2011)	India	Lower middle income	Private university hospital	Rural	Case series
Brown and Baublis (1977)	USA	High income	Public university hospital	Urban	Surveillance study
Büyükyavuz et al. (2006)	Turkey	Upper middle income	Public university hospital	Suburban	Surveillance study
Cabrera and Davis (1961)	USA	High income	Unknown	Urban	Case series
Crivaro et al. (2009)	Italy	High income	Public university hospital	Urban	Intervention study
Epstein et al. (1951)	USA	High income	Private hospital	Urban	Case series
Grundmann et al. (1993)	Germany	High income	Public university hospital	Urban	Case series
King and Murphy (1964)	USA	High income	Not-for-profit hospital	Urban	Case series
Lee (2008)	Malaysia	Upper middle income	Private hospital	Urban	Case-control
Mendis et al. (1976)	Sri Lanka	Lower middle income	Maternity hospital	Urban	Case series
Molina-Cabrillana et al. (2013)	Spain	High income	Public university hospital	Urban	Case series
Mosayebi et al. (2011)	Iran	Upper middle income	Maternity and gynecology hospital	Urban	Case series
Mutlu et al. (2011)	Turkey	Upper middle income	Public university hospital	Urban	Case-control
Muyldermans et al. (1998)	Belgium	High income	Public-private university hospital	Urban	Case-control
Naze et al. (2010)	France	High income	Unknown	Urban	Case series
Plotkin and McKitrick (1966)	USA	High income	Unknown	Rural	Cohort study
Pegues et al. (1994)	Guatemala	Lower middle income	Public teaching hospital	Urban	Case series
Randrianirina et al. (2009)	Madagascar	Low income	Public pediatric hospital, public military hospital	Urban	Case series
Thong et al. (1981)	Malaysia	Upper middle income	Private university hospital	Urban	Case series
Verweij et al. (1998)	Netherlands	High income	Public university hospital	Urban	Case series
Walker et al. (2014)	Northern Ireland	High income	Varies	Mostly rural	Cross-sectional
Wilson et al. (1961)	USA	High income	Public university hospital	Urban	Case series
Yapicioglu et al. (2012)	Turkey	Upper middle income	Public university hospital	Urban	Case series
Zheng et al. (2016)	China	Upper middle income	Public university hospital	Urban	Case series

Table 2
Condensed data extraction table.

Study	Infectious agent	Water source	Number neonates affected	Outcomes for neonates	Additional populations investigated
Abrahamsen et al. (1989)	*Flavobacterium meningosepticum*	Sinks, used rubber stoppers for the milk bottles and cleaned teats that were stored in water	8	Septicaemia (2), septicaemia and meningitis (2), colonization (4)	Septicaemia in one infant (> 28 days); colonization of two infants (> 28 days); all staff were negative
Antony and Prasad (2011)	*Enterobacter cloacae*	Water used to bathe neonates	18	Death (8), septicaemia (10)	All staff and mothers were negative
Brown and Baublis (1977)	*Pseudomonas aeruginosa*	Sink drains, nasopharyngeal catheter rinse bottles	81	Death (3, +3 unrelated), sepsis (22), pneumonia (34), bronchitis/tracheitis (13), unspecified infections (12)	None
Büyükyavuz et al. (2006)	*Klebsiella pneumoniae; coagulase negative Staphylococcus*	Formula heater water	20	Septicaemia (20)	None
Cabrera and Davis (1961)	*Flavobacterium meningosepticum*	Leaking sink trap	44	Death (9, +1 unrelated), hydrocephalus (3), clinical symptoms (1), nasal colonization (30)	All staff were negative
Crivaro et al. (2009)	*Pseudomonas aeruginosa*	Sinks	135	Death (4), sepsis (1), pneumonia (5), urinary tract infection (1), colonization (124)	None
Epstein et al. (1951)	*Salmonella oranienburg*	Waterbath for reheating milk bottles	18	Death (3), clinical symptoms	All staff and mothers were negative
Grundmann et al. (1993)	*Pseudomonas aeruginosa*	Faucets, sink traps	6	Meningitis (1), septicemia (1), bronchopneumonitis (1), unspecified infections (3)	None
King and Murphy (1964)	*Pseudomonas aeruginosa, Escherichia coli, Proteusspecies, Aerobacter cloacae*	Water baths used for formula bottles	Unknown	Diarrhea	None
Lee (2008)	*Burkholderia cepacia*	Ventilator water traps, humidifier water trap	25	Death (1), Septicaemia (24)	Death of infant (> 28 days)
Mendis et al. (1976)	*Salmonella bareilly*	Sink, taps	516	Death (12), mild pyrexia (75), colonization with or without diarrhea (429)	Colonization of 91 staff
Molina-Cabrillana et al. (2013)	*Pseudomonas aeruginosa*	Faucets	6	Pneumonia (3), conjunctivitis (3)	Pneumonia in three infants (> 28 days), conjunctivitis in three infants (> 28 days)
Mosayebi et al. (2011)	Flavobacterium sepsis	Distilled water and stills	45	Death (8), respiratory distress (27), lethargy (7), poor feeding (7), cyanosis (2), hypoglycaemia (1), tachypnoea (1)	None
Mutlu et al. (2011)	*Spingomonas paucimobilis*	Distilled water used for humidifying incubators and mechanical ventilators	13	Death (1), sepsis (12)	None
Muyldermans et al. (1998)	*Pseudomonas aeruginosa*	Water bath used to thaw fresh frozen plasma	5	Death (3 unclear if related), colonization (1)	None
Naze et al. (2010)	*Pseudomonas aeruginosa*	Commercial bottled mineral water used to prepare milk, tap water samples, faucets, sink, sink drains	42	Death (1), septicaemia (1), colonization (40)	None
Plotkin and McKitrick (1966)	*Flavobacterium meningosepticum*	Saline solution used to wash infants' eyes at birth	2	Death (1), permanent brain damage (1)	None
Pegues et al. (1994)	*Serratia marcescens*	Tap water	26	Death (23), fever/sepsis/meningitis (26)	None
Randrianirina et al. (2009)	*Klebsiella pneumonia*	Tap water used to rinse aspiration tubes	9	Death (3), fever and respiratory distress (6)	Colonization of staff member (1), fever and respiratory distress in infant (> 28 days) (1)
Thong et al. (1981)	*Flavobacterium meningosepticum*	Hand basins, babies' bath basins, stock bottles of aqueous chlorhexidine	11	Death (2), hydrocephalus (2), fever and clinical symptoms (3), colonization of throat (4)	Throat colonization of two postnatal mothers (2), all staff negative
Verweij et al. (1998)	*Stenotrophomonas maltophilia*	Tap water from three outlets used for washing infants	5	Death (1), septicaemia (1), endotracheal colonization (3)	None
Walker et al. (2014)	*Pseudomonas aeruginosa*	Neonatal unit taps	2 neonatal units	Death (4)	None
Wilson et al. (1961)	*Pseudomonas aeruginosa*	Aerators in faucets	1	Death (1)	None
Yapicioglu et al. (2012)	*Pseudomonas aeruginosa*	Water and filters of electronic faucets in patient rooms and lab	11	Death (2), ventilator-associated pneumonia (3), blood stream infection (6)	Ventilator-associated pneumonia in infant (> 28 days) (1)
Zheng et al. (2016)	*Pseudomonas aeruginosa*	Incubator water	17	Death (1), pneumonia (16)	None

Table 3
Proposed criteria for reporting of waterborne nosocomial infections.

Keyword	Description
Setting	Further description of setting, including whether the healthcare facility was located in a rural or urban area and the country income level
HCF water system	Description of the HCF's water system (i.e. source, reliability, additional treatment processes used)
HCF water safety plan	Description of building-level water safety plan, if one exists
HCF routine water surveillance	Existing or proposed guidelines for routine surveillance of water quality in HCF, if they exist
Water testing	Description of all water sources, reservoirs, and transmission routes tested, with disaggregated results, and additional description of any excluded from testing
Non-water testing	Description of all non-water environmental reservoirs tested, with disaggregated results
Hand hygiene	Existing or proposed practices for hand disinfection among healthcare workers, and whether or not healthcare workers' hands were tested as potential transmission route
Pathways	Explanation of potential pathways between water source, reservoir, or transmission route and patients
Causal evidence	Evidence of causal relationship between acquired infection and water source, reservoir, or transmission route including a discussion of temporality (i.e. Bradford Hill criteria)

Epstein et al., 1951; Thong et al., 1981). One study found colonization of two mothers (Thong et al., 1981) and two found all tested mothers to be negative for the microbe of interest (Antony and Prasad, 2011; Epstein et al., 1951). Five studies (20%) described the infection and/or colonization of infants older than 28 days, with the oldest at 146 days (Epstein et al., 1951; Lee, 2008; Molina-Cabrillana et al., 2013; Randrianirina et al., 2009; Yapicioglu et al., 2012).

Fourteen studies (56%) identified risk factors for nosocomial waterborne infection in neonates. None of the studies mentioned risk factors for mothers or caretakers. Nine studies noted most or all affected neonates were either preterm (Antony and Prasad, 2011; Crivaro et al., 2009) or premature (Cabrera and Davis, 1961; Grundmann et al., 1993; Mendis et al., 1976; Mosayebi et al., 2011; Mutlu et al., 2011; Wilson et al., 1961; Yapicioglu et al., 2012). Seven studies noted that affected neonates were debilitated, had underlying disease, required the highest level of care, or had prolonged stays in the HCF (Antony and Prasad, 2011; Brown and Baublis, 1977; Grundmann et al., 1993; Randrianirina et al., 2009; Wilson et al., 1961; Yapicioglu et al., 2012; Zheng et al., 2016). Four reported low birthweights (Antony and Prasad, 2011; Crivaro et al., 2009; Mosayebi et al., 2011; Pegues et al., 1994). One study found neither birthweight nor gestational age was significantly different between the neonates infected and the controls (Muyldermans et al., 1998), and another found no significance in prematurity between those affected and unaffected (Abrahamsen et al., 1989). Two studies found neonates subject to frequent use of antimicrobials or exposure to invasive procedures were more at risk (Pegues et al., 1994; Verweij et al., 1998).

3.3. Causes of infections

The causal agents of clinical disease included the following 12 bacteria: *Pseudomonas aeruginosa* (n = 10, 43%), *Flavobacterium meningosepticum* (n = 4, 17%), unspecified *Flavobacterium* (n = 1, 4%) *Klebsiella pneumoniae* (n = 2, 9%), *Burkholderia cepacia* (n = 1, 4%), *Enterobacter cloacae* (n = 1, 4%), *Salmonella bareilly* (n = 1, 4%), *Salmonella oranienburg* (n = 1, 4%), *Serratia marcescens* (n = 1, 4%), *Spingomonas paucimobilis* (n = 1, 4%), coagulase negative *Staphylococcus* (n = 1, 4%), and *Stenotrophomas maltophilia* (n = 1, 4%). One study did not mention the cause of infection, but noted that *Pseudomonas aeruginosa, Escherichia coli, Proteus* species, and *Aerobacter cloacae* were found in contaminated water linked to a diarrheal outbreak (King and Murphy, 1964).

In 24 of the 25 cases, the infectious agent was isolated from tap water, an aqueous solution, water reservoir (water bath, ventilator, humidifier, or incubator), sink(s), and/or faucet(s). In each, one or more of these sources were concluded to be a primary transmission route and/or environmental reservoir. The remaining study was unable to speciate the organisms found in the tap water, but noted elevated total and fecal coliform in the tap water and confirmed malfunctioning of the well-water chlorination system (Pegues et al., 1994). Thirteen of these studies (52%) used genotypic or phenotypic methods to determine whether the strain isolated from the patients was identical to that in the water source (Antony and Prasad, 2011; Brown and Baublis, 1977; Crivaro et al., 2009; Grundmann et al., 1993; Mutlu et al., 2011; Muyldermans et al., 1998; Naze et al., 2010; Plotkin and McKitrick, 1966; Thong et al., 1981; Verweij et al., 1998; Walker et al., 2014; Yapicioglu et al., 2012; Zheng et al., 2016).

The most commonly colonized water sources, reservoirs, and transmission routes were tap water, sinks, and/or faucets, which were found to be contaminated in 15 studies (60%). Water baths were contaminated in three studies (12%). Additional sources of contamination included water used to bathe neonates, rinse bottles, formula heater water, humidifier and ventilator water, distilled water, bottled mineral water, a saline solution, aqueous chlorhexidine, and incubator water. The authors of six of the studies (24%) believed healthcare workers' handwashing with contaminated water was a contributing factor in the transmission of infection to the neonates (Antony and Prasad, 2011; Brown and Baublis, 1977; Cabrera and Davis, 1961; Crivaro et al., 2009; Verweij et al., 1998; Wilson et al., 1961).

Twenty-one studies (84%) described sampling non-water-related environmental reservoirs. The most commonly tested were incubators, air, healthcare workers' hands, disinfectants, soap, floors and walls, and various equipment and instruments. Nine studies (36%) isolated the implicated species from non-water reservoirs, including soap (Yapicioglu et al., 2012), healthcare workers' hands (Brown and Baublis, 1977; Crivaro et al., 2009; Pegues et al., 1994), bronchial suction tubing (Thong et al., 1981), a formula heater (Büyükyavuz et al., 2006), the handles of a hamper (Cabrera and Davis, 1961), sponges (Wilson et al., 1961), and nasogastric tubing (Randrianirina et al., 2009).

3.4. Outcomes measured

Twenty-three studies reported isolation of the infectious agent from one or more neonates in addition to reporting clinical symptoms of infection of one or more neonates. One of the remaining studies was an investigation into taps at multiple HCFs and only reported number of deaths at these HCFs (Walker et al., 2014). The other was a short article that provided few details about the affected neonates (King and Murphy, 1964). Twenty studies (80%) reported death of one or more neonate(s), though one study noted it was unclear whether the nosocomial waterborne infection was the cause of the deaths (Muyldermans et al., 1998).

3.5. Control measures and recommendations for prevention

Twenty-one studies (84%) discussed control measures implemented to stop the spread of infection. The most frequent measures were cleaning, replacing, and/or fixing faucets and/or sinks (Abrahamsen et al., 1989; Cabrera and Davis, 1961; Grundmann et al., 1993; Thong et al., 1981; Wilson et al., 1961; Yapicioglu et al., 2012), isolating infected neonates (Abrahamsen et al., 1989; Antony and Prasad, 2011; Crivaro et al., 2009; Epstein et al., 1951; King and Murphy, 1964), improving hand disinfection compliance or implementing use of alternative hand disinfectants among hospital staff (Antony and Prasad, 2011; Brown and Baublis, 1977; Crivaro et al., 2009; Pegues et al., 1994; Verweij et al., 1998), sterilizing or disinfecting water before use by boiling or other methods, particularly in regards to washing neonates (Antony and Prasad, 2011; Molina-Cabrillana et al., 2013; Thong et al., 1981; Verweij et al., 1998), and replacing water baths with dry incubators (King and Murphy, 1964; Muyldermans et al., 1998).

Eighteen studies (72%) discussed or recommended long-term strategies for prevention of future infection. Common themes included increased surveillance and timely identification of infection (Antony and Prasad, 2011; Büyükyavuz et al., 2006; Crivaro et al., 2009; Epstein et al., 1951; Mendis et al., 1976; Molina-Cabrillana et al., 2013; Mosayebi et al., 2011; Muyldermans et al., 1998; Thong et al., 1981; Zheng et al., 2016) and addressing problems with faucets by replacing electronic faucets or cleaning or replacing aerators (Verweij et al., 1998; Walker et al., 2014; Wilson et al., 1961; Yapicioglu et al., 2012). None of the studies recommended any organizational or systemic facility changes as a strategy for prevention.

4. Discussion

This systematic review is the first to report in-depth on waterborne nosocomial infection in neonates and mothers. The causal agent of clinical disease was most commonly isolated from sinks and faucets, which were also points of intervention. No studies were found that reported exclusively on mothers or emphasized mothers as a primary affected population.

The studies included were heterogeneous in reporting results. Several lacked information, including the age of the infants or the number of exposed neonates, which could have been used to calculate attack rates or otherwise conduct a *meta*-analysis. This demonstrates a need for more standardized reporting of nosocomial infections in the future in order to more comprehensively synthesize the information required to inform policy, practice, and research. Based on data provided and omitted from studies included in this review, we propose a list of criteria to report waterborne infections in HCFs (Table 3). Standardized reporting will help with future *meta*-analytic studies.

4.1. Cause of infection

The infectious agents identified through this review were all bacterial agents as listed in Table 2. A previous review on waterborne nosocomial outbreaks included most of these bacteria species and emphasized the large disease burden of *P. aeruginosa* in particular (Anaissie et al., 2002). The United States Centers for Disease Control and Prevention (CDC) includes *P. aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophlia*, *Serratia marcescens*, *Sphingomonas* spp., and *Enterobacter* spp. on its list of prevalent waterborne organisms in healthcare settings (Sehulster and Chinn, 2003).

The most frequently identified contaminated water sources, reservoirs, or transmission routes among the studies in this review were tap water, sinks, and faucets, which is consistent with previous reviews on nosocomial waterborne infection (Anaissie et al., 2002; Exner et al., 2005). Anaisse, et al. notes the buildup of biofilms in the distribution lines or tanks as a primary cause of this, resulting from water stagnation and/or poorly designed or aging systems (Anaissie et al., 2002). Healthcare workers' handwashing with this contaminated water was hypothesized as a transmission route in six studies in this review. Crivaro, et al. and Brown, et al. found healthcare workers' hands to be contaminated with the microbes of interest in their studies (Brown and Baublis, 1977; Crivaro et al., 2009). Brown, et al. also examined the spread of the microbe through airborne water droplets from contaminated tap water and found an affected radius of 1.8 m around sinks, suggesting microbes can readily reach healthcare workers' gowns (Brown and Baublis, 1977). Additionally, the outbreak described by Randrianirina, et al. spread between two hospitals with shared staff members who were thought to be responsible for the transmission of the microbe (Randrianirina et al., 2009). Bathing patients or washing medical equipment with contaminated water were transmission routes found in several of these studies and in previous literature (Anaissie et al., 2002). The majority of the studies included in this review tested environmental sources other than water sources, such as incubators, air, and soap. However, most of these sources were not colonized and most studies concluded they were not a contributing transmission route.

Four of the 25 studies explicitly stated they were unable to conclude whether the water source, reservoir, or transmission route caused the patient infections(s) or vice versa (Brown and Baublis, 1977; Crivaro et al., 2009; Grundmann et al., 1993; Walker et al., 2014). Nine of the studies established a causal relationship through observing that the spread of infection was stopped soon after an intervention that addressed the contaminated water source, reservoir, or transmission route (Cabrera and Davis, 1961; King and Murphy, 1964; Mendis et al., 1976; Molina-Cabrillana et al., 2013; Mosayebi et al., 2011; Muyldermans et al., 1998; Naze et al., 2010; Randrianirina et al., 2009; Yapicioglu et al., 2012). Almost half (n = 12, 48%) did not discuss temporality in the observed infections or outbreaks.

4.2. Patient risk factors

Low birthweight, preterm or premature birth, underlying disease, routine antimicrobial use, and exposure to invasive procedures were reported patient risk factors for nosocomial waterborne infection in neonates in several of the studies in this review. Sohn, et al. conducted a study on nosocomial infection in NICU patients, which focused on both waterborne and non-waterborne infection, and similarly found low birthweight as a significant patient risk factor. Infants with birthweights $\leq$1500 g were found to be 2.69 times more likely to acquire a nosocomial infection, and over fifty percent of the acquired infections in the NICU were in infants with birthweights $\leq$1000 g (Sohn et al., 2001). Baltimore, et al. also noted birthweight as the strongest patient risk factor in neonatal nosocomial infection, and cited poor immune defenses and life support systems such as ventilators and catheters as additional risk factors (Baltimore, 1998). The studies by Abrahamsen, et al. and Muyldermans, et al. were in contrast to the other studies included in this review and in contrast with the literature, as they concluded birthweight and/or gestational age were not significant in determining which neonates acquired infections (Abrahamsen et al., 1989; Muyldermans et al., 1998).

4.3. Antimicrobial resistance

The problem of antimicrobial resistance complicating therapy for neonates was a common theme among the studies in this review. Eleven of the 25 studies noted that one or more strains of the infectious microbe showed resistance to two or more classes of antimicrobial agents. Two studies noted the infectious microbe was susceptible to all antibiotics tested (Molina-Cabrillana et al., 2013; Muyldermans et al., 1998). This is similar to the findings by Anaisse, et al., which found 76% of the waterborne microbes that caused nosocomial outbreaks and were tested for susceptibility to antimicrobials were resistant to two or more classes (Anaissie et al., 2002). In a review on neonatal nosocomial infection, Baltimore, et al. states the high prevalence of antibiotic use in the NICU promotes antibiotic resistance in infectious agents (Baltimore, 1998). In the outbreak studied by Randrianirina, et al. in Madagascar − the only low-income country included in this review − the infectious agent was resistant to nine classes of antimicrobials and three neonates died because their mothers could not afford treatment (Randrianirina et al., 2009).

4.4. Control and prevention

Contaminated sinks and taps were the most commonly implicated transmission route, and several studies prioritized addressing these areas in their control measures. Removing colonized aerators, cleaning taps with disinfectant, and/or fixing leaking sinks were important steps in controlling several of the outbreaks (Cabrera and Davis, 1961; Grundmann et al., 1993; Wilson et al., 1961). Removing and replacing electronic faucets was vital in another outbreak, as electronic faucets have increased likelihood of being colonized due to the low water pressure and stagnant water in the column (Exner et al., 2005; Yapicioglu et al., 2012).

A prevention emphasis among the studies was education of and proactivity among healthcare providers. This encompasses handwashing behaviors and use of sterile water for bathing neonates. Baltimore, et al. states that handwashing is the "least expensive and most effective" way to prevent the spread of infection among patients (Baltimore, 1998). From a historical perspective, Ignaz Semmelweis – a Hungarian physician and one of the first pioneers of hand disinfection – demonstrated in 1847 that effective hand disinfection could decrease maternal mortality rates from 16% to 3% within several months (Pittet and Boyce, 2001; Semmelweis, 1861). Several outbreaks included in this review were controlled by encouraging the use of alcohol rubs or alternative handwashing agents for hand disinfection or by implementing educational programs for staff on the importance of handwashing (Antony and Prasad, 2011; Brown and Baublis, 1977; Crivaro et al., 2009; Verweij et al., 1998). Using sterile water rather than tap water for washing preterm and at-risk neonates was suggested in other studies (Thong et al., 1981; Verweij et al., 1998). Overall, there was a theme of the importance of active surveillance and monitoring of sinks and taps in neonatal units (Antony and Prasad, 2011; Büyükyavuz et al., 2006; Crivaro et al., 2009; Molina-Cabrillana et al., 2013; Thong et al., 1981; Verweij et al., 1998; Zheng et al., 2016). Furthermore, it was noted that timely identification and response to infections is vital for controlling them (Crivaro et al., 2009).

4.5. Information gaps and proposed guidelines for reporting

Several information and knowledge gaps were identified through this review. There were few studies identified from LMICs – despite evidence suggesting that the maternal and neonatal disease burden is greatest in these settings (Lawn et al., 2010). Water supply infrastructure problems are different in LMICs as compared to high-income countries (World Health Organization and UNICEF, 2015). Pegues, et al. discusses contributions to the outbreak in a hospital in Guatemala City, Guatemala included limited supply of and low quality antiseptics and lack of sinks in addition to the malfunctioning of the well-water chlorination system, all concerns that may be especially applicable in other LMICs (Pegues et al., 1994). Problems may be particularly acute in small facilities in rural areas where sources may not be in the building or may be unreliable, forcing staff to collect water from distant sources and store water in the facility, which may introduce additional contamination (Bain et al., 2014; Shields et al., 2015). Improvements to HCF monitoring and surveillance systems in LMICs may help document the extent of the problem and identify areas that have high levels of exposure to water contamination (Cronk et al., 2015). Upgrades to reliable, safe, piped water in these areas would be an optimal solution (Bartram et al., 2015); use of packaged water may be an appropriate short-term solution (Williams et al., 2015). These supplies would benefit from safe management and the implementation of building-level water safety plans to prevent contamination (Cunliffe et al., 2011).

ORION (Outbreak Reports and Intervention Studies of Nosocomial Infection) is a 22-item checklist intended to raise the standard of reporting nosocomial infection by emphasizing transparency and the use of appropriate statistics (Stone et al., 2007). Based on the information synthesized from studies in this review, we created a supplemental list with items especially relevant for waterborne nosocomial infection (Table 3). Much of this information is not consistently reported in available literature. For example, only one of the 25 studies described existing or proposed guidelines for routine surveillance of the water quality in the hospital. Improvements in reporting waterborne nosocomial infection would allow for a more comprehensive understanding of the burden of disease and inform practice and research into this problem.

4.6. Limitations

A limitation of this study was that the original search strategy did not include terms for neonatal and maternal health or specific locations in health care facilities, such as intensive care units. Limitations of the studies included in this review included the heterogeneity of the studies. Additionally, in studies, it was difficult to establish causation. Because all of the studies isolated the infectious agent from the water source, reservoir, or transmission route after the infection(s) manifested, it was not possible to draw definitive conclusions about temporality.

5. Conclusion

We documented transmission routes, environmental reservoirs, and patient risk factors common in waterborne nosocomial infection of neonates, confirming these infections are preventable and can be controlled. Information gaps in the included studies were used to propose additional criteria for guidelines on reporting nosocomial outbreaks. Additional studies are necessary to determine the global burden of disease and develop strategies for prevention of further waterborne nosocomial infection in this vulnerable population. Improving safe management of water supplies in maternity settings would reduce unnecessary morbidity and mortality among neonates and their mothers.

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