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Review

The Presence of Opportunistic Premise Plumbing Pathogens in Residential Buildings: A Literature Review

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Abstract: Opportunistic premise plumbing pathogens (OPPP) are microorganisms that are native to the plumbing environment and that present an emerging infectious disease problem. They share characteristics, such as disinfectant resistance, thermal tolerance, and biofilm formation. The colonisation of domestic water systems presents an elevated health risk for immune-compromised individuals who receive healthcare at home. The literature that has identified the previously described OPPPs (*Aeromonas* spp., *Acinetobacter* spp., *Helicobacter* spp., *Legionella* spp., *Methylobacterium* spp., *Mycobacteria* spp., *Pseudomonas* spp., and *Stenotrophomonas* spp.) in residential drinking water systems were systematically reviewed. By applying the Preferred reporting items for systematic reviews and meta-analyses guidelines, 214 studies were identified from the Scopus and Web of Science databases, which included 30 clinical case investigations. Tap components and showerheads were the most frequently identified sources of OPPPs. Sixty-four of these studies detected additional clinically relevant pathogens that are not classified as OPPPs in these reservoirs. There was considerable variation in the detection methods, which included traditional culturing and molecular approaches. These identified studies demonstrate that the current drinking water treatment methods are ineffective against many waterborne pathogens. It is critical that, as at-home healthcare services continue to be promoted, we understand the emergent risks that are posed by OPPPs in residential drinking water. Future research is needed in order to provide consistent data on the prevalence of OPPPs in residential water, and on the incidence of waterborne homecare-associated infections. This will enable the identification of the contributing risk factors, and the development of effective controls.

Keywords: opportunistic premise plumbing pathogens; drinking water; biofilm; disinfectant resistance; antimicrobial resistance

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1. Introduction

Access to safe drinking water and sanitation has been recognized by the United Nations General Assembly as a human right [1]. Diseases such as cholera and typhoid have decreased in developed countries because of effective drinking water disinfection and distribution [1]. The recognition of additional waterborne illnesses, such as pneumonia, bloodstream infections, and skin diseases, has increased in recent decades [2,3]. The World Health Organization estimated that, in 2016, 1.9 million deaths could have been prevented with access to safe water, sanitation, and hygiene [1]. Despite approximately 94% of the United States (US) population having access to public water systems, there are an estimated 7.2 million waterborne infections each year [2,4]. Of these, the CDC has estimated that over 2.3 million waterborne enteric illnesses, and 96,000 waterborne respiratory illnesses, were acquired domestically [3]. This disease transmission is commonly attributed to aging infrastructure, unregulated private systems, and inconsistent disinfection protocols [5]. Once municipal water reaches residential properties, the microbial water quality can be difficult to maintain because of warm- and cold-water outlets, showers, and home appliances, which create unique environmental niches [6].

Opportunistic premise plumbing pathogens (OPPPs) are waterborne microorganisms that inhabit water distribution systems and premise plumbing [7]. OPPPs have been distinguished from other drinking water contaminants as they are adapted to growth and proliferation in drinking water systems [8]. This growth can be promoted and influenced by water stagnation, increased water residence times, the application of subinhibitory disinfectant concentrations, and fluctuating water temperatures [9,10]. Because of the complex design and age of residential plumbing infrastructure, the maintenance of parameters such as these is an ongoing challenge [11]. OPPPs share characteristics, such as disinfectant resistance, biofilm formation, amoeba digestion resistance, and growth under oligotrophic conditions. Although *Legionella pneumophila*, *Pseudomonas aeruginosa*, and *Mycobacterium avium* have been considered model OPPPs, the definition has expanded to include species such as *Acinetobacter baumannii*, *Stenotrophomonas maltophila*, *Helicobacter pylori*, *Aeromonas hydrophila*, and *Methylobacterium* spp. [7]. Of all the waterborne disease transmission in the US in 2014, Legionnaires' disease, pneumonia caused by *Pseudomonas* spp. and nontuberculous Mycobacteria infection have been attributed with the largest number of deaths [3]. *Legionella* spp. infection almost exclusively presents as a nontransmissible respiratory infection, such as Legionnaires' disease or Pontiac fever [12], whereas other OPPPs, such as *P. aeruginosa, Mycobacteria* spp., and *A. baumannii*, each cause a range of potentially transmissible and antimicrobial-resistant infections, including pneumonia, septicaemia, and dermal infection, which further complicate their management [7].

Legionnaires' disease is the only OPPP-caused infection that is a nationally notifiable disease in the US. The CDC reported that, in 2018, there were approximately 10,000 cases of Legionnaires' disease [3]. However, it has been suggested that the incidence of Legionnaires' disease was underestimated, and that the true number of cases may be 1.8 to 2.7 times higher than what is reported. Additionally, the origins of these infections are rarely identified, as environmental sampling is typically only conducted in response to extended outbreaks. Outbreaks in domestic settings are less easily detected because of the inherent low numbers of exposed occupants at individual premises; although the sum total of exposed individuals is likely to exceed those in large buildings. As such, it is difficult to quantify the total public health risk that is associated with various environmental reservoirs. The elderly, newborns, and those with compromised immune systems are especially vulnerable to waterborne infections. The number of individuals with conditions that may put them at risk of OPPP infection, such as advanced age, cancer, and immunodeficiency, are increasing [3]. Life expectancy has increased by more than six years since 2000, and the number of cancer diagnoses worldwide is set to increase by 47% in 2040 [13]. At-home healthcare has emerged as an alternative to extensive inpatient hospital stays [14,15]. Services such as chemotherapy, tracheotomy care, and ventilator support, are being facilitated by government healthcare and disability support schemes in countries such as the United Kingdom, the US, and Australia [16–18]. These "at home" alternatives are receiving further attention in the wake of the COVID-19 pandemic because of the need to reduce the burden on the healthcare system and to support those with potential long-term respiratory side effects [19]. When in a hospital or healthcare facility, a patient's risk of healthcare-associated infection (HAI) and exposure to environmental risks has been minimised by the implementation of infection control and prevention guidelines, with varying success [20,21]. Despite such initiatives, the US CDC reported significant increases in four of the six monitored HAIs from 2019–2020, even with decreased surveillance activities due to shortages in personnel and equipment [22]. Conversely, patients receiving healthcare in residential properties may have poor access to plumbing, sanitation, and ventilation, which are overlooked by these guidelines [15]. Major outbreaks of OPPP infection are typically associated with larger buildings, such as hospitals, which has resulted in drinking water guidelines that focus on the unique risks that are posed by this infrastructure. Without the consistent environmental surveillance of residential properties, which can vary significantly in size, age, occupancy, and infrastructure quality, it is difficult to identify and quantify the unique risks that are posed by OPPPs in these settings. If healthcare services continue to move patient care away from the hospital environment, further research is required in order to identify and quantify the potential risks, and to tailor infection surveillance and prevention guidelines to the patient and to their property.

Previous literature reviews have identified and characterized emerging OPPPs in order to increase awareness and to encourage novel control procedures in healthcare settings [3,8,23–27]. It is evident that OPPPs, and other clinically relevant bacterial species, are present in drinking water, and that they pose a significant public health threat to many demographics. However, this risk is not reflected appropriately in the current infection control and surveillance guidelines, as water-related devices are consistently underestimated as sources of infection in outbreak response investigation protocols [28]. This systematic review uniquely focuses on the role of residential drinking water in the transmission of OPPP infection. The common water-related devices, surveillance protocols, and detection methods are discussed. It is essential that the water industry, homeowners, and healthcare providers understand the scope and risks that are posed by OPPPs in residential buildings. This will facilitate the implementation of effective control protocols as at-home healthcare services progress as an alternative to hospital admission for at-risk individuals.

2. Materials and Methods

This systematic review was based on an adapted version of the PRISMA statement that is presented in [29]. Relevant studies were identified using two different databases, Web of Science and Scopus, by using the search terms that are presented in Table 1. A detailed search strategy was established in order to ensure a thorough review of all of the identified OPPPs in residential drinking water.

Table 1. Complete search strategy and all keywords used to identify relevant literature.

Search Terms Employed to Identify Relevant Literature
Stenotrophomonas OR *Aeromonas* OR *Acinetobacter* OR *Legionella* OR *Mycobacterium* * OR "nontuberculous mycobacteria *" OR *Pseudomonas* OR *Methylobacterium* or *Helicobacter* or "opportunistic premise plumbing pathogen *" or "opportunistic waterborne pathogen *" or "legionnaires disease" or legionellosis or "pontiac fever" or pneumonia
AND
Home or house or residence * or domestic or household or private
AND
Water or potable or shower or tap * or drain or bath or sink or bathroom or plumbing or faucet or biofilm or aerosol or "drinking water"

'*' indicates wildcard symbol used when variations of the search term may be possible.

All of the titles and abstracts of the published literature were manually reviewed to ensure that they reported the presence of *Aeromonas* spp., *Acinetobacter* spp., *Helicobacter* spp., *Legionella* spp., *Methylobacterium* spp., *Mycobacterium* spp., *Legionella* spp., or *Stenotrophomonas* spp., to the genus level. The study must also have reported these presences in a residential drinking water source or water-related device. Studies were excluded if they were not written in English, if they were reviews, if they reported on clinical infection but did not identify a contributing residential water source, or if they investigated wastewater. The study site, reservoir, pathogen, country and year of the study, bacterial isolation methods, and antimicrobial characteristics were collected from each article, as appropriate.

3. Results

A total of 3402 papers were retrieved from Scopus and Web of Science by using the search terms identified (Table 1). After applying the inclusion and exclusion criteria (Figure 1), a total of 214 papers were included for review, and they are presented in Table S1.

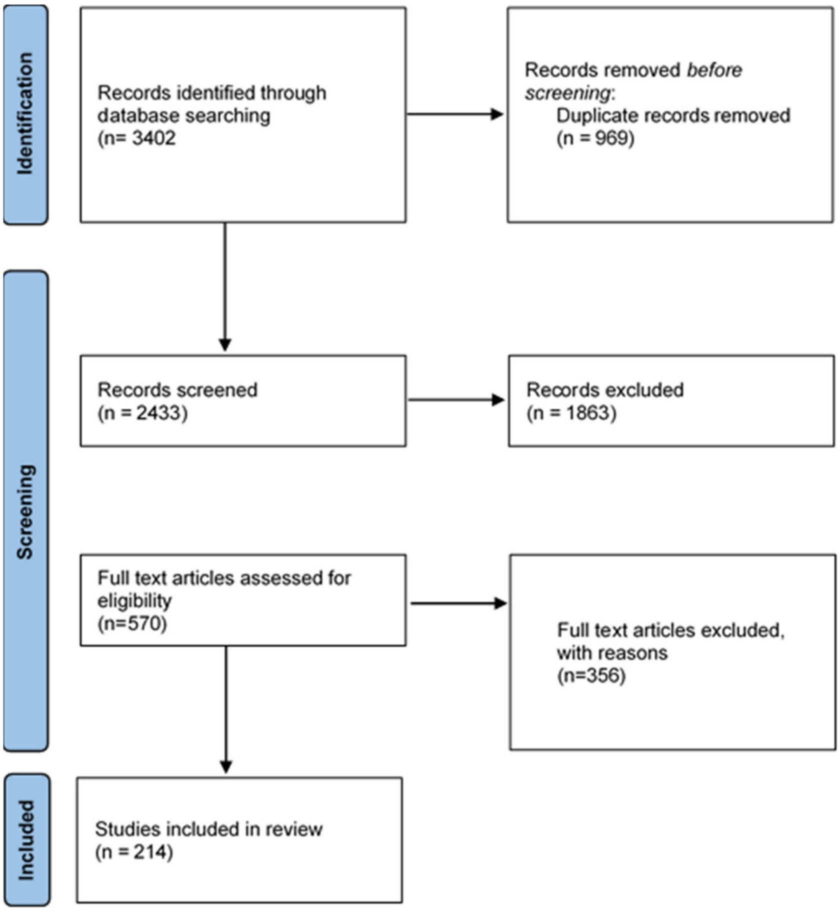

Figure 1. Flow diagram presenting the search strategies used, based on the PRISMA statement reporting guidelines for systematic literature reviews [29].

3.1. Study Sites

Of the 214 papers that were included for review, 82 studies were from Europe, 66 were from North America, 43 were from Asia, 11 were from Africa, 7 were from Oceania, and 2 were from South America (Figure 2, Table S1). A total of 3 studies investigated the residential drinking water from two or more countries from different continents [30–32]. A total of 191 studies sampled water from private houses, 7 from residential drinking water distribution systems (DWDS), 1 from an accommodation site, 1 from an apartment building, and 1 from a dormitory (Table S1). A total of 12 studies sampled from two or more sites that included both private houses and public or healthcare facilities, such as retirement homes, hotels, universities, commercial buildings, and schools [9,33–43]. OPPPs were found in taps and tap components, such as: handles and aerators (103 studies); shower and shower components, such as shower heads and hoses (62 papers); potable water samples (51 studies); hot-water systems (16 studies); drain holes (16 studies); baths (15 studies); water storage (6 studies); ice and ice machines (3 studies); rainwater (3 studies); sink surfaces and U bends (3 studies); cooling towers (2 studies); private wells (2 studies); biofilm (1 study); a building inlet (1 study); a garden hose (1 study); a garden sprinkler (1 study); a washing machine (1 study); a water meter (1 study); and a water purifier (1 study) (Table S1).

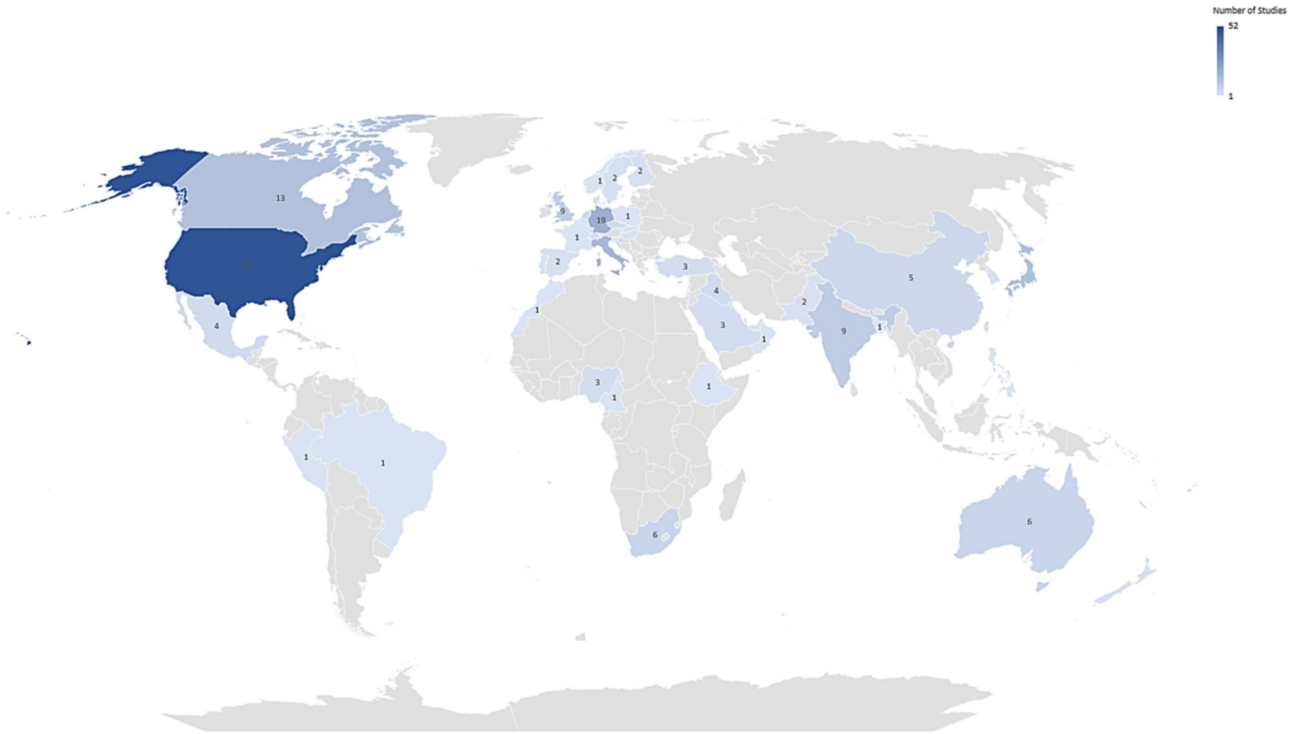

Figure 2. Map displaying the global distribution of all studies reporting the presence of one or more opportunistic premise plumbing pathogens in residential properties. Number of studies conducted in each country is indicated by colour intensity. Colour intensity increases as the number of studies increases.

3.2. Pathogens Identified and Prevalence

A total of 149 studies detected OPPPs solely from potable water samples, 27 from only biofilm samples, and 17 from both water and biofilm samples. A total of 70 studies reported the concentration of one or more OPPPs in potable water, and 12 studies reported the concentration of OPPPs in biofilm samples (Table 2). A total of 21 studies identified OPPPs within environmental samples; however, they did not report the prevalence from potable water or biofilm samples, specifically. A total of 8 studies isolated OPPPs from private well-water sources, and 3 studies found higher rates of contamination in well water when compared to municipal water [44–51].

A total of 64 studies identified bacterial species other than the designated OPPPs, such as *Achromobacter* spp., *Agrobacterium* spp., *Alcaligenes* spp., *Bacillus* spp., *Bosea* spp., *Brevibacillus* spp., *Brevundimonas* spp., *Campylobacter* spp., *Chlamydiales* spp., *Chromobacterium* spp., *Desulfovbrio* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Flavobacterium* spp., *Gallionella* spp., *Klebsiella* spp., *Kocuria* spp., *L. monocytogenes*., *Lysobacter* spp., *Microbacterium* spp., *Micrococcus* spp., *Moraxella* spp., *Nocardia* spp., *Paenibacillus* spp., *Pasteirella* spp., *Plesiomonas* spp., *Polaromonas* spp., *Rhodococcus* spp., *Salmonella* spp., *Serratia* spp., *Shigella* spp., *Staphylococcus* spp., *Streptococcus* spp., *Sulfuricurvum* spp., *Tatumella* spp., *V. cholerae*., *Xenophilus* spp., and *Yersinia* spp. (Table S1).

A total of 30 studies investigated clinical cases where the infection was linked to contaminated residential drinking water (Table S1). These included: 20 papers that investigated *Legionella* spp. infection; 7 papers that investigated *Mycobacterium* spp. infection; 2 papers that investigated *Pseudomonas* spp. infection; and 1 paper that investigated a case of *Aeromonas* spp. infection. All of the cases of *Legionella* spp. and *Mycobacterium* spp. were respiratory infections, and there were investigations of enteric and bacteraemia *Aeromonas* spp. infections, respectively, and one investigation of a dermal *Pseudomonas* spp. infection. An epidemiological investigation in response to a community-acquired Legionnaires' disease case found that the patient did not have their hot water tanks sustained above the recommended 60 °C temperature [52]. *Pseudomonas* spp. caused an estimated 15,000 pneumonia hospitalisations and 730 deaths in the US in 2014 [3]. However, only two studies that are included in this review investigated and identified the patients' residences as the sources of infection.

Table 2. Summary of reported prevalence and concentrations of opportunistic premise plumbing pathogens detected in residential drinking water infrastructure.

Opportunistic Premise Plumbing Pathogen	**Number of Studies**	**Clinical Case Investigations**	**Prevalence and Pathogen Concentration**	
			Drinking Water	**Biofilm**
Legionella spp.	93	20	2.4 to 86.7% (1 to 10^6 CFU/mL)	1.1 to 100% (5.4×10^2 to 28.6×10^3 CFU/swab)
Mycobacterium spp.	60	7	0.6 to 100% (1 to 1.7×10^4 CFU/mL)	2.5 to 100% ($<10^1$ to 10^7 cells/cm^2)
Pseudomonas spp.	60	2	7.14 to 100% (1 to 640 CFU/mL)	1.2 to 100% in biofilm samples (1×10^2 to 1.5×10^5 CFU/swab)
Aeromonas spp.	20	1	0.7 to 32.4% (5 to 333.3 CFU/mL)	3.9 to 77.5% (concentrations not reported)
Acinetobacter spp.	14	0	4.4 to 80% (concentrations not reported)	1.6 to 2.2% (concentrations not reported)
Stenotrophomonas spp.	8	0	1.5 to 100% (concentrations not reported)	11 to 100% (concentrations not reported)
Methylobacterium spp.	7	0	12 and 46% (concentrations not reported)	46% (>10 CFU/mL)
Helicobacter spp.	5	0	7 to 12% (concentrations not reported)	N/A

3.3. Antimicrobial Resistance

Several antimicrobial-resistant (AMR) OPPP strains were identified by the studies that were included for review. Nine studies performed disc diffusion tests following the European Committee on Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute Guidelines [38,49,50,53–58]. Two studies performed broth microdilution [59,60], two studies used VITEK-2 ID cards (bioMérieux, Marcy l'Etoile, France) [61,62], two studies identified antibiotic-resistant genes [63,64], and three studies did not specify which method they employed [65–67]. Antimicrobial-resistant *Pseudomonas* spp. was detected in nine studies, most commonly from taps (four studies), water (two studies), showers (one study), and a private well (one study) [38,49,50,53,56,58,61,63,66]. Six of these studies found *Pseudomonas* spp. strains that were resistant to two or more of the antibiotics tested, with two of these studies reporting isolates resistant to five or more antibiotics, such as the antibiotic combination, amoxicillin/clavulanic acid, and the broad-spectrum antibiotic, chloramphenicol. An antibiotic-resistant gene that was carrying fragments identified in *P. aeruginosa* isolated from residential drinking water was found to carry the *aph*(3′)-I determinant, which encodes resistance to aminoglycoside antibiotics, such as kanamycin and neomycin [63].

Four studies reported AMR *Aeromonas* spp., with the highest resistance to the broad-spectrum β-lactam antibiotic, ampicillin, compared to the other antibiotics tested [55,57,62,65]. A shower and a bath were linked to cases of clinical AMR *P. aeruginosa* and *M. avium* infection, respectively; however, the specific AMR profiles were not described [66,67]. AMR *Acinetobacter* spp., *L. pneumophila*, and *S. maltophila* were identified in one study [49,54,61,67]. Two studies identified multiple AMR OPPPs; however, it is unclear which antibiotics each isolate was resistant to, as the results were presented as the total resistance [59,64]. The antibiotic resistance genes, *bla* CMY-2, *bla* ACT/MIR and *bla* OXA-48, were identified in shower-drain biofilm samples that contained the OPPPs: *P. aeruginosa*, *S. maltophila*, *A. lwoffii*, and *A. hydrophila* [64].

The total chlorine levels were found to be below the regulatory values in several studies that were included for review, including all of the residential drinking water samples taken from the Limassol DWDS, which returned residual chlorine levels below the assay detection limit (0.01 mg/L) [68,69]. *Legionella* spp. was found to persist in contaminated water-related devices, despite repeated hyperchlorination at 50 mg/L [70]. Attempts to reduce *Pseudomonas* spp. and *Acinetobacter* spp. contamination on a water filtration unit by using household bleach and chlorine was unsuccessful, and re-emergence was seen after a few days [71].

3.4. Detection Methods

There was significant variation in the methods that were used to detect the target OPPPs from environmental water samples (Table S1). Culture was the most used isolation technique (162 studies). Specifically, 71 studies performed membrane filtration followed by the inoculation of selective broth or agar. A total of 11 studies enriched the environmental sample by inoculating broth followed by subculture on selective agar (Table S1). Of the papers that investigated *Pseudomonas* spp., a variety of selective media were used for isolation, such as blood, MacConkey, cetrimide, Sabouraud dextrose, m-PAC, phenol red, MPA, NAC, and R2A. Middlebrook 7H10 agar was the most commonly used selective agar for the isolation of *Mycobacterium* spp.; however, other selective media were used, such as: Lowenstein–Jensen slopes (eight studies) [72–79]; Ogawa media (four studies) [37,73,78,79]; Herrolds egg yolk (one study) [80]; modified Stonebrink (one study) [80]; and R2A agar (two studies) [81,82]. *Aeromonas* spp. was inconsistently cultured on a variety of media, such as blood, nutrient, IBB, ampicillin-dextrose, MacConkey, Aeromonas, phenol red, Xylose deoxycholate citrate, m-endo, and eosin methylene blue agar. *Helicobacter* spp. was isolated by culture on blood agar (two studies) [42,83], and on HP medium (one study) [84]. A total of 14 studies referenced specific International Organization for Standardization protocols, most commonly, ISO 11731—Water quality enumeration of *Legionella* (11 studies) [58,85–95]. Molecular techniques, such as PCR, FISH, whole genome sequencing, and 16S RNA sequencing, were used in 34 studies (Table S1). A combination of culture and molecular techniques for OPPP detection was used in 16 studies. Nine of these studies investigated the presence of *Legionella* spp. in viable, and in viable but nonculturable, states (VBNC) (Table S1). Three studies that were conducted in response to clinical cases did not specify the methods that were used for the OPPP bacterial detection [32,96,97].

4. Discussion

The designation of a bacterial species as an OPPP is an arbitrary classification that is based on the presence of the shared characteristics that increase their growth and proliferation in drinking water and premise plumbing. These include features such as disinfectant resistance, biofilm formation, amoeba resistance, and growth under low-nutrient conditions [7]. The classification of OPPPs has expanded beyond the model organisms, *Legionella* spp., *Pseudomonas* spp., and *Mycobacterium* spp., to include species such as *A. baumannii*, *A. hydrophila*, *H. pylori*, *Methylobacterium* spp., and *S. maltophila*, in response to epidemiological studies [8]. These additional waterborne pathogens have been highlighted, as they meet the previously described arbitrary characteristics and they have been found at numerous points throughout plumbing infrastructure [36,44,98,99]. However, the focus on the ability of a pathogen to grow ubiquitously, from the treatment facility through to the point of consumption, has overlooked numerous clinically relevant species.

Several WHO-designated critical and high-priority pathogens, including *Enterobacter* spp., *Klebsiella pneumoniae*, and *Staphylococcus aureus*, were identified, along with the OPPPs that are included in this review, with frequencies of up to 83, 33, and 70%, respectively (Table S1). Studies have shown that it is not only possible for these pathogens to contaminate water-related devices, such as shower heads, tap faucets, and drains, but these contaminated sources can also be responsible for HAI outbreaks [23,100–102]. *S. aureus* is commonly omitted from consideration as an OPPP, as it is more often associated with surfaces such as light switches and doorknobs, despite possessing many OPPP characteristics. Clinical and environmental *S. aureus* isolates have demonstrated strong biofilm formation, particularly under disinfectant stress [103,104], as well as resistance to chlorine compounds [105,106], survival under multiple nutrient-limiting conditions in high cell densities [107,108], and proliferation in *Acanthamoeba polyphaga* [109]. Source-water and distribution-system tracking will likely miss the presence of these human flora pathogens, as it has been suggested that the contamination is likely to be occurring at the point of use via contaminated users and via cross-contamination from the surrounding environmental surfaces [33,62]. One study that investigated the microbiological diversity of domestic and food service business ice cubes found 31 different species dominated by the OPPPs, *Acinetobacter* spp. and *Pseudomonas* spp., in addition to pathogenic *Staphylococcus* spp. and *Bacillus* spp. [110]. Complex biofilm communities can confer protection to pathogenic species that are not ideally adapted to the premise plumbing environment. A study that investigated the microbial quality of an urban DWDS in Cyprus found that 85% of the drinking water samples were contaminated with one or more genera of bacteria, including *Pseudomonas* spp., *Staphylococcus* spp., *Bacillus* spp., *Acinetobacter* spp., *Enterococcus* spp., *Enterobacter* spp., and *Aeromonas* spp. [68]. These highly heterogeneous communities promote the transfer of AMR via horizontal gene transfer and/or vertical transmission [27,111]. When considering future drinking water disinfection protocols and infection control guidelines, it is essential to understand how different environmental niches may be favorable to different pathogens.

4.1. Control of Opportunistic Premise Plumbing Pathogens

A multibarrier approach has been suggested as the most effective approach to control the growth and proliferation of OPPPs. This risk-based approach allows for the failure of one barrier to be compensated for by the effective maintenance of the additional barriers [112]. The barriers that are used in the production of safe drinking water include the protection of the source water, the maintenance of the infrastructure, filtration, and disinfection [113]. However, the biological stability of drinking water is dynamic, and it can be affected by variables such as the nutrient availability, the disinfectant selective pressure, and the temperature, which are unique to each distribution system. The identification of the barriers where interventions can be applied is a prerequisite for this approach. The singular, complex, and diverse nature of building water system environments may compromise the successful implementation of strategies that are aimed at reducing the microbial load [6]. Reducing the levels of biodegradable organic matter and the assimilable organic carbon in drinking water prior to distribution has been shown to reduce biofilm formation and growth in premise plumbing [114]. Ironically, disinfection agents such as monochloramine and chlorine, which are aimed at reducing the microbial load, may cause an increase in the assimilable organic carbon because of the oxidation of organic carbon, which results in the potential re-growth of the microorganisms in DWDSs [114,115]. It is essential to monitor the microbial, engineering, and chemical parameters of drinking water on a routine and high-frequency basis throughout the distribution system in order to validate the efficacy of the current barriers, particularly at the point of use. If these barriers are found to be inadequate, additional stages of disinfection, or a re-evaluation of the identified barriers, can be instigated by water utilities and homeowners in order to minimise the uncontrolled growth of OPPPs.

Current drinking water treatment principles are tailored to waterborne pathogens that primarily originate from human and animal faecal contamination. Disease from these organisms is generally contracted via ingestion. However, the diseases with the largest numbers of deaths attributed to waterborne transmission in the US were infections with non-tuberculous mycobacteria, *Pseudomonas* spp., and Legionnaires' disease [3]. In the majority of these cases, ingestion is not the route of infection. OPPPs are characterised by their resistance to commonly used disinfectants, such as chlorine. When primary disinfection strategies are developed for faecal indicator bacteria, the premise plumbing environment will select for the dominance of disinfectant-resistant pathogens [8]. Consequently, these strategies may select for diseases that are acquired by means other than the faecal–oral route. The US EPA National Primary Drinking Water Regulations state that chloramines (4 mg/L), chlorine (4 mg/L), and chlorine dioxide (0.8 mg/L) are added to drinking water to control microorganisms. The WHO reviewed the national drinking water quality guidelines of 104 countries and found that 66 countries had set regulatory values for the chlorine in the municipal drinking water. This value ranged from 0.1 to 5 mg/L, and it was not always clear if this value referred to the free or total chlorine [116]. As a consequence of this variation, in addition to other environmental variables, such as climate, the persistence of OPPPs in DWDSs, and the subsequent risk of infection, will differ between counties. It is difficult to maintain disinfectant residual throughout the distribution system because of the reactions with dissolved nutrients, secreted protective exopolysaccharides, and sediments. Water utility companies are responsible for managing the water treatment throughout the distribution network, to the property meter. Once the water enters a premises, the water quality is the responsibility of the property owner. Larger commercial buildings, such as hospitals, may opt to conduct additional onsite water treatment to manage waterborne healthcare-acquired infections; however, this rarely happens in residential properties [113]. Often, residential homeowners are not aware of the water quality changes that may occur from the water meter to their tap, or of the infrastructure that may be contributing to these changes. When present in premise plumbing biofilms, OPPPs may become more tolerant to disinfection methods. Not all OPPPs are resistant to the same levels of residual disinfection, and the maintenance of a residual level that is high enough to control highly resistant pathogens, such as *Mycobacterium* spp. and *Legionella* spp., would be problematic. Factors such as water stagnation, temperature fluctuations, and the physical integrity of premise plumbing infrastructure can influence the efficacies of residual disinfectants. Sublethal concentrations of disinfectants such as chlorine may reduce the population diversity and select for the growth of disinfectant-resistant OPPPs [7].

The maintenance of the water temperature has been highlighted in global drinking water guidelines as a factor that can be manipulated to minimise pathogen growth. The WHO guidelines recommend that cold water be stored below 20 °C, and that hot water be stored above 60 °C [117]. However, both hot- and cold-water temperatures can be difficult to maintain during seasonal changes, and in large or old buildings. For example, the larger building sizes in Flint, Michigan, have been linked to higher levels of recoverable *Legionella* spp., when compared to single-story buildings, because of the zones of warm stagnant water that are favourable to bacterial growth [118]. Once pathogens have colonised premise plumbing, and particularly when they are present as a biofilm, hot-water flushing may be rendered ineffective. *L. pneumophila* was isolated from the bathroom and kitchen hot-water taps of a 1972 apartment after a case of potentially domestically acquired Legionnaires' disease was reported in a one-week-old newborn. Epidemiological investigations found that the water leaving and returning to the heat exchanger was below the recommended hot-water temperatures of 53 and 40 °C, respectively. The hot-water temperatures were subsequently increased, and no *Legionella* spp. were detected from the water leaving the hot-water exchanger. However, *Legionella* spp. were still detected in the hot water returning to the heat exchanger, which indicates the colonisation of the plumbing infrastructure [119]. The heating element of an electrically heated water-storage tank is suspended in the water, and does not reach any sediment at the bottom of the tank that is likely to harbor OPPPs [120]. Instantaneous hot-water systems have been suggested as an appropriate alternative to continuous-flow or water-storage tanks to minimise the amount of warm water that remains stagnant in residential properties [121].

Point-of-use (POU) filters have been suggested as a method to reduce the exposure to OPPPs from a contaminated water source or device [122]. These POU filters may be used in conjunction with point-of-entry filters, which can be installed at the properties main water intake in order to address the water quality degradation from the municipal

DWDS [123]. This intervention has been effective in healthcare settings at eradicating *Legionella* spp. and *P. aeruginosa*, and it has resulted in the elimination of infection [124,125]. A cost–benefit assessment estimated that the installation of POU devices as the final stage of water treatment could prevent 3.4 million cases of disease and mortality due to waterborne pathogens, which would result in USD 1814 of averted costs per disease case [126]. As with other barriers, the maintenance of POU filters is critical. Bacterial numbers may amplify in the POU filter if they are not maintained, and if it is not operated properly [127]. Biofilms on plumbing fixtures, such as tap faucets and shower heads, provide a source of nutrients and protection for pathogens, such as *S. aureus* and *A. baumannii*, which can disseminate AMR. Cross-contamination between the kitchen environment and water-related devices during inappropriate cleaning practices has been identified as a source of bacterial transmission [128]. Beta-lactam resistant genes were detected in *S. maltophila* and *P. aeruginosa* shower-drain isolates [64]. This colonisation may occur if an individual is a carrier of the antimicrobial-resistant infection, and it is of particular concern when considering the colonisation of shared plumbing fixtures. Significant growth of *P. aeruginosa* was found in a nursing home whirlpool bath after a resident with a known *P. aeruginosa* toe infection used the shared facility daily along with other residents, irrespective of incontinence, infection, or skin problems [129]. Carbapenem-resistant OPPPs, such as *Acinetobacter* spp. and *P. aeruginosa*, have been identified as antibiotic-resistant threats by the CDC, and have resulted in 41,100 infections and 3400 deaths, combined, in 2017 [130]. If installed and maintained properly, POU filters may be an appropriate and affordable additional protection barrier for the increasing vulnerable population receiving healthcare at home [131].

The growth of OPPPs in drinking water and water-related devices may be unavoidable, but their impact is manageable. Although OPPPs are identified on the basis of their shared characteristics, they are members of widely different taxonomic groups and, therefore, they react to prevention measures differently. The current drinking water guidelines must acknowledge the growing complexity of plumbing infrastructure and the limitations of disinfection procedures on dynamic bacterial communities. It is not sufficient to rely solely on the water industry to provide and maintain safe drinking water, from treatment to the point of use. Additional preventative measures should be considered on an individual basis for people who are considered to be at particular risk of developing a waterborne HAI, such as the elderly, infants, and those with weakened immune systems [50,132].

4.2. Pathogen Detection from Environmental Sources

Culture-based methods for the detection of indicator bacteria have long been held as the "gold standard", as they detect viable target organisms. However, an examination of the full spectrum of potentially pathogenic microorganisms is not a feasible part of routine monitoring protocols [24]. The number of pathogens that are targeted by culture-based epidemiological studies is limited by the selective media that are chosen prior to sampling, and by the time that is required to handle the samples. One of the defining characteristics of an OPPP is its ability to adapt and proliferate in nutrient-poor environments, which often results in slowed growth rates, or the conversion to a VBNC state [12]. For example, OPPPs such as *Legionella* spp., *Mycobacterium* spp., and *Methylobacterium* spp. may take up to 14 days before the first appearance of colonies on agar [7]. Nutrient-rich selective agars and pretreatment steps, such as heating or acidification, are typically used to combat competitive overgrowth by faster-growing organisms [133]. These selective media have some drawbacks, as they may inhibit or restrict the growth of the target organisms, and they may also induce the VBNC state [12].

Challenges may arise when trying to enumerate VBNC bacteria by using culture-based methods [134–137]. VBNC bacteria are stressed or injured cells that are characterised by their lack of proliferation on agar, which leads to an underestimation of the viable cells in a sample. Although they are difficult to enumerate on routine agar, VBNC cells are not considered dead, as they have an intact membrane, contain undamaged genetic material, and are metabolically active. Nutrient-depleted media, such as R2A agar, have been recommended to enhance the recovery of environmental waterborne pathogens [138]. The growth of OPPPs on selective media was used by 162 studies in this review, which included 11 different types of media for *Pseudomonas* spp. International standard methods have been published for the enumeration of the OPPPs, *L. pneumophila* and *P. aeruginosa*, from environmental water samples [139,140]. Only 15 and 3% of the studies that have investigated the presence of *Legionella* spp. and *Pseudomonas* spp., respectively, have referenced the ISO protocols. The US Environmental Protection Agency recommends ISO 11731 and the CDC standard culture methods to monitor the presence of *Legionella* spp. in premise plumbing. It is valuable to maintain consistent sampling and testing protocols in order to understand and implement effective risk-assessment protocols. To date, such international standards have not been published for the enumeration of the OPPPs, *Acinetobacter* spp., *Aeromonas* spp., *Helicobacter* spp., *Methylobacterium* spp., *Mycobacterium* spp., and *Stenotrophomonas* spp. from environmental water samples. This lack of standardisation has resulted in significant variation between the sampling techniques and the enumeration protocols that were employed by the studies that are included in this review.

Several nucleic acid and immunology-based protocols have been developed to address the limitations that are associated with the traditional culture-dependent methods. These include techniques such as polymerase chain reaction (PCR), microarrays, and fluorescence in situ hybridisation (FISH) [141–143]. The CDC have recommended PCR methods for routine *Legionella* spp. testing in conjunction with spread plate culture techniques. Similar to many OPPPs, *Legionella* spp. have been shown to replicate intracellularly within macrophagic hosts, which results in a thickened outer membrane, greater resistance to environmental stress, and the ability to readily enter a VBNC state. Seven of the studies that were included in this review used both culture and PCR methods for the detection of *Legionella* spp. (Table S1). Although PCR techniques are considered to be more sensitive than culture-based techniques, the commonly used protocols do not distinguish between the DNA from viable, injured, or dead cells that persists in the environment, which may contribute to the overestimation of pathogens in a sample [144]. Propidium monoazide (PMA) quantitative PCR is a practical alternative that can differentiate between live, dead, and membrane-damaged cells. PMA is an intercalating molecule that selectively binds to the DNA of viable and membrane-damaged cells. This bond inhibits the PCR amplification of dead bacterial DNA, thereby reducing the likelihood of false positive results and the overestimation of the pathogen concentration [145]. Alternative techniques, such as FISH, have been proposed to bridge the gap between the underestimation of contamination by culture, and the potential overestimation by PCR [146]. Buchbinder et al. (2002) compared the specificity and sensitivity of culture, PCR, and FISH for the detection of *Legionella* spp. in residential drinking water [147]. It was found that, although PCR was significantly more sensitive than FISH, FISH was more specific (72%, compared to 47% for PCR). It was suggested that, because the FISH assay was able to detect VBNC cells, it is potentially a better alternative than PCR for future routine testing protocols. However, this approach is limited by the high costs that are associated with the user training, the protocol optimization, and the need for high pathogen densities that may not be present in many environmental samples [148].

4.3. Epidemiological Investigations

There are several drinking water quality guidelines that are referenced globally, such as the US EPA Safe Water Drinking Act, the EU Drinking Water Directive, and the WHO Guidelines for Drinking Water Quality [117,149,150]. These guidelines suggest that the testing for microbial and chemical contaminants should be used as an indication of the water quality. Countries such as Japan, Singapore, Malaysia, Australia, and South Africa have cited these guidelines when developing national drinking water quality standards [151]. The US EPA's revised total coliform rule was released to identify and reduce the potential pathways for faecal DWDS contamination. This rule states that total coliform samples must be collected at sites throughout the DWDS. The frequency of routine sampling is dependent on the number of people that are served by the public water system, and on the type of contaminant that is being tested. This is supported by the WHO Guidelines for Drinking Water Quality, which state that the drinking water legislation should be informed by system-specific risk assessments. For example, Singapore relies heavily on reservoir water as a source of drinking water and recreational use, which has resulted in 28 waterborne microbial indicators that are used in the monitoring of the water quality [151]. The drinking water infrastructure in many African countries is struggling to keep up with the increasing population and urbanisation, which may lead to water shortages and contamination. This significant threat to public health is exacerbated by the fact that there are currently no water quality guidelines for many of these countries [151]. The water quality testing within private residences is not routinely performed by water service providers. However, if a residence is supplied by a private water supply, such as well water or rainwater, the US EPA recommends regular testing by a certified laboratory. Legionnaires' disease is the only OPPP-caused disease that is on the national notifiable diseases register in the US, Australia, Hong Kong, the Netherlands, and the United Kingdom [152]. Many countries, including China, India, and Malaysia, do not have any OPPP-related diseases in their national infectious disease surveillance systems [153]. Only 30 studies that are included in this review were linked to clinical cases of infection, despite the US CDC estimating that approx. 96,000 waterborne respiratory illnesses were acquired domestically [3] (Table S1). Dose and exposure response models are an essential aspect to quantifying the human health risks of a pathogen, and they can be used to inform future regulatory policies [154]. Of the reviewed studies that investigated clinical infection, only 13 reported the concentration of the pathogen found at the exposure site, including 12 studies reporting *Legionella* spp. infection, and only 1 study reporting *Mycobacterium* spp. infection [52,70,155–165]. These cases of clinical infection are typically only published as case reports because of the unique nature of the cases, which include persistent re-infection, antimicrobial resistance, or a unique patient demographic. Risk-based modelling has been conducted on many OPPPs in the past, and, for the most part, the key exposure pathways, such as water aspiration, have not been considered and will continue to be overlooked by the water quality guidelines until there is more consistent published data [166–168].

5. Conclusions

Residential drinking water and water-related devices have been neglected as sources of OPPP infection in national drinking water and infection control guidelines. Although some potential OPPPs may not be as ubiquitous in premise plumbing as the model waterborne pathogens, their presence at point-of-use outlets presents a significant infection risk that must not be underestimated by the infection control and prevention guidelines. This review examined previously defined OPPPs in residential plumbing; however, it was also found that many of these studies identified pathogens such as *Staphylococcus* spp. and *Enterobacter* spp., which do not meet the current definition, but which have been linked to clinical infection that resulted from contaminated plumbing infrastructure. The tailoring of the currently ineffective water quality treatment plans to address the growth of the identified waterborne pathogens is essential in order to provide safe drinking water throughout the entire distribution system. Water utility providers must consider the potential selective impacts that these measures may have on other clinically relevant species that can adapt to high-stress environments, and this may lead to a change in the current OPPP definition. Effective and reproducible microbial water quality surveillance protocols are essential to understanding the risk factors, monitoring the chemical and biological stability of the drinking water, and, therefore, to predicting and preventing future public health threats. Relying on a single water quality control measure to consistently reduce the total microbial load of the drinking water may be ineffective against diverse OPPPs. Despite the literature, which clearly identifies residential plumbing infrastructure as a consistent reservoir for OPPPs, these sources continue to be overlooked as public health risks to vulnerable populations that receive healthcare at home. This is reflected by the limited information that is provided by many of the infection control guidelines [116,117,169,170]. The growth of bacterial pathogens in premise plumbing may be unavoidable; however, it can be managed with an appropriate multibarrier approach that minimises disinfectant resistance, reservoirs, biofilm formation, and thermotolerance. Comprehensive and consistent epidemiological investigations of suspected domestically acquired OPPP infections are essential to the development of quantitative microbial risk-assessment models, and to informing the infection control and prevention guidelines, which are lagging behind the demand for at-home healthcare services.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/w14071129/s1: Table S1: Summary of reports and studies identifying opportunistic premise pluming pathogens in residential drinking water systems. References [9,30–110,119–121,124,127,128,132,136,141,147,155–165,171–291] are cited in the Supplementary Materials.

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