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Review

Moving from the traditional paradigm of pathogen inactivation to controlling antibiotic resistance in water - Role of ultraviolet irradiation

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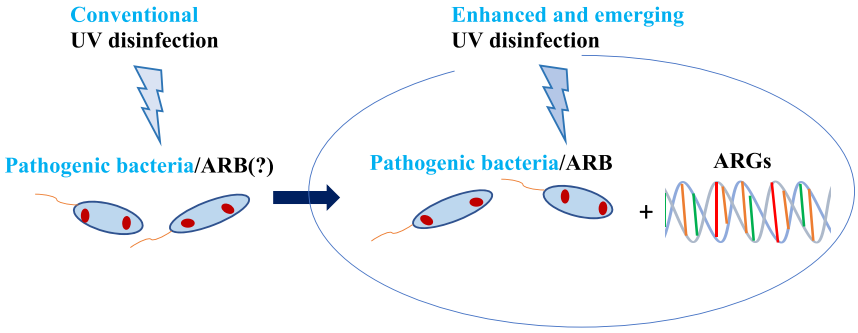
HIGHLIGHTS

- Change in perspective on UV disinfection to include control of antibiotic resistance
- Unique features of UV-LEDs are discussed for their potential to control antibiotic resistance.
- Disinfection using UV lamps provides important insights into future needs/challenges.
- Direct comparison is needed between UV-LEDs for different ARB and ARGs inactivation.

GRAPHICAL ABSTRACT



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ABSTRACT

Ultraviolet (UV) irradiation has proven an effective tool for inactivating microorganisms in water. There is, however, a need to look at disinfection from a different perspective because microbial inactivation alone may not be sufficient to ensure the microbiological safety of the treated water since pathogenic genes may still be present, even after disinfection. Antibiotic resistance genes (ARGs) are of a particular concern since they enable microorganisms to become resistant to antibiotics. UV irradiation has been widely used for disinfection and more recently for destroying ARGs. While UV lamps remain the principal technology to achieve this objective, UV light emitting diodes (UV-LEDs) are novel sources of UV irradiation and have increasingly been reported in lab-scale investigations as a potential alternative. This review discusses the current state of the applications of UV technology for controlling antibiotic resistance during water and wastewater treatment. Since UV-LEDs possess several attractive advantages over conventional UV lamps, the impact of UV-LED characteristics (single vs combined wavelengths, and operational parameters such as periodic or pulsed and continuous irradiation, pulse repetition frequencies, duty cycle), type of organism, and fluence response, are critically reviewed with a view to highlighting the research needs for addressing future disinfection challenges. The energy efficiency of the reported UV processes is also evaluated with a focus on relating the findings to disinfection efficacy. The greater experience with UV lamps could be useful for investigating UV-LEDs for similar applications (i.e., antibiotic resistance control), and hence identification of future research directions.

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Contents

1. Introduction

The application of ultraviolet (UV) light technology in water and wastewater treatment over recent decades has increased significantly and continues to grow in two broad areas: disinfection (including antibiotic resistant bacteria (ARB) and genes (ARGs)), and oxidation of organic contaminants. Traditional UV-driven processes using mercury lamps are well established and there are several full-scale applications around the globe (Dotson et al., 2010; van der Hoek et al., 2014). The ability to achieve disinfection without the need for chemicals and negligible formation of disinfection by-products (DBPs) are some of their major advantages over chlorine, the most widely used disinfectant (Mori et al., 2007). However, the sustainability of UV technology in terms of energy consumption remains one of the major drawbacks. Furthermore, the fragility of UV lamps, their short lifespan, use of mercury and thus problematic disposal after use, and high heat output needing large cooling facilities, are some of the limitations of the conventional UV lamps.

With increasing applications of UV radiation in water and wastewater treatment, there is potential for the use of more sustainable UV light sources. UV light emitting diodes (UV-LEDs) have emerged as a most promising new UV light source in the past decade since they have longer life, are less fragile, and are free of toxic components such as mercury. An increasing number of lab-scale investigations utilising UV-LEDs for disinfection has been reported over recent years. One of their advantages is the ability to generate UV radiation at specific wavelengths which could be exploited to improve treatment efficiency by designing treatment systems for specific applications. Using combinations of wavelengths can lead to additive and potentially synergistic impact and therefore increased efficiency of disinfection.

Understandably, the well-established UV lamp disinfection technology provided the basis for the first applications of UV-LEDs reported by Crawford et al. (2005) who investigated the inactivation of *E. coli* using 270–295 nm UV-LEDs. Drawing on a significant number of investigations into the disinfection efficiency of UV-LEDs since 2005 commercial application of UV-LEDs for water disinfection has now commenced (METAWATER, 2017). A summary of the application of UV-LEDs for water disinfection is provided by Song et al. (2016).

Conventional water disinfection is primarily designed to kill or inactivate pathogens and regulations are based on requiring certain extents of log inactivation that may vary for different species and strains of microorganisms. Recently, the need for a shift in approach from conventional pathogenic inactivation to destroying the genes, particularly those that confer antibiotic resistance to bacteria, has been highlighted in several investigations (Chang et al., 2017; McKinney and Pruden, 2012). Antibiotic resistance is the ability of bacteria to survive, and even thrive, in the presence of antibiotics (Pruden, 2014). Extensive use of antibiotics for human and animal health, and to promote growth in animals, has accelerated the process of antibiotic resistance which could limit the ability to treat common infectious diseases (WHO, 2018). UV irradiation is one of the most promising technologies for addressing this emerging threat of antibiotic resistance, which involves inactivation of ARB and ARGs, and has been increasingly reported in recent years in applications using UV lamps.

UV-LEDs, although yet to be investigated for the purpose of ARGs inactivation, have been widely reported for conventional disinfection applications. Therefore, findings related to their special features are reviewed and discussed to: (1) summarise the progress of their applications over the past decade, and (2) to highlight their potential advantages and the implications for future applications for controlling antibiotic resistance. In particular, the impact of the specific characteristics of UV-LEDs such as variable wavelengths, capacity for pulse and continuous irradiation and duty cycle are discussed with regard to their impact on disinfection and repair of microorganisms. In addition to UV photolysis, there are emerging applications of advanced oxidation processes (AOPs) for the inactivation of ARB and ARGs by using UV lamp-based systems. Due to the increasing applications of conventional UV lamp systems for controlling antibiotic resistance, reported findings are reviewed with the aim of identifying their shared characteristics with UV-LEDs for similar applications. Moreover, energy efficiency for inactivation of various microorganisms using different wavelength UV-LEDs is discussed. Although a direct comparison between the energy efficiency of UV-LEDs and LP mercury lamps is not appropriate, a brief overview of the findings of relevant studies is provided to relate them to the differences in the state-of-the-art. Research gaps related to the application of UV technology using UV lamps and UV-LEDs for controlling antibiotic resistance are highlighted and recommendations for future work are made.

2. UV-based treatments

UV irradiation alone and in combination with several oxidants (as AOPs) has been used for the disinfection of water. In this section, we provide a brief explanation of the mechanism of UV photolysis, followed

by an introduction to different AOPs and their mechanisms, their advantages and limitations, and figures-of-merit for estimating energy efficiency of UV-based processes.

2.1. Mechanisms of UV disinfection

UV irradiation is traditionally divided into four regions: UVA (315–400 nm), UVB (280–315 nm), UVC (200–280 nm) and vacuum UV (VUV, 100–200 nm) (Oppenländer, 2007; Phillips, 1983). UVC irradiation has been used widely as a primary disinfectant in drinking water and wastewater treatment to achieve effective inactivation of a variety of pathogenic microorganisms including bacteria, viruses, and protozoa (Morita et al., 2002), and to avoid the production of disinfection by-products (DBPs) (Linden et al., 2002). The most effective germicidal wavelengths depend on the species of microorganisms and predominantly range between 260 and 280 nm (Kalisvaart, 2004). A significant amount of research has been carried out in this range since protein has a major peak at 280 nm whereas DNA has a peak on the UV absorption curve at 260 nm (Kalisvaart, 2004). However, several studies have used higher wavelengths (i.e., >280 nm) at which the generation of UV irradiation is cheaper compared with the lower UV-LED wavelengths (i.e., 254–280 nm).

The mechanisms of the inactivation of microorganisms by UV are dependent on the irradiation wavelength. For example, the absorption of UV irradiation by DNA results in photochemical changes leading to inactivation of microorganisms by affecting their ability to replicate (Dotson et al., 2012). UVC radiation is of particular interest since it induces a direct germicidal effect by causing the formation of cyclobutane pyrimidine dimers (CPDs), a major photoproduct, in the DNA (Hamamoto et al., 2007). Other lesions such as 6–4 photoproducts (about 10% of CPD) and their Dewar isomers are also formed, but at much lower ratios (Harm, 1980). The DNA damage can be repaired via enzymatic reactions, and the mechanism is dependent on the species of microorganism, UV fluence (Zimmer and Slawson, 2002), temperature (Salcedo et al., 2007), and physiological state. Two different mechanisms are distinguished, photoreactivation and dark repair, depending on light availability (Süss et al., 2009). During photoreactivation, the photolyase enzyme binds to CPD in the DNA and results in reversal of the damage by using the energy of light (310–480 nm) (Oguma et al., 2001; Sinha and Häder, 2002). Dark repair is a multi-enzyme process that involves replacing the damaged DNA with undamaged nucleotides in the absence of light. Repair of DNA damage induced by conventional mercury lamps is well established and MP mercury lamps have proven superior to LP mercury lamps for reducing DNA repair (Oguma et al., 2002).

UVA inactivates microorganisms by promoting the formation of active species and provided adequate bacterial damage is achieved, it can lead to diverse irreparable damage in the cell (Friedberg et al., 1995; Chatterley and Linden, 2010; Hamamoto et al., 2007). These reactive intermediates are predominantly reactive oxygen species (ROS) that are produced via photo oxidation of oxygen and lead to oxidative damage to DNA, proteins and cell membranes and cause growth delay. Singlet oxygen ($^1O_2$) and the hydroxyl radical (HO•) are the major damaging oxidative species generated (Petersen et al., 2000). A broad range of UV irradiation could therefore be advantageous to achieve both direct and indirect damage to the microorganisms and to minimise photoreactivation efficiency. For example, polychromatic medium pressure (MP) mercury UV lamps which emit UVA together with UVC and UVB have been demonstrated to be superior to a monochromatic low-pressure (LP) UV lamp for controlling *E. coli* photoreactivation (Oguma et al., 2002; Zimmer and Slawson, 2002).

2.2. UV-based advanced oxidation processes (AOPs)

UV-based AOPs include the processes that rely on UV irradiation and its combination with various radical promoters (Miklos et al., 2018). Some of the most investigated AOPs include UV/H_2O_2, UV/chlorine, UV/peroxymonosulfate (PMS), UV/peroxydisulfate (PDS), H_2O_2/Fe^{2+}/UV (photo-Fenton), UV/O_3, and UV/TiO_2. AOPs are based on the in-situ generation of reactive species such as HO•, Cl•, $Cl_2^{\bullet-}$ and $SO_4^{\bullet-}$ and their reaction with target contaminants (Miklos et al., 2018). These AOPs have been extensively studied for the degradation of organic contaminants in water and wastewater. Recently, there has been increasing interest in investigating their potential for disinfection to achieve both economic viability and improved disinfection. The selection of an AOP is important for disinfection applications since different processes possess certain advantages and disadvantages which are important to take into account. Other factors such as water matrix, regulatory requirements, and treatment objectives of the plant also need to be considered. A brief description of the above mentioned AOPs is provided below.

UV/H_2O_2 is one of the most widely investigated AOPs that relies on the oxidative ability of HO•. Due to its electrophilic nature, HO• (redox potential of 1.8–2.7 V) (Buxton et al., 1988) can non-selectively oxidise almost all electron-rich organic molecules, eventually converting them to CO_2 and water (Legrini et al., 1993). The process has disadvantages such as the high reaction rate between H_2O_2 and HO• leading to scavenging of radicals and hence reduction in its effectiveness (Matilainen and Sillanpää, 2010). It is therefore important that the concentration of H_2O_2 is optimised. Furthermore, removal of residual H_2O_2 after treatment is required since only ~5–10% of the chemical is used during the treatment process (Rosenfeldt et al., 2013). Nonetheless, UV/H_2O_2 is a highly efficient water treatment process with several commercial applications and is therefore a good candidate to compare with other AOPs.

Given both UV and chlorine are strong disinfectants, they could be combined to minimise the inherent disadvantages of the individual processes such as high UV fluence requirements for certain microorganisms and formation of DBPs during chlorination. High doses of chlorine have also been demonstrated to elevate the average resistance of ARBs (Huang et al., 2013). Similarly, UV irradiation can also lead to selective increase in antibiotic resistance as demonstrated by Huang et al. (2016) and Zhang et al. (2017). The UV/chlorine AOP could be more efficient than UV/H_2O_2 due to the higher molar absorption coefficient and quantum yield (i.e., the ratio of the number of photons emitted to the number of photons absorbed) of UV/HOCl (1.4 ± 0.18 Mol/Es) compared with UV/H_2O_2 (1.0 Mol/Es). This can reduce the energy requirement for contaminant degradation by 30–75% (Sichel et al., 2011; Watts and Linden, 2007). In fact, UV/chlorine has been proposed to be a more cost-effective AOP than UV/H_2O_2 primarily due to the requirement for post-treatment quenching of the oxidant (Watts et al., 2012). Moreover, Cl• is a more selective oxidant than HO• (Fang et al., 2014).

UV/PMS and UV/PDS have also gained significant attention as the redox potentials of PMS (+1.82 V) and PDS (+2.08 V) are higher than that of H_2O_2 (+1.76 V) (Betterton and Hoffmann, 1990; Bard et al., 1985). $SO_4^{\bullet-}$ generated during these processes is an electrophilic radical that is more selective than HO•, with a redox potential in the range of 2.5–3.1 V (Neta et al., 1988). A recent study reported the first full-scale application of UV/PMS for damaging ARGs (Rodríguez-Chueca et al., 2019). UV/$SO_4^{\bullet-}$ is a more selective process and some studies have demonstrated it to be superior to the UV/H_2O_2 process in lab-scale experiments (Khan et al., 2014; Xiao et al., 2016). However, it is more sensitive to changes in the composition of water matrix when compared with UV/H_2O_2 (Ahn et al., 2017). The mechanisms of radical formation are dependent on process parameters in addition to the design of the system and the physicochemical properties of water, whereas the efficiency of disinfection is dictated by the scavenging of radicals as well as other parameters such as radical mass transfer and hydrodynamics (Miklos et al., 2018).

Combining UV irradiation with ozone has shown synergistic (Wu et al., 2016) or greater (Bustos et al., 2010) microbial inactivation. The UV/O_3 process could be superior to UV/H_2O_2 treatment, taking into account the higher absorption coefficient of ozone (ε_{254} = 3300/M cm) compared with H_2O_2 (ε_{254} = 19.6/M cm) (Legrini et al., 1993).

However, mass transfer limitations due to the low solubility of ozone in water and the low efficiency of its photolysis are some of the issues associated with this process (Shu and Huang, 1995). Another AOP that has been investigated widely at lab-scale for disinfection is UV/TiO_2. However, contrary to UV/H_2O_2 it has very limited commercial application due to several challenges such as the need for TiO_2 recovery after treatment. Post-treatment challenges such as the production of iron oxide sludge are also a major limitation of the photo-Fenton process which can be effective for treating a wide range of water matrices. The practical application of this process is also limited due to the need for acidic conditions (Pignatello et al., 2006), however, it has recently been shown to be effective at near neutral pH for the inactivation of microorganisms (Giannakis et al., 2016).

Measuring the electrical efficiency of AOPs is important to critically assess their operational cost and sustainability (Miklos et al., 2018). Figures-of-merit have been developed to assess the electrical energy efficiency of UV-based processes for both water and air treatment (Bolton and Stefan, 2002). The most common figure-of-merit is electrical energy per order (E_{EO}) which is defined as the electrical energy in kilowatt hours (kWh) needed to decrease the concentration of a contaminant or microbes by one order of magnitude (90% removal) in a unit volume [e.g., 1 m^3 (1000 L)] of water. The E_{EO} values (kWh/m^3/order) are calculated with the following equation (Bolton and Stefan, 2002):

$$E_{EO} = \frac{1000\,Pt}{V\,\log^{c_i}/_{c_f}} \quad (1)$$

Eq. (1) is valid for mercury UV lamps but is not valid for UV-LEDs.

It should be noted that Eq. (1) is applicable to batch systems whereas Eq. (2) (Bolton and Stefan, 2002) applies to flow-through systems:

$$E_{EO} = \frac{1000\,Pt}{F\,\log^{c_i}/_{c_f}} \quad (2)$$

where P is the rated power which is the UV lamp power at the wall in kW, V the volume (L) of water, t (h) is the time of treatment, F is the water flow rate (m^3/h) in the flow-through system, and c_i and c_f are the initial and final concentrations (mol/L) of contaminant, respectively. Therefore, the E_{EO} metric is applicable only to the decay of contaminants that follow first-order kinetics over the entire UV treatment time. It is therefore important that the kinetics of the degradation or inactivation are clearly stated when applying the concept of E_{EO}.

3. UV-LEDs as alternative source of UV irradiation

UV-LEDs are a mercury-free source of mono (single LED chip) or a polychromatic (multiple LED chips) UV radiation (Kheyrandish et al., 2017). They have several advantages over mercury UV lamps such as durability (Crawford et al., 2005), flexibility of design (Würtele et al., 2011), ability to tailor emission spectrum, no chemical risk (Hirayama et al., 2014), no warm-up period (Chatterley and Linden, 2010), and much longer life-time (achieved for UVA/B, and improving for UVC LEDs) (Chen et al., 2017). Further details on the lifespan of UV-LEDs are provided in Section 7. Like conventional diodes, UV-LEDs are comprised of a chip of semi-conducting material impregnated or doped with impurities to create a *p-n* junction capable of emitting light in a narrow wavelength range in the form of electroluminescence (Taniyasu et al., 2006).

The wavelength of light emitted depends on the band gap energy of the type and content/composition of the semiconductor materials and the concentration of doped impurity ions (Chen et al., 2017; Vilhunen et al., 2010). The shortest emission wavelength reported to date is 210 nm (Taniyasu et al., 2006). The main materials used in the construction of UV-LEDs are semiconducting crystals of compounds containing aluminium, nitrogen, and gallium (Taniyasu et al., 2006). Further details on the light generation mechanisms of UV-LEDs, their chip fabrication, lamp packaging, emission wavelength engineering and other properties can be found in a recent review on the fundamental aspects of UV-LEDs by Chen et al. (2017).

Significant improvements in UV-LEDs have taken place over the last several years with greatly improved affordability and output power (up to 4000 mW), particularly at the higher wavelengths (320–400 nm) (Galbraith, 2016). Wavelengths in the range 360–380 nm demonstrate the highest efficiencies with some approaching the efficiency equivalent to blue LEDs (Galbraith, 2016). Recently, development of a commercial scale high power (30 mW per LED) UV-LED (285 nm) set-up for water treatment with a capacity of 2000 m^3/day was reported (METAWATER, 2017). A UV-LED with a much higher output power (100 mW at 278 nm) has also been developed although the details are not available (Wright, 2017). Further discussion on the recent improvements and future of UV-LEDs is provided in Section 7.

4. Impact of operational characteristics of UV-LEDs on disinfection

4.1. Impact of single UV wavelength on disinfection and repair of microorganisms

A summary of the investigations carried out using different UV-LED wavelengths for disinfection along with other operational characteristics and experimental conditions is given in Table 1. The value of the inactivation rate constant k (cm^2/mJ) is calculated from the linear plot of the log inactivation and delivered UV fluence for comparison between different wavelengths and microorganisms. The higher the value of k, the lower the UV fluence to achieve the same level of inactivation required because of the greater sensitivity of the microorganisms.

Photoreactivation and dark repair of microorganisms after disinfection using UV-LEDs has been investigated only recently. Li et al. (2017) investigated the photoreactivation and dark repair of *E. coli* using 265 nm and 280 nm UV-LEDs individually and in combination under different intensities. The authors noted no difference in photoreactivation between 265 nm UV-LEDs (33%, UV fluence of 7.27 ± 0.51 mJ/cm^2) and a 254 nm LP mercury lamp (34%, UV fluence of 8.69 ± 0.50 mJ/cm^2) for 3-log inactivation of *E. coli*. It was found that 280 nm was the most effective wavelength as it led to the least photoreactivation efficiency (16%, UV fluence of 10.24 ± 1.01 mJ/cm^2). The authors also investigated the combination of 265 and 280 nm UV-LEDs in two different relative fluence combinations with the UV fluence of 50% and 75% of the total UV fluence for 280 nm. At 50% UV fluence for the 265 + 280 nm combination, for 3-log *E. coli* inactivation photoreactivation (32%, UV fluence of 8.38 ± 0.54 mJ/cm^2) was comparable with that achieved by using 265 nm UV-LED or 254 nm LP mercury lamps. However, when the UV fluence for 280 nm was increased to 75%, a decrease in the photoreactivation efficiency (25%, UV fluence of 9.19 ± 0.45 mJ/cm^2) was observed.

These results demonstrate that 280 nm was superior compared with 265 nm in terms of reducing the photoreactivation under fairly similar total UV fluence conditions (Li et al., 2017). A similar trend was observed for 4.5-log *E. coli* inactivation. However, increasing the UV fluence to achieve 4.5-log inactivation resulted in lower photoreactivation. For example, using 265 nm UV-LEDs, only 8.5% cf. 33% photoreactivation occurred when the UV fluence was increased to 10.91 ± 0.76 mJ/cm^2 from 7.27 ± 0.51 mJ/cm^2, corresponding to 4.5- and 3-log inactivation. This agrees with the earlier finding that increasing UV fluence leads to minimising the photoreactivation events (Guo et al., 2013c). The level of dark repair was markedly lower compared with photoreactivation, and was similar for both LP UV (0.26%) and 265 nm UV-LEDs (0.26%). Consistent with the general trends of inactivation and photoreactivation, the repair after irradiation using 280 nm UV-LEDs was lower (0.11%), and was fairly comparable with the combination of 265 and 285 nm (75%) for both 3- and 4.5-log inactivation.

Moreover, the authors performed ESS (endonuclease sensitive site) assay and noted that the increase in molecular length after exposure

Table 1
Log inactivation of various microorganisms by UV-LEDs under different operational conditions.

Log inactivation	Organism	λ (nm)	UV fluence (mJ/cm^2)	k (cm^2/mJ)	Distance (cm) from water surface	Distance (cm) between LEDs	Number of LEDs	Output power (mW)	Volume (mL)	Reference
1.9	*E. coli*	270	3.6	0.528	1	1–2	–	–	–	Crawford et al., 2005
1	*E. coli*	365	55,263	0.00008	2	–	–	–	–	Hamamoto et al., 2007
1	*E. coli*	365	13,846	0.00007	2	–	8	–	–	Mori et al., 2007
3–4	*E. coli K12*	276	–	–	1	–	10	6.1	25	Vilhunen et al., 2009
3–4	*E. coli K12*	269	–	–	1	–	10	3.4	25	Vilhunen et al., 2009
1	*E. coli*	265	5.9	0.169	0.5–4	–	3	–	7	Chatterley and Linden, 2010
1	*E. coli*	255	3.3	0.303	4	1.5–2	8, 4	2.4, 2	–	Bowker et al., 2011
1	*E. coli*	275	2.4	0.417	4	15–2	8, 4	2.4, 2	–	Bowker et al., 2011
2.5	*E. coli*	260	12.8	0.195	–	–	7	–	100	Nelson et al., 2013
1	*E. coli K12*	265	2.7	0.370	1.7	1	9	9.9	10	Oguma et al., 2013
4	*E. coli K12*	265	10.8	0.370	1.7	1	9	6.3	10	Oguma et al., 2013
7	*E. coli*	280	–	–	1	–	1	0.55	10	Chevremont et al., 2012
2,7	*E. coli*	365	–	–	1	–	1	350	10	Chevremont et al., 2012
4	*E. coli K12*	280	13.8	0.290	1.7	1	9	11.7	10	Oguma et al., 2013
1	*E. coli K12*	310	94.8	0.011	1.7	1	9	9.9	10	Oguma et al., 2013
>4	*E. coli 25,922*	255	41	–	–	–	–	–	50	Crook et al., 2015
5	*E. coli*	282	~78	~0.06	–	–	–	0.97	–	Gross et al., 2015
3.5–6.3	*E. coli O157:H7*	275	0.17–1.67	20.6–3.8	–	–	–	–	–	Shin et al., 2016
3	*E. coli*	265, 285	7.2, 10.2	0.4, 0.29	4	–	–	–	5	Li et al., 2017
4.5	*E. coli*	265, 285	10.2, 15.3	0.44, 0.29	4	–	–	–	5	Li et al., 2017
>3	*E. coli*	260, 280	≤12	–	4	–	–	–	5	Beck et al., 2017
5	*E. coli*	282	~78	~0.06	–	–	–	0.97	–	Gross et al., 2015
3.5–6.3	*E. coli O157:H7*	275	0.17–1.67	20.6–3.8	–	–	–	–	–	Shin et al., 2016
3	*E. coli 15,597*	254	30	0.1	–	–	–	–	30	Zhou et al., 2017
4	*E. coli 25,922* *E. coli 11,229* *E. coli 15,597*	265, 365	–	–	0.7	–	–	0.7, 3 W	15	Xiao et al., 2018
2.5	*E. coli*	265	4.9	0.51	2	–	1	10	50	Song et al., 2018
3	*B. subtilis*	269	400	0.008	1	1	39	4.56	30	Würtele et al., 2011
3	*B. subtilis*	282	400	–	1	1	35	6.65	30	Würtele et al., 2011
3.8	*B. subtilis*	282	~78	~0.04	–	–	–	0.97	–	Gross et al., 2015
3.1	*B. subtilis*	265	125	0.02	–	–	–	–	5	Li et al., 2018
2.1		280	125	0.007						
1	*T7*	275	4.3	0.233	4	1.5–2	8, 4	2.4, 2	–	Bowker et al., 2011
1	*T7*	255	5.1	0.196	4	1.5–2	8, 4	2.4, 2	–	Bowker et al., 2011
1	*φX174*	280	2.8	0.357	–	–	–	–	–	Aoyagi et al., 2011
1	*φX174*	255	1.7	0.588	–	–	–	–	–	Aoyagi et al., 2011
1	*Qβ*	255	12.5	0.080	–	–	–	–	–	Aoyagi et al., 2011
1	*Qβ*	280	28.7	0.035	–	–	–	–	–	Aoyagi et al., 2011
1	*MS2*	255	12.8	0.078	–	–	–	–	–	Aoyagi et al., 2011
2	*MS2*	260, 280	30.3, 38.5	–	4	–	–	–	5	Beck et al., 2017
1	*MS2*	255	26.1	0.038	4	1.5–2	8, 4	2.4, 2	–	Bowker et al., 2011
1	*MS2*	280	30.5	0.033	–	–	–	–	–	Aoyagi et al., 2011
3.2	*MS2*	265	41	0.078	–	–	–	–	–	Aoyagi et al., 2011
2.3	*MS2*	265	60	0.038	–	–	–	–	–	Bowker et al., 2011
1	*MS3*	275	28.6	0.035	4	1.5–2	8, 4	2.4, 2	–	Bowker et al., 2011
~2.7	MS2	265	40	0.07	2	–	1	10	20	Song et al., 2018
~3.2	MS2	255	60	0.05	–	–	–	–	–	Hull and Linden, 2018
~3.3		265	60	0.05						
~3.7		285	100	0.04						
3	*Adenovirus*	260, 280	64–68	–	4	–	–	–	5	Beck et al., 2017
1	*Feline calicivirus*	265, 280, 300	8.8, 9.9, 142.9	0.113, 0.101, 0.007	8	–	–	–	10	Oguma et al., 2018

TE, tertiary effluent; GW, Greywater; Target microorganisms purchased except for Crook et al. (2015) and Nelson et al., (2013) who used both purchased and naturally occurring *E. coli* in GW, and in TE, respectively.

to 280 nm LEDs followed by photoreactivation was lower compared with LP UV and 265 nm UV-LEDs (Li et al., 2017). It essentially implies that fewer dimers were repaired after irradiation using 280 nm UV-LEDs. These results were also consistent with the plate counts demonstrating that the overall log inactivation was greater after irradiation using 280 nm UV-LEDs when photoreactivation was considered (Li et al., 2017). The authors concluded that the reduced photoreactivation after irradiation using 280 nm UV-LEDs was due to the damage to photolyase and/or other related enzymes.

In a later study, Oguma et al. (2018) investigated the impact of UV irradiation generated by 285 nm UV-LEDs on heterotrophic bacteria (Htbc) for point of use application in flow through operation (flow rate of 1 mL/min). No regrowth of Htbc was observed for up to 24 h, presumably due to the lag time needed to repair the UV-induced damage

and/or initiation of regrowth. After UV irradiation (reduction equivalent dose (RED) of 20.1 mJ/cm^2) the Htbc showed either negative or lower concentration compared with the non-treated samples during the first 5 days of storage. RED is "the UV dose derived by entering the log inactivation measured during full-scale reactor testing into the UV dose-response curve that was derived through collimated beam testing" (USEPA, 2006). It was noted that the concentration of bacteria was similar on day 6 for both treated and non-treated samples but the UV-treated samples showed greater bacterial count on day 7 (Oguma et al., 2018). The authors assumed this apparent enhanced bacterial count was due to a 1-day lag time for treated samples but noted that further investigation was warranted to confirm their hypothesis. The authors also found that UV irradiation changed the composition of the bacterial community resulting in enrichment of *Methylobacterium* cf. *Novosphingobium* species. Importantly, *Methylobacterium* species are considered UV resistant. During the 7-day regrowth period, the profile of *Methylobacterium* species showed similar growth curves at the studied flow rates of 0.5 and 1 L/min. It was concluded that the bacterial count on day 0 of storage or straight after irradiation was the principal factor in determining their regrowth profile. The RED of 78 mJ/cm^2 was needed to achieve 1-log inactivation of *Methylobacterium* species at the flow rate of 1 L/min. These results demonstrate that further research determining the impact of UV irradiation using UV-LEDs on selection of bacteria is needed under different experimental conditions.

4.2. Impact of combined UV wavelengths on disinfection and repair of microorganisms

The impact of sequential UVA (365 nm) and UVC (265 nm) radiation generated by UV-LEDs on the inactivation, photoreactivation and dark repair of four *E. coli* strains was investigated by Xiao et al. (2018). The study showed the resistance to UV irradiation generated using 265 nm followed the trend: *E. coli* ATCC 25922 < *E. coli* ATCC11229 < *E. coli* ATCC 15597 < *E. coli* ATCC 700891. This trend is in agreement with an earlier study comparing the inactivation of three *E. coli* strains (ATCC11229, ATCC 15597, ATCC 700891) using a LP mercury lamp (Quek and Hu, 2008). *E. coli* strain ATCC 700891 is considered an ARB with resistance to ampicillin and streptomycin and *E. coli* ATCC 15597 is considered UV resistant (Quek and Hu, 2008). Xiao et al. (2018) reported that the contact time required to achieve 4-log inactivation of the four strains ranged between 7 and 16 min using 265 nm UV-LEDs under constant UV intensity (0.127 mW/cm^2) conditions. UVA-LEDs (365 nm) did not lead to any significant inactivation of the *E. coli* after 30 min irradiation at UV intensity of 6 mW/cm^2. During sequential UVA-UVC disinfection under different UVA (0–120 mJ/cm^2) and UVC fluences (0.635–2 mJ/cm^2), an increase of 0.5 to 1.3-log inactivation was noted for the three strains ATCC11229, ATCC 15597 and ATCC 700891. Despite the insignificant *E. coli* inactivation by UVA alone, it led to a synergistic effect when used in combination with UVC irradiation.

For ATCC 25922, pre-radiation by UVA (UV fluence 120 mJ/cm^2) led to a decrease of 0.5–1.2-log in inactivation under the investigated UVC fluences between 0.635 and 0.825 mJ/cm^2 (Xiao et al., 2018). Investigating the synergistic/adverse effect of UVA pre-radiation in the sequential disinfection process for *E. coli* ATCC 15597 and 25922, the authors concluded that the generation of ROS was not responsible for the observed effects during the sequential UVA-UVC process considering the very low fluences used in their study. Similarly, no significant generation of CPDs occurred after UVA pre-radiation as evaluated by enzyme-linked immunosorbent assay (ELISA). For *E. coli* ATCC 15597, the total generation of CPDs was 18% higher than for UVC alone, demonstrating that UVA pre-radiation promoted their formation upon subsequent UVC irradiation and led to the enhanced inactivation. Insignificant difference in CPD formation was observed between individual UVC and sequential UVA-UVC exposure for ATCC 25922 despite lower inactivation after the sequential process. The lower inactivation of ATCC 25922 during the sequential process was attributed to its enhanced resistance after UVA pre-radiation due to enhanced translesion DNA response (TLS). The TLS response is activated by specialised DNA polymerases that enable the formation of new DNA strands. The UV sensitive strains exhibited higher TLS capacity than the UV resistant strains (Kuban et al., 2012) and ATCC 25922 was considered as one of the most UV sensitive strains.

Xiao et al. (2018) also investigated photoreactivation and dark repair of the four *E. coli* strains. During UVC disinfection, *E. coli* ATCC 15597 and 700891 exhibited greater photoreactivation compared with ATCC 11229 and 25922. The effect of UVA pre-radiation was not significant in terms of photo-repair for all the investigated strains which was attributed to the low UVA fluence used. Dark repair ability was, however, found to be significantly inhibited after UVA pre-radiation; it decreased from 16%, 12%, 10%, and 16% to 3%, 1%, 2%, 3%, for *E. coli* 15597, 11229, 700891, and 25922, respectively, after 2 h.

Direct comparison between bacterial inactivation and repair of DNA using UVC alone and in combination with higher wavelengths using UV-LEDs was carried out for *Vibrio parahaemolyticus* (Nakahashi et al., 2014). *V. parahaemolyticus* is a gram-negative bacterium which causes food poisoning via sea water and uncooked seafood. The authors observed a synergistic effect when UVA- and UVC-LEDs were used simultaneously. They hypothesised this synergistic effect was due to inactivating a recovery system, such as the SOS response, used for the repair of damaged DNA; the bacterial SOS response repairs DNA that has been severely damaged by UV irradiation. Similarly, the synergistic effect of UVB (285 nm) and UVC (255, 265 nm) on the inactivation of MS2 was reported by Hull and Linden (2018), which was attributed to simultaneous damage to DNA and proteins.

Coupling UVA- and UVC-LEDs has also been reported to be superior to single UVC-LED wavelength both for disinfection and minimising reactivation of bacteria in wastewater effluent (Chevremont et al., 2012). The authors showed that inactivation of all investigated bacterial communities (mesophilic bacteria, fecal enterococci, total coliforms, and fecal coliforms) was higher when the wavelengths were coupled (280/365 nm and 280/405 nm) compared with single wavelength UV-LEDs. For example, the UV fluence response was 1.6 and 7.7 mJ/cm^2 per log inactivation for 280/365 nm and 280/405 nm, respectively, which were much lower than UVA alone. For UVA, the UV fluence response was 12.5 mJ/cm^2 for 365 nm and 88 mJ/cm^2 for 405 nm. Consistent with the general findings, UVC alone was much more effective than UVA irradiation, i.e., 1 mJ/cm^2 per log inactivation achieved at both 254 and 280 nm. The investigation of DNA repair showed no repair after 20 h of irradiation at room temperature (25 °C) and under light which was due to the combined effect of direct and indirect damage inflicted by the combination of UVA (280 nm) and UVC (365 nm) as discussed in Section 2.1.

Another study (Beck et al., 2017) and an earlier study by Oguma's group (Oguma et al., 2013), however, reported no synergistic effect of combining dual or multiple wavelength UV-LEDs. Beck et al. (2017) investigated the inactivation of *E. coli*, MS2 coliphage, HAdV2, and *Bacillus pumilus spores* using 260 nm and 280 nm UV-LEDs both individually and in combination. The authors concluded that the combination of wavelengths did not provide any advantage over individual wavelength UV-LEDs. Comparing the individual wavelengths (265, 280, 310 nm) with different combinations, Oguma et al. (2013) observed a decrease in inactivation of *E. coli* for combined wavelengths (265/280, 280/310, 265/310 or 265/280/310 nm). The difference in the findings could be due to several factors. Firstly, a direct and fair comparison is not possible between these studies since each used different UV-LED wavelengths, water matrices, experimental conditions (batch vs flow through system), and different microbial strains. The other possible reason that could contribute to the difference in the findings even under similar conditions, is the method for calculation of UV fluence, as these studies were carried out before the standard protocol for determining UV fluence (Kheyrandish et al., 2018) was introduced. Nonetheless, knowledge of how multiple wavelengths of UV-LEDs compare with single

wavelength UV-LEDs for both bacterial inactivation and DNA repair is critical for their practical application. This would also allow comparing such results with those for LP and medium pressure UV lamps.

4.3. Pulse vs continuous irradiation

The ability of UV-LEDs to switch on and off without the need of a warm-up time enables the use of pulsed irradiation (PI) which cannot be achieved with mercury UV lamps. In addition to improved effectiveness, PI is a potential way to further lower energy consumption and extend the lifetime of UV-LEDs, partly because pulsing helps to maintain junction temperature below the critical threshold that can cause overheating and damage (Lenk and Lenk, 2011). The impact of pulse and continuous irradiation has been discussed in a previous study (Song et al., 2016). Therefore, this section only briefly discusses this concept and considers the most recent findings so that readers can obtain an understanding of this unique feature of UV-LEDs.

A recent comparative study for the inactivation of *E. coli* and MS2 in laboratory water, and *E. coli* and total coliforms in wastewater, under continuous and pulse irradiation conditions using 265 nm UV-LEDs was carried out by Song et al. (2018). Under similar UV fluence (4.9 mJ/cm^2), the authors found little enhanced germicidal effect on *E. coli* for pulsed irradiation compared to continuous irradiation at different frequencies (0.1 Hz–1 k Hz) and duty rates (10–90%) (the percentage of the exposure time of total operating time, or fraction of illumination period to the total operation period) in buffered lab water. This contrasts with previous studies that reported enhanced inactivation of *E. coli* (Wengraitis et al., 2013), *Bacillus globigii* (Tran et al., 2014), and *Candida albicans* and *E. coli* biofilms (Li et al., 2010) under pulsed irradiation using 272, 269, and 365 nm UV-LEDs, respectively. Song et al. (2018) reported a marginal decrease in the inactivation of *E. coli* at 90% and 75% duty rates. Similar findings were reported for total coliforms and *E. coli* in wastewater and MS2 in buffered water. Considering the similar level of inactivation achieved by pulse and continuous irradiation, it is anticipated that the mechanisms of disinfection are fairly similar for UV-LEDs of currently available output power and intensity. However, further investigation would be needed to confirm this hypothesis.

Despite the difference in the findings, comparison between the studies mentioned above needs to be considered with caution due to the difference in the wavelengths, operational conditions (different duty rates and frequencies), species of microorganisms and disinfection medium (microbial suspension in water or biofilm on culture plates). Another potential factor leading to these differences is the method and approach to measuring the UV fluence since Song et al. (2018) found that the UV fluence delivered could not be simply assumed to be equivalent for pulse and continuous irradiation modes based on the irradiation time. For example, Li et al. (2010) assumed that similar UV fluence was delivered during pulse mode for 50% duty cycle by irradiating the sample for twice as long as that of continuous irradiation. Song et al. measured the UV fluence using two different chemical actinometry methods (iodide-iodate (KI) actinometry and ferrioxalate (FeOx) actinometry) and found that the delivered UV fluence was higher during pulse mode than during continuous mode based on calculated irradiation time. This difference in the UV fluence under comparable irradiation time was attributed to the imperfection of pulse waveforms during pulse mode, which was thought to be due to issues related to the UV-LED and DC power supply (Song et al., 2018).

These results demonstrate that additional validation, for example, using chemical actinometry, could be required to make a direct and appropriate comparison between different irradiation modes. Future studies are therefore encouraged to consider these aspects to verify these initial findings of Song et al. (2018) using different UV-LED wavelengths and under various operational conditions. Such efforts are also important to enable a direct comparison between different studies using other microorganisms. As pointed out by Bohrerova et al. (2008) and concluded from this discussion, it is evident that one of the main problems in interpreting pulse irradiation results is the approach used to compare them with the findings from continuous mode irradiation. It highlights the need for a standardized approach for pulse irradiation systems for determining UV fluence, similar to conventional mercury lamp systems. It is important to note that pulsation could affect the performance of UV-LEDs, which needs to be investigated to weigh up the potential drawbacks against the possible performance enhancements.

Most of the literature findings on pulse irradiation were based on studies using powerful xenon lamps and UV-LED based pulsed irradiation has been investigated less. Enhanced disinfection efficiency of pulsed irradiation generated by xenon lamps compared with continuous irradiation by LP UV lamps has been reported for water disinfection (Bohrerova et al., 2008) and food decontamination (Elmnasser et al., 2007). Pulsed irradiation generated by xenon lamps, however, differs considerably from that of UV-LEDs with regard to the emission spectrum, intensity, pulse frequency and duty rate (Song et al., 2016). Moreover, pulsation allows better thermal management by minimising heat generation due to the cooling period between pulses and maximising the pulse intensity of UV-LEDs (Krishnamurthy et al., 2004).

Clearly additional research should be carried out to determine the impact of pulsation using different wavelength UV-LEDs for different microorganisms. Limited studies have been conducted to investigate the inactivation of some microorganisms (i.e., MS2) under different modes of irradiation (Song et al., 2018) and the potential differences between different microorganisms are not well understood. Furthermore, no study has looked into the impact of pulse cf. continuous irradiation on ARGs, which is recommended to be performed in future studies. Additionally, it is worth comparing pulse and continuous irradiation in terms of repair of the microorganisms for further understanding of the potential differences in inactivation mechanisms.

5. UV irradiation for controlling environmental antibiotic resistance

5.1. Controlling antibiotic resistance determinants by UV disinfection

Thus far, most studies have employed conventional LP UV lamps to control antibiotic resistance (ARGs and ARBs). Considering the specific characteristics of UV-LEDs and their advantages over LP UV lamps as described in Section 3, it is expected that UV-LEDs will become promising alternatives to UV lamps in future. It is therefore relevant to evaluate the literature on conventional UV lamp systems, because of not only their greater application to ARG and ARB inactivation, but also the objectives shared with the UV-LEDs for such applications.

5.2. ARB inactivation using UV irradiation

A recent investigation looked at the inactivation of six antibiotic-resistant *E. coli* strains isolated from the influent of a WWTP by UVC irradiation using a LP UV lamp in a collimated beam set up (Zhang et al., 2017). Using nine antibiotics, the authors demonstrated that the inactivation curves for five antibiotic-resistant *E. coli* and one antibiotic-sensitive *E. coli* showed two phases: an initial phase showing fast kinetics (Phase 1) and a subsequent phase with slow kinetics or tailing (Phase 2). The six *E. coli* strains could be divided into two groups based on the inactivation curves. The first group consisted of the SER2 and *E. coli* ATCC 25922 strains for which the inactivation curves entered the tailing phase at UV fluence of 8 mJ/cm^2. The second group consisted of multiple antibiotic resistant *E. coli* (SER6-1, SER6-2, INR6 and INR8) for which the tailing phase started at UV fluence of 20 mJ/cm^2, markedly greater than for the other two strains.

According to the literature, tailing during UV irradiation could potentially be attributed to the formation of microbial self-aggregates due to changes in surface characteristics (lipids) and the production of extracellular polymers during UV irradiation as reported by Rainey et al. (1993) and indirectly evidenced by Kollu and Ormeci (2015).

Other studies (Blatchley et al., 2001; Mamane-Gravetz and Linden, 2005) have reported similar results after exposure to a comparable UV fluence (15–25 mJ/cm^2). It has been reported that antibiotic-resistant organisms produce a greater amount of capsular material than antibiotic-sensitive strains (Liu et al., 2011). Encapsulation is an important bacterial protection mechanism, and is prevalent for bacteria in the natural environment (Reilly and Kippin, 1981). The production of this capsular material by antibiotic-resistant organisms could promote the formation of microbial self-aggregates (Zhang et al., 2017) which consequently contribute to a higher UV fluence requirement for reaching the tailing phase (Kollu, 2014).

A summary of the various investigations for the inactivation of ARBs by UV irradiation is provided in Table 2.

Inactivation of a strain of *E. coli* different from those used by Zhang et al., (2017), ampicillin resistant *E. coli* (CGMCC1.1595), using UV lamp irradiation at 254 nm demonstrated that exposure to a fluence between 5 and 20 mJ/cm^2 led to an inactivation of approximately 2-log (Pang et al., 2016). The difference between inactivation at UV fluence of 5 and 20 mJ/cm^2 was fairly small (<0.5-log) considering the 4-fold increase in fluence. Increasing the UV fluence to 40 mJ/cm^2 (typical for water disinfection) resulted in >5.5-log inactivation of the ampicillin resistant *E. coli*. Using a similar UV fluence of 5 mJ/cm^2 inactivation of about 3-log was reported by Guo et al. (2009), which was 1-log higher than that reported by Pang et al. (2016). Since *E. coli* inactivation follows different kinetics for different strains, and the *E. coli* strains and the water matrices used in these studies were different, the findings cannot be directly compared. Pang et al. (2016) hypothesised that the *E. coli* CGMCC 1.1595 incubation conditions allowed for tolerance to low dose UV irradiation in their study and that possibly co-selection of both UV irradiation and ampicillin resistance took place upon ampicillin addition during cultivation of the organism.

A comparison of the inactivation levels of various culturable tetracycline resistant bacteria isolates using a 254 nm UV lamp was undertaken by Sullivan et al. (2017). The bacterial isolates investigated included *Aeromonas*, *Acinetobacter*, *Chryseobacterium*, *E. coli*, *Pseudomonas*, and *Serratia*. UV fluence of 69.8 mJ/cm^2 (the lowest UV fluence in the test range of up to 279 mJ/cm^2) gave >4-log inactivation of all isolates, except for *Acinetobacter* which was the most susceptible to UV irradiation with >5-log inactivation. Although a further increase in the UV fluence resulted in increased inactivation of all isolates, the increase was not statistically significant ($p > 0.05$). After 24 h, most of the isolates experienced regrowth and repair after UV disinfection. Templeton et al. (2009) reported similar findings and observed that the inactivation of ampicillin and trimethoprim resistant *E. coli* by UV was similar to that of antibiotic-sensitive *E. coli* in phosphate buffer.

Using a 254 nm collimated beam UV lamp set-up, Huang et al. (2013) investigated the inactivation of tetracycline-resistant bacteria (TRB) and antibiotic-sensitive *E. coli* in phosphate buffer. Both antibiotic-sensitive and TRB strains of *E. coli* showed the same tolerance to UV irradiation (*t*-test, $p > 0.05$). UV fluence of 10 mJ/cm^2 led to ≥4-log inactivation of tetracycline-resistant *E. coli* and increasing the UV fluence to 80 mJ/cm^2 enhanced the inactivation to 6-log. These results agree with those of McKinney and Pruden (2012) who reported >4 log inactivation of tetracycline resistant *E. coli* in phosphate buffer after UV fluence of ~8 mJ/cm^2 but the reduction in wastewater was ~1-log lower at similar UV fluence.

Huang et al. extended their work in a later study of the impact of UV fluence (2–20 mJ/cm^2) on heterotrophic bacteria and TRB inactivation

Table 2
Inactivation of ARBs by UV irradiation.

Mode	Peak λ	Source	Volume (mL)/flow rate	Target	Log inactivation	Source	UV dose (mJ/cm^2)	*k* (mJ/cm^2)	Matrix	Reference
Bench scale collimated beam	NG	LP and MP Lamp	10	Various *E. coli* strains[c]	4	Purchased	6–13 for LP and 4.5–9 for MP	0.66–0.30 and 0.88–0.44	*E. coli* suspension in sterile DW	Quek and Hu, 2008
Bench scale collimated beam	254	Lamp	10	MRSA, VRE, *E. coli*[d] and *P. aeruginosa*[e]	4–5	Purchased	10–20	0.4–0.25, 0.015–0.01	PB and filtered WW effluent	McKinney and Pruden, 2012
UVA/LED/TiO_2	365	LEDs	30 (18 LEDs)	*E. coli* ATCC 700891[c]	3	Purchased	688–870	0.004–0.003	*E. coli in sterilized DW*	Xiong and Hu, 2013
Bench scale collimated beam	254	Lamp	15	*E. coli* CGMCC 1.1595[f]	4–6	Purchased	10–80	0.4–0.075	PBS	Huang et al., 2013
UVA/TiO_2	370 (320–400)	Lamp	200	*Various E. coli* strains[g]	BDL	Purchased	150–180 min	–	*E. coli* in Ringer solution	Dunlop et al., 2015
Bench scale collimated beam	253.7	Lamp	15	TRB	3	Isolated from SE	20	0.15	Secondary effluent	Huang et al., 2016
Bench scale collimated beam	254	Lamp	15	*E. coli* CGMCC 1.1595[h]	>5.5[a]	Purchased	40	0.13	*E. coli* suspension in PBS	Pang et al., 2016
Batch	254	Lamp	20	TRB isolates	>4[b]	NG	69.8	0.057	Re-suspended isolate culture	Sullivan et al., 2017
Batch	254	Lamp		*Various E. coli strains*[i]	5–6	Isolated from SE	20	–	PBS	Zhang et al., 2017
Batch	265, 365	UV-LEDs		*E. coli* 700,891[c]	4, <0.1	Purchased	–	–	*E. coli* suspension in milliQ	Xiao et al., 2018

NG, not given; DW, distilled water; WW, wastewater; SE, secondary effluent; PB, phosphate buffer; MRSA, Methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant *Enterococcus*; TRB, tetracycline resistant bacteria; ThRB, thiosulphate-reducing bacteria.

[a] Value considered 5.5.
[b] Value considered 4.
[c] Resistant to ampicillin and streptomycin.
[d] Resistant to β-lactam, aminoglycoside, quinolone, macrolide, sulfonamide, and tetracycline antibiotics.
[e] Multiantibiotic resistant.
[f] Tetracycline resistant.
[g] Rifampicinresistant and chloramphenicol resistant.
[h] Ampicillin resistant.
[i] Resistant to a number of antibiotics including tetracycline, ampicillin, streptomycin and sulfamethoxazole.

in secondary effluent using the same 254 nm collimated beam set-up (Huang et al., 2016). The authors also explored the inactivation and dark repair potential of 16 tetracycline-resistant strains isolated from the secondary effluent to investigate if there was any genus of TRB that expressed tolerance to UV irradiation or high reactivation potential after disinfection. They reported that the UV fluence of 20 mJ/cm^2 led to 3-log inactivation of TRB which was lower than that for heterotrophic bacteria (>4.0-log) in the secondary effluent, resulting in a significant increase in the proportion of TRB in the effluent. The tetracycline-resistant *Enterobacter-1* was found to be the most tolerant to UV irradiation among the investigated strains.

The TRB isolates and heterotrophic bacteria successfully reactivated (dark repair) in the secondary effluent even at the UV fluence of 20 mJ/cm^2. The final inactivation ratio of tetracycline-resistant *Enterobacter-1* was only 1.18-log for UV fluence of 20 mJ/cm^2 after 22 h incubation, which was close to that of TRB (1.18-log) and heterotrophic bacteria (1.19-log) (Huang et al., 2016). Similarly, an increase in bacteria resistant to tetracycline was reported by others along with almost doubling of the proportion of TRB after UV disinfection (Guo et al., 2013a, 2013b). An earlier study conducted on fecal coliforms suggested an increase in resistance to tetracycline after UV disinfection (Staley et al., 1988). Therefore, the potential health risk associated with increased concentration of TRB and the reactivation of tetracycline-resistant enterobacteria, as well as other ARBs, in reclaimed secondary effluent needs to be considered during wastewater reclamation and reuse when UV disinfection is applied to such water matrices.

Furthermore, the impact of water quality parameters, including the presence of suspended solids and humic acids has been widely reported to decrease the efficiency of UV disinfection (Liang et al., 2013; Loge et al., 1999; Mamane, 2008; Templeton et al., 2005). Coliform bacteria, which are typically between 1 and 10 μm in size, have been shown to be shielded during the UV disinfection of wastewater by being enmeshed within particles >10 μm in diameter (Emerick et al., 2000). Since a higher UV fluence is needed for microbial inactivation in the presence of particles and humic substances, that required for inactivation of ARGs would be expected to be even higher.

It is important to highlight that the damage induced by LP mercury lamps is related to pyrimidine and purine nucleobases since these biomolecules absorb most UV at 254 nm (Dodd, 2012). Considering the absorption spectrum of protein has a peak around 280 nm, UV at this wavelength could result in damaging repair enzymes and prevent DNA repair. As mentioned in Section 4.1, the damage caused by LP mercury lamps can be repaired by enzymes such as photolyase (Ingraham, 1994). Therefore, it would be advantageous to use combined UV wavelengths to simultaneously damage enzymatic repair proteins in addition to DNA (as discussed in Section 2.1). It was reported that when DNA repair mechanisms are considered in final inactivation efficiency, polychromatic MP mercury lamps could be superior to LP mercury lamps depending on the type of microorganism (Oguma et al., 2002). For example, the final inactivation efficiency of *E. coli* was greater for MP lamps than for LP lamps (Oguma et al., 2002).

MP mercury lamps have a fixed spectrum making it difficult to identify and relate the effects and mechanisms to particular wavelengths (Song et al., 2016). Furthermore, the peak intensities of MP mercury lamps occur at wavelengths based on the emission properties of mercury (Chatterley and Linden, 2010). A unique advantage of UV-LEDs over UV lamps is that UV-LED-based systems can incorporate a LED array of different UV wavelengths allowing custom designed units for the specific target and/or a broad range of targets for maximising the combined effect (Chatterley and Linden, 2010). Taking this critical advantage of combining different UV wavelengths into account, a combination of low and high wavelengths could be very useful for causing wide-ranging and irreversible damage and consequently minimising reactivation potential. More studies are therefore needed to identify the best combinations of wavelengths for different microorganisms, to not only investigate the potential synergistic effects, but also to explore the benefits of the combined wavelengths for minimising subsequent repair.

5.3. ARGs inactivation using UV irradiation

Water is one of the major routes of microbial dissemination in nature and is recoganised as a significant reservoir of antibiotic resistance (Rizzo et al., 2013). Antibiotic resistance is transferred by two mechanisms: vertical gene transmission in which the genetic information is inherited from the parent cells, or horizontal gene transfer (HGT), during which a bacterium lacking resistance gains the resistance genes other than from its parent cell and becomes resistant (i.e., antibiotic resistant bacteria, ARB). The three mechanisms that are responsible for HGT include conjugation (transfer of DNA from a donor cell to an acceptor cell during direct cell-cell contact), transduction (bacteriophage introduces ARGs into microbial cells), and transformation (competent microbes pick up free DNA from the environment) (Ochman et al., 2000; Thomas and Nielsen, 2005). One of the important differences in these resistance transfer mechanisms is the viability or infectivity requirements of the donor source. Indeed, vertical gene transmission and conjugation only occurs if the bacterium carrying the gene is viable to enable its passage to the recipient cell. Similarly, the virus carrying the gene must be infective for successful transduction. However, transformation does not require a viable or infective donor microorganism since bacteria in the environment can obtain ARGs from extracellular DNA (Chang et al., 2017). Disinfection or other treatment processes conventionally designed to inactivate microorganisms therefore do not guarantee hindering the environmental spread of ARGs.

The HGT of DNA fragments using mobile genetic elements, in particular class 1 integrons, is considered a major contributor to the evolution and dissemination of antibiotic resistance (Gillings, 2017). The association of these mobile elements with human activities and their considerable success in spreading genes, including ARGs, has even prompted the suggestion of using them as a proxy for anthropogenic pollution (Gillings et al., 2015) and to consider them as an environmental pollutant (Gillings, 2018). ARGs are therefore of serious concern since they are typically associated with mobile genetic elements, enabling them to be passed between microorganisms including from dead to living cells by transformation. Different forms of ARGs, including DNA carried within bacteria and viruses, as well as extracellular, AKA cell-free, DNA, are present in water (Zhang et al., 2018) with the potential to transfer resistance through the above-mentioned mechanisms.

It is therefore important to move beyond the traditional paradigm of pathogen inactivation as the sole aim of disinfection (McKinney and Pruden, 2012) and include ARGs in future disinfection strategies. ARGs are emerging contaminants and inactivation of ARB alone is not sufficient as DNA could still be present which could contribute to antibiotic resistance through different mechanisms (Ferro et al., 2017). Much fewer studies have focused on ARGs inactivation using UV irradiation compared with bacterial inactivation. A comparison of the inactivation rate constant k (cm^2/mJ) for ARGs given in Table 3 shows that the values calculated are much lower than for bacterial inactivation (Table 2), demonstrating a much higher UV fluence requirement for damaging DNA to avoid transformation.

5.3.1. ARGs inactivation in pure water matrices

A few studies have been performed on the inactivation of ARGs using LP mercury lamps. A recent study investigated the loss of the ampicillin resistance gene $bla_{\text{TEM-1}}$ and tetracycline resistance gene *tet*A in plasmid pWH1266 using 254 nm at UV fluence of up to 430 mJ/cm^2 (Chang et al., 2017). The transformation efficiency (the ratio of the ARB colonies detected on selective plates (containing selected antibiotic) to the total colonies detected on non-selective plates (without antibiotic)) of *Acinetobacter baylyi* was also studied under different fluence conditions (11–430 mJ/cm^2). Approximate UV fluence required per $\log_{10}$ loss of transformation efficiency was found to be 20–25 mJ/cm^2. Although

Table 3
Inactivation of ARGs by UV irradiation.

Mode	Peak λ	Source	Volume (mL)/flow rate	Target	Log inactivation	UV dose (mJ/cm^2)	k (cm^2/mJ)	Matrix	Reference
Full scale	NG	NG	130 mgd	*tet*R	0	30,100	NG	WW effluent	Auerbach et al., 2007
Bench-scale collimated beam	254	Lamp	10	*mec*A, *van*A, *tet*A, and *amp*C	3–4	200–400	0.4–0.25, 0.015–0.01	PB and WW effluent	McKinney and Pruden, 2012
Batch	254	Lamp	1500	*sul*1, *tet*G, and *intI*1	2.5–2.7	12,477	0.0002	WW effluent	Zhuang et al., 2015
Batch	254	Lamp	1800	*sul*1, *tet*X, *tet*G, *intI*1, and 16S rRNA	<1[a]	62.4, 124.8, 249.5	0.016, 0.008, 0.004	WW effluent	Zhang et al., 2015
Collimated beam	254	Lamp	NG	bla_{TEM-1}, *tet*A	1[b]	20–25	0.05–0.04	Plasmid suspension in DNase free water	Chang et al., 2017
Bench-scale quasi-collimated beam	254	Lamp	120	amp^R, Kan^R	4	60–140	0.11–0.07, 0.15–0.09	Phosphate buffer	Yoon et al. (2017)
Bench-scale quasi-collimated beam	254	Lamp	120	amp^R	4	150	0.06	Phosphate buffer	Yoon et al. (2018)

NG, not given; mgd, million gallons per day. WW, wastewater; PB, phosphate buffer.
[a] Value considered 1.
[b] 1-log reduction per UV fluence of 20–25 mJ/cm^2.

bla_{TEM-1} and *tet*A genes degraded at different rates, the rate of transformation efficiency loss after UV treatment was the same for both resistance genes on the same plasmid. This finding suggested that the transformation inactivation mechanism could be the same for both types of resistance genes. Although the *tet*A gene is larger than the bla_{TEM-1} gene, the first order reaction rate measured with qPCR was faster for bla_{TEM-1} than that for *tet*A (Chang et al., 2017) suggesting that DNA size alone could not be used to predict reactivity of a genome with UV irradiation. A possible reason for greater damage to the smaller gene could be the number of adjacent thymine bases as concluded by McKinney and Pruden (2012).

A comparison of the impact on intracellular and extracellular DNA at four UV fluences (50, 100, 200 and 400 mJ/cm^2) showed that *amp*C and *tet*A were more recalcitrant than *mec*A and *van*A in both intracellular and extracellular forms (McKinney and Pruden, 2012). According to the authors, the disappearance of ARG amplicons correlates with the number of adjacent T-T bases in the amplicon targets ($r = -0.93$). Considering these findings and relating them to those of Chang et al. (2017) regarding the length of the genes and associated reaction rates, it can be said that the T–T base content of DNA is more important than DNA size when predicting a genome's reactivity with UV irradiation at 254 nm (Chang et al., 2017). According to Chang et al. the bla_{TEM-1} gene contained ~1.5 times the number of adjacent T–T bases than *tet*A, but was only 72% the length of *tet*A, and the bla_{TEM-1} gene reacted ~1.2 times faster than *tet*A.

Furthermore, McKinney and Pruden (2012) suggested that the cell envelope played a role in protecting *van*A in *Enterococcus faecium* and *amp*C in *Pseudomonas aeruginosa* from UV attack, which represent a Gram-positive and a Gram-negative ARB, respectively. They concluded that *amp*C present in *P. aeruginosa* was highly resistant to UV, which could be attributed to the large amount of polymeric substances produced by the bacteria. In fact, intracellular *amp*C was even found to be detectable after UV fluence as high as 1000 mJ/cm^2. This variable response of ARGs was found to correlate with the potential thymine dimer sites with *amp*C having the least dimer sites and was therefore less susceptible to UV damage. The gene *mec*A, which carried the most dimer sites, was the most readily damaged ARG. The findings were consistent with a recent investigation in which comparable loss of ampicillin and kanamycin resistant genes was reported and which was related to the fairly similar number of adjacent thymine sites in the genes (Yoon et al., 2017). At UV fluence of 40 mJ/cm^2, the reductions in extracellular (e)-ARGs and intracellular (i)-ARGs (present within *E. coli*) in phosphate buffer were 1.8–2.6-log and 1.1–1.6-log, respectively. A much higher UV fluence was required to achieve 4-log damage of ARGs, e.g., the required UV fluences were 60–90 mJ/cm^2 for e-ARGs and 100–140 mJ/cm^2 for i-ARGs.

Some of the findings of Yoon et al. (2017) are in contrast to those reported by McKinney and Pruden (2012). For example, Yoon et al. concluded that the damage to i-ARGs occurred slowly (by a factor of ~1.7 ($p < 0.05$)) compared with the damage to the e-ARGs, demonstrating that the cellular components could play a protective role against the UV-induced i-ARG damage. However, McKinney and Pruden (2012) reported insignificant difference in the damage rates of extracellular and intracellular *tet*A genes during UV treatment of *E. coli* SMS-3-5. These differences in the findings might be related to the different *E. coli* strains and/or experimental conditions (e.g., the initial cell concentration). Moreover, Yoon et al. reported that the rates of ARG damage were fairly similar for both amp^R and kan^R (e-ARG, pH 8, $p = 0.84$; i-ARG, pH 7, $p = 0.18$; i-ARG, pH 8, $p = 0.56$) or were marginally lower than those of kan^R by a factor of 1.3 (e-ARG, pH 7, $p < 0.05$). The similar role of the cell envelope protecting the ARGs was reported for *van*A in *Enterococcus faecium* and *amp*C in *Ps. aeruginosa*, with *amp*C being the ARG most resistant to UV. The authors noted the presence of markedly more extracellular polymeric substances produced by the *Ps. aeruginosa* during cell plating. These findings indicate that the cell structure may play a protective role for different microorganisms, and whether this can be reduced or impacted by operating conditions needs to be determined. This would also help to explain the difference in findings as noted for Yoon et al. (2017) and McKinney and Pruden (2012).

Using a similar LP UV set-up as in their earlier investigation, Yoon et al. (2018) determined the loss of transformation efficiency of amp^R present in *E. coli* grown on LB agar plates and its damage during qPCR after UV and UV/H_2O_2 (10 mg H_2O_2) treatment. Four different amplicon lengths were selected for qPCR analysis which included 192 bps, 400 bps, 603 bps and 851 bps. For UV fluence of 40 mJ/cm^2, the loss of transformation efficiency of e-ARG was 1- and 1.3-log after UV only and UV/H_2O_2 treatment, respectively. Correspondingly, a much higher UV fluence (150 and 125 mJ/cm^2) was needed for achieving 4-log reductions in transformation efficiency of i-ARG. However, a similar UV fluence (150 mJ/cm^2) was reported for e-ARG for 4-log reduction in transformation efficiency. The fluence-based first-order rate constants (k) were fairly similar (0.061–0.064 cm^2/mJ) for both treatment processes under the UV fluences investigated except for UV/H_2O_2 for e-ARG for which the rate was slightly higher (0.073 cm^2/mJ).

In agreement with the others (Chang et al., 2017; McKinney and Pruden, 2012), Yoon et al. (2018) concluded that the extent of gene damage was greater for larger amplicon size due to a higher number of adjacent pyrimidine dimer sites available for UV attack. A comparison

between the transformation assay and qPCR demonstrated that the rate of gene damage as determined by qPCR was lower for the smallest amplicon size (192 bps) (up to 4-fold) compared with loss of transformation efficiency. The rates obtained for transformation assays were, however, comparable with qPCR results for 400 and 603 bps. The largest amplicon size (851 bps) yielded higher (1.1–2.5-fold) gene damage rate compared with that obtained for loss of transformation efficiency. These findings highlight the need for establishing a potential correlation between transformation and qPCR assays.

Consistent with their previous findings, Yoon et al. (2018) found that the ARG damage rate was higher for e-ARG compared with i-ARG during both UV and UV/H_2O_2 treatment. For example, for the largest amplicon, the e-ARG damage rates ranged between 0.1 and 0.18 cm^2/mJ compared with 0.072–0.073 cm^2/mJ for i-ARG during UV and UV/H_2O_2 treatment. These results also demonstrate fairly similar rates of damage for i-ARGs during both treatments but higher (0.18 cm^2/mJ) for e-ARGs for UV/H_2O_2 compared with UV photolysis only treatment (0.1 cm^2/mJ). These results were attributed to enhanced degradation of e-ARGs by HO• which in the case of i-ARGs was not able to reach the genes due to scavenging by either cell membrane or cytoplasmic components.

The authors concluded that the rate of loss of transformation efficiency was fairly comparable during both UV and UV/H_2O_2 treatments for e-ARGs, however, their loss as measured by qPCR varied by up to 1.8-fold. These results indicate that qPCR quantified the e-ARG damage caused by direct UV photolysis, HO•, and/or ROS. Transformation assays, however, only detected the damage related to direct UV photolysis. It was attributed to potential repair of the damage caused by HO• and ROS during the transformation assays. Therefore, despite the enhanced ARG loss as quantified by qPCR assay, the corresponding transformation efficiency was not reduced. This finding is consistent with that of Chang et al. (2017) reporting qPCR providing conservative assessment of the transformation ability of ARGs. It is therefore important to understand how transformation and qPCR assays (using different amplicon lengths including the whole genome) compare when repair is potentially minimised by using higher UV fluences or multi-wavelength UV-LEDs.

5.3.2. ARGs inactivation in wastewater matrices

Inactivation of ARGs in real wastewater has been increasingly reported in recent years. As shown in Table 3, when using UVC lamps, very high UV fluence was required for the inactivation of various ARGs (*tet*G, *sul*1, *intI*1) and 16s rRNA. Yoon et al. (2017) investigated the role of organics by determining the rate of ARG (*amp* and *kan*) damage in a wastewater effluent (DOC 5.2 mg/L). The authors reported that only marginally higher UV fluence was needed for ARGs inactivation in wastewater effluent compared with phosphate buffer. Similarly, McKinney and Pruden (2012) concluded no significant difference in the inactivation of ARGs in phosphate buffer and wastewater effluent (TOC 4.61 mg/L). However, the UV fluence required to achieve 3- to 4-log inactivation of ARGs (*mec*A, *van*A, *tet*A, *amp*C) was much higher (200–400 mJ/cm^2) compared with that reported by Yoon et al. (2017). It is worth noting that the wastewater samples used in both studies were filtered for turbidity removal before the UV treatment.

Even higher UV fluence requirements (up to 12,477 mJ/cm^2) were reported in another study for achieving approximately 2.5-log reduction of four ARGs (*sul*1, *tet*G, *intI*1, and 16 s rDN) in wastewater (COD, 13–29 mg/L) (Zhuang et al., 2015). Some factors which may affect the degree of inactivation of ARGs are the use of pure strains as in the case of McKinney and Pruden (2012) whereas those used by Zhuang et al. (2015) were mixed due to their presence in the municipal wastewater. The impact of other wastewater constituents such as bicarbonate alkalinity which ranged between 165 and 185 mg/L in the study of Zhuang et al. (2015) cannot be overlooked. Furthermore, the use of shorter length amplicons could limit the potential damage to the DNA and make the comparison of the results difficult. As mentioned earlier, it has been shown that the shorter amplicon used in qPCR leads to underestimation of the damage to DNA and therefore loss of the biological function of ARGs (Chang et al., 2017; McKinney and Pruden, 2012).

The authors (Zhuang et al., 2015) established a correlation between the removal of COD and other parameters and found that it showed significant correlation with *tet*W ($R = 0.636$, $p < 0.05$), *intI*1 ($R = 0.829$, $p < 0.01$) and *sul*1 ($R = 0.832$, $p < 0.10$) which was attributed to COD that could result in changing the microbial community composition. The negative impact of water matrix (presence of COD, organics, turbidity, suspended solids) on UV-based processes in water and wastewater treatment is well known. An earlier investigation (Auerbach et al., 2007) reported no inactivation of ARGs in wastewater effluent even after subjecting it to a very high UV fluence of 30,100 mJ/cm^2. It is important to highlight that the penetration of UV irradiation is significantly impacted by the presence of organic matter, turbidity and suspended solids, and it is therefore important to consider the impact of the water matrix in order to reduce the irradiation requirements and so improve energy/cost effectiveness.

Similarly, Zhang et al. (2015) investigated the inactivation of the ARGs *sul*1, *tet*X, *tet*G, *intI*1, and 16s rRNA genes present in a municipal wastewater treatment plant effluent (COD, 39 mg/L). At UV fluence of 249.5 mJ/cm^2, log inactivation values of *tet*X and 16s rRNA genes were 0.58 and 0.60, respectively, while for others it ranged from 0.36 to 0.40. These levels of inactivation are much lower than those for McKinney and Pruden (2012). Although it is not possible to draw a direct comparison between different studies, it is evident that the inactivation of ARGs in municipal wastewater effluent requires very high UV fluence when compared with the pure strains in simple water matrices. It should be emphasised that the UV fluence requirements are generally very high in real and complex wastewater matrices due to the demand exerted by the wastewater constituents.

Limited research has been carried out on the inactivation of ARB and no investigations of the inactivation of ARGs using UV-LEDs have been published to date. As a result, no direct comparison of different wavelength UV-LEDs for inactivation of ARGs is available. It therefore is important to investigate the extent of damage to ARGs (both i- and e-ARGs) under specific UV wavelengths both alone and in different combinations. Some of the research needs are common for both UV lamps and UV-LEDs. For example, of the investigations reported thus far using UV lamps, few have looked at transformation efficiency, the potential of which after different log inactivation of ARGs is important to understand. It should, however, be noted that a high ARG log inactivation may not necessarily imply complete loss of transformation ability. Because of repair mechanisms, the extent of DNA damage needed to make the ARG useless, to inactivate the gene permanently, or to make the ARG unsuitable for HGT is not known. Future studies therefore need to investigate DNA damage, as quantified by qPCR, and compare it with the transformation efficiency of the same UV-treated DNA to benchmark the DNA damage needed for unsuccessful HGT and to measure the potential for antibiotic resistance expression after UV treatment.

5.4. UV-based AOPs for inactivation of ARB and ARGs

As mentioned earlier, UV/H_2O_2 is one of the most widely investigated and applied AOPs in water and wastewater treatment and relies on the photolysis of H_2O_2 to generate HO• (Parsons, 2004). Some studies have drawn a comparison between direct UV photolysis and AOPs for damaging DNA. For example, the inactivation efficiency of plasmid-encoded ARGs both in e-ARG and i-ARG forms during water treatment with chlorine, UV (254 nm), and UV/H_2O_2 (10 mg/L) was investigated in a recent study (Yoon et al., 2017). The authors used qPCR analysis to quantify the damage to the *amp*R (850 bp) and *kan*R (806 bp) amplicons (initial plasmid copies were 10^{14}/mL) which are located in the pUC4K plasmid. The e-ARGs were damaged faster, i.e., ~1.5-fold greater damage occurred during UV/H_2O_2 compared with UV only treatment ($p < 0.01$ for all cases, except *amp*R at pH 8) in phosphate buffer

solution at all investigated UV fluences (40–140 mJ/cm^2). The UV fluence required for 4-log e-ARG inactivation was 60–90 mJ/cm^2 using UV only whereas the corresponding UV fluence using UV/H_2O_2 was ~50 mJ/cm^2 except for *amp*R which needed 90 mJ/cm^2 at pH 8. However, in the wastewater effluent, the contribution of HO• to i-ARG damage was negligible for UV/H_2O_2 which was most likely the result of scavenging of HO• by organics and inorganics.

A UV-based AOP (UV/H_2O_2) using 20 mg/L H_2O_2 and a wide spectrum 250 W lamp equipped with a UV filter (main emission 320–450 nm) was investigated for its potential to inactivate ARG bla_{TEM} (Ferro et al., 2016). It should be noted that the wavelength range used in this study is not typically used in disinfection applications, and the range of wavelengths used can significantly impact the resulting treatment efficacy. The gene was quantified before and after treatment using qPCR. The detection limit of residual antibiotic resistant *E. coli* colonies was set at 5 CFU/mL (initial concentration of 10^5 CFU/mL) which was obtained after 240 min treatment (~2000 mJ/cm^2). However, bla_{TEM} was found to be present at a concentration of 2.8×10^6 copies/mL which was close to the initial value (not given by the authors) even after 300 min (UV fluence of 25,000 mJ/cm^2). Similarly, no effect was observed on DNA extracted from cell cultures after 90 min (3.8×10^8 copies/mL). It is noteworthy that the UV fluence applied was extremely high and would not be practical for real applications. Even at such high fluences, the treatment process could select for certain ARGs resulting in potential transfer of antibiotic resistance to the environment.

The impact of pH, H_2O_2 dose and time of UV irradiation using a 254 nm UV lamp was investigated for the inactivation of *sul*1 (1.91×10^5–2.19×10^6 copies/mL), *tet*X (1.26×10^7–6.31×10^7 copies/mL), *tet*G (1.66×10^5–1.51×10^6 copies/mL), *intI*1 (5.25×10^5–3.31×10^6 copies/mL), and 16 s rRNA genes (4.37×10^7–3.72×10^9 copies/mL) (Zhang et al., 2016). A rapid inactivation of ARGs (≥1-log) was noted during the first 5 min of irradiation at H_2O_2 concentration of 340 mg/L and pH of 3. This H_2O_2 concentration and pH were considered best of the investigated range since inactivation of ARGs was negatively impacted below and above these values. Increasing the irradiation time led to a gradual increase in the inactivation such that the log reduction of *sul*1, *tet*X, *tet*G, *intI*1, and 16 s rRNA genes was 2.83, 3.48, 3.05, 2.98, and 2.64, respectively, under the best pH (pH 3) and H_2O_2 dose (300 mg/L) conditions.

UV/TiO_2 has been investigated for the inactivation of microorganisms including ARB as well as associated ARGs (Dunlop et al., 2015; Rizzo et al., 2014; Xiong and Hu, 2013). A recent study investigated the inactivation of ARB and ARGs (*mec*A and *amp*c) using a 254 nm LP mercury lamp in the presence of a thin TiO_2 film prepared by a dip coating method (Guo et al., 2017). The authors also investigated the impact of matrix (phosphate buffer cf. drinking water) and the addition of H_2O_2 on the inactivation efficiency. They reported ~4.5–5.0- and ~5.5–5.8-log reduction of ARB (initial concentration not given) during UV/TiO_2 treatment at UV fluence of 6 and 12 mJ/cm^2, respectively. Under similar conditions, a much higher UV fluence was needed to achieve a comparable inactivation of ARGs, i.e., 120 mJ/cm^2 for 5.8- and 4.7-log reduction of *mec*A and *amp*C (initial concentration not given), respectively. Furthermore, the authors noted that an increase in the dosage of H_2O_2 (ranged over 340–3400 mg/L) enhanced (up to ~1.5-log) the inactivation efficiencies of both ARB and ARGs.

Investigating the impact of H_2O_2 alone and UV/H_2O_2 treatment, Guo et al. (2017) noted that UV irradiation improved the inactivation efficiency of *mec*A and *amp*C by 1.3- and 2.2-log units, respectively. For a UV fluence of 120 mJ/cm^2, approximately 2.3–2.9- and 1.4–2.7-log inactivation of *amp*C and *mec*A was achieved with different concentrations (340, 1700 and 3400 mg/L) of H_2O_2. With the addition of thin TiO_2 film, the inactivation of *mec*A and *amp*C improved to 2.7–3.4- and 2.7–3.2-log, respectively. No matrix effect was reported by the authors, but these findings need to be considered with caution since they did not report the composition of the water, except turbidity which was 1.8 NTU.

Xiong and Hu (2013) investigated a photocatalytic disinfection system using TiO_2 film for the inactivation of antibiotic resistant *E. coli* ATCC 700891 (contains ampicillin and streptomycin resistance markers, initial concentration of 6×10^4 CFU/mL) using UVA-LEDs (365 nm). Under the intensity range of 6–8 mW/cm^2, the UV fluence requirement for 3-log inactivation decreased from 870 mJ/cm^2 to 688 mJ/cm^2. Increasing the circle time (the authors used "circle" instead of conventionally used "cycle" time and they defined circle time as one "on" plus "off" time, and focused on the effect of pulse frequency) from 20 to 2000 ms decreased log inactivation of *E. coli* from 1.26 to 0.54. They postulated that the lower pulse frequency and longer circle time provided more recovery time for bacterial repair which resulted in slowing down their inactivation at similar UV dose.

Due to increasing applications of UV lamp-based AOPs for controlling the spread of antibiotic resistant determinants, the use of UV-LEDs for such applications is expected to be the focus in coming years. Although there are no reports to date of using UV-LEDs as an AOP for damaging ARB and ARGs, the common challenges that could influence the inactivation and potential reactivation of ARB are those closely related to the impact of operating parameters in the application of conventional UV-based AOPs. However, this is only relevant if the ARB and ARG inactivation mechanisms and speciation of radicals generated are similar during irradiation by UV-LEDs and conventional mercury UV lamps at similar wavelengths. Another important concern is that AOPs, like UV alone, might lead to enhanced resistance and selective increase in some bacterial strains. The highly oxidizing conditions damage the cell walls and membranes as well as internal components (enzymes, DNA) which could lead to selecting resistant strains with greater capacity to resist such stresses (Süss et al., 2009). Under certain circumstances, both UV photolysis and AOPs have been shown to increase the relative abundance of both ARB and ARGs, even in the absence of direct selection by a specific antibiotic (Ferro et al., 2017; Zhuang et al., 2015). Like UV disinfection, defence and repair mechanisms can also lead to the survival of ARB (Rizzo et al., 2013). Optimisation of the process and understanding the mechanism of selection is therefore important to be addressed in future studies.

5.5. UV/chlorine combination for disinfection

UV irradiation can be combined with chlorine for achieving greater disinfection efficiency than that of each individual disinfectant. UV photolysis of chlorine generates a diverse range of highly reactive species such as HO•, and Cl• (redox potential of 2.4 V) (Beitz et al., 1998; Watts and Linden, 2007). However, HO• was found to be >5-fold the concentration of Cl• and therefore contributes more to the process performance (Chuang et al., 2017). The generation of HO• during a UV/chlorine AOP showed a synergistic effect due to damage to the viral genome (Rattanakul and Oguma, 2017). It must be noted that the pH has to be carefully controlled when HOCl is used in the UV/chlorine AOP since it significantly affects the molar absorption coefficient (Miklos et al., 2018). The photodecay rates during the UV/chlorine process depend mainly on UV wavelength which is related to the wavelength dependent molar absorption coefficient rather than quantum yield (Omary and Patterson, 2017; Yin et al., 2018). The photodecay rate of chlorine was also shown to increase with increasing pH at any wavelength.

Inactivation of *B. subtilis* spores was investigated in collimated beam experiments using 265 nm and 280 nm UV-LEDs both alone and as an AOP coupled with chlorine (Li et al., 2018). The water matrices used were phosphate buffer and reclaimed water collected from a membrane bioreactor wastewater treatment plant. At UV fluence of 125 mJ/cm^2, the inactivation rate constants for 265 nm and 280 nm irradiation were 0.024 and 0.017 cm^2/mJ increasing to 0.046 and 0.035 cm^2/mJ after UV/Cl (4 mg/L) treatment, respectively. The authors also

investigated the UV fluence of 40 mJ/cm^2 (recommended fluence for 4-log inactivation of pathogenic microorganisms) during the primary combined step followed by either UV or chlorine as a post treatment, i.e., UV/Cl-UV and UV/Cl-Cl. The enhancement of the inactivation of spores increased markedly during both processes with UV/Cl-Cl showing greater inactivation than with UV/Cl-UV. The inactivation rate of spores increased 2.1- and 1.6-fold for 265 and 280 nm, respectively, after UV/Cl-Cl treatment compared with Cl alone treatment. It was concluded that the role of HO• was crucial during the treatment as also shown in other investigations for the inactivation of *B. subtilis* using other AOPs (i.e., UV/H_2O_2) (Cho et al., 2006). The authors reported lower inactivation of spores when present in reclaimed water, both for 265 and 285 nm during the UV/Cl-Cl process. However, the increase in the reaction rates was 2.3- and 1.7-fold after UV/Cl-Cl compared with Cl_2 only treatment, which was fairly similar for phosphate buffer as mentioned above.

Using LP mercury lamps, the sequential UV/chlorination process was investigated for *sul*1, *tet*X, *tet*G, *intI*1, and 16 s rRNA genes in municipal wastewater effluent (Zhang et al., 2015). Compared with UV alone, sequential UV/chlorination led to synergistic values ranging between 0.006 and 0.031-log removals for the investigated genes (Zhang et al., 2015). 16 s rRNA showed the highest synergy whereas *tet*X showed the least. It is also important to note that the amplicon length used in this study was short (163–280 bp) which, as mentioned earlier in Section 5.3.2, makes it hard to evaluate the overall damage to the genes. It must also be noted that the concentration of chlorine in the sequential process was 25 mg/L which is much higher than used in practice which rarely exceeds 2 mg/L (Government of Canada, 2016).

Both sequential and simultaneous UV/chlorine disinfection was evaluated by Shang et al. (2007) for MS2 inactivation. When compared with chlorine alone, the sequential and the simultaneous processes in the primary disinfection stage resulted in enhanced MS2 inactivation rates by 1.5–2.7 times upon secondary disinfection with chlorine. Importantly, the UV fluence used was 51 mJ/cm^2 which is not very high considering the value generally recommended (40 mJ/cm^2) for pathogenic inactivation. Sequential and simultaneous UV/chlorine processes were also investigated for inactivation of adenovirus and MS2 using 254 nm LP mercury lamps (Rattanakul et al., 2014; Rattanakul et al., 2015). Using a much lower chlorine dose of 0.15 mg/L and with UV fluence of 50 mJ/cm^2, Rattanakul et al. (2015) achieved 4-log inactivation of HAdV-5 with the combined chlorine/UV process. This level of inactivation was much higher than individual UV treatment which required a UV fluence of 100 mJ/cm^2 for achieving 2-log inactivation. Furthermore, the authors found that pre-treatment with chlorine could increase the viral sensitivity to subsequent UV irradiation since it had a synergistic effect on HAdV-5 inactivation, but not for the UV followed by chlorine process. Similar results were reported in their earlier investigation for HAdV-5 (Rattanakul et al., 2014). They also investigated inactivation of MS2 and reported it was also synergistic for combined UV and chlorine treatment with 2.3-fold greater inactivation than for the individual processes. The sequential UV-chlorine and chlorine-UV processes were also investigated for MS2 inactivation, and both treatments showed synergistic effect for MS2 inactivation in terms of time-based inactivation rates. The inactivation rate during chlorine-UV sequential treatment was noted to be higher (0.11 s^{-1}) compared with the combined process (0.09 s^{-1}), which was in agreement with their earlier findings for HAdV-5.

The combination of UV and chlorine could also be advantageous for minimising the potential for selection of resistant microorganisms due to lower chlorine requirements which would also be beneficial in lowering the formation of DBPs. Reduced UV fluence is another potential advantage that could consequently reduce the energy and total cost of the combined UV/Cl treatment. However, research in this particular area is rather limited. Nonetheless, a combination of chlorination and UV irradiation appears to be a good way to not only improve the inactivation of ARGs and ARB, but also to reduce the possibility of bacterial re-growth in water distribution systems, minimise microbial selection and the formation of DBPs.

6. Energy assessment

Estimation of E_{EO} using UV-LEDs at various wavelengths (265 nm, 280 nm, 300 nm) was carried out for 3-log inactivation of *Ps. aeruginosa*, *Legionella pneumophila*, and surrogate microorganisms, including *E. coli*, bacteriophage *Q*b, and *B. subtilis* spores (Rattanakul and Oguma, 2018). A comparison of the E_{EO} with a 254 nm LP mercury lamp was also made. Of the UV-LEDs, 300 nm was the most energy intensive wavelength for all microorganisms and the highest E_{EO} required (17.4 kWh/m^3) was for the *B. subtilis* spores followed by *Q*b (7.44 kWh/m^3). A similar trend was observed for 265 nm and 280 nm UV-LEDs with lower E_{EO} needed for the bacterial species compared with the *B. subtilis* spores and *Q*b, although that needed for the spores was lower than for *Q*b at these wavelengths.

It was shown that irradiation at 280 nm required almost half the energy as at 265 nm for a similar level of inactivation. The greater energy efficiency for 280 nm (WPE, 0.019) compared 265 nm (WPE, 0.006) was attributed to the difference in WPE (the germicidal emission output per electrical energy input) (Oguma et al., 2018). UV-LEDs emitting at 280 nm were therefore the most energy efficient for all of the microorganisms investigated. The highest E_{EO} required for 300 nm UV-LEDs was attributed to the lowest inactivation of all microorganisms despite the highest WPE (0.026). The E_{EO} value reported by Rattanakul and Oguma (2018) for *E. coli* inactivation using 280 nm UV-LEDs was lower (1.04 kWh/m^3) compared with Beck et al. (2017). The lower E_{EO} for 280 nm was attributed to the ~4-fold higher WPE compared with that for Beck et al. (2017). Moreover, the strains of *E. coli* used in these two studies were different. According to Rattanakul and Oguma (2018), the LP mercury lamp was the most efficient compared with all UV-LED wavelengths with E_{EO} ranging between 0.006 and 0.064 kWh/m^3. For example, LP mercury lamps required 25–40-fold less energy than the 265 nm UV-LEDs for 3-log inactivation of the microorganisms studied. Similar to the findings for UV-LEDs, the E_{EO} requirement using the LP mercury lamp was lower for the bacterial species than for the bacteriophage *Q*b and *B. subtilis* spores.

A comparison of the energy efficiency was made for 260 nm and 280 nm UV-LEDs both individually and in combination for inactivation of *E. coli*, MS2 coliphage, HAdV2, and *B. pumilus* spores (Beck et al., 2017). For 1-log inactivation of *E. coli*, 260 nm was the least efficient (0.464 kWh/m^3) in terms of energy requirements compared with 280 nm (0.347 kWh/m^3) and the combination of 260 and 280 nm (0.379 kWh/m^3) UV-LEDs. For MS2, the combination of both wavelengths was slightly more energy efficient than the individual wavelengths, but the results were not statistically significant. For 2-log inactivation of *B. pumilus*, the required E_{EO} was fairly similar for 280 nm (19.4 kWh/m^3) and 260 nm (19.7 kWh/m^3) with combined wavelengths having the lowest E_{EO} (17.8 kWh/m^3). Similar results were reported for 2-log inactivation of HAdV2, with 260 nm being slightly more energy intensive (5.1 kWh/m^3) compared with 280 nm (4.4 kWh/m^3) and the combination of both wavelengths (4.972 kWh/m^3). The authors compared LP and MP mercury lamps. They concluded that the LP mercury lamp was the least energy intensive for *E. coli* and MS2 whereas a comparable E_{EL} (electrical energy per 2-log reduction) was noted for HAdV2 for the two lamps. Although the MP UV lamp was 2.3-fold more energy efficient than the LP UV lamp, enhanced inactivation (~2.3-fold) of HAdV2 at low wavelengths (<240 nm) during MP UV irradiation resulted in comparable E_{EL} for both lamps. Similar results were reported for *B. pumilus* regarding E_{EL}. These findings would be useful in the future development and application of the UV-LEDs which could irradiate in the lower UVC range (<240 nm) and achieve enhanced inactivation for some microorganisms.

The energy required to achieve certain level of inactivation is a useful indicator for comparing UV lamps and UV-LEDs but also different UV-

LED wavelengths. However, for comparison to be valid and appropriate between different studies, it is important that the differences in target microorganisms, system design, WPE, peak wavelengths and other operational factors (mode of irradiation, duty cycle, etc.) are considered. It is therefore important that these aspects are realised since it is anticipated that increasing attention will be paid to the energy aspect (between different UV-LED wavelengths and UV lamps) in future investigations.

A comparison with LP mercury lamps at this stage may not be fair since they are markedly more electrically efficient than UV-LEDs. Although higher (up to ~22% for 365 nm) WPE has recently been reported for UVA-LEDs as discussed later in Section 7, it currently stands at 1–3% for UVC-LEDs, which is much lower than that for LP UV lamps (30–40%) (Autin et al., 2013). While the special features of UV-LEDs such as pulse irradiation is shown to reduce energy demand when compared with continuous irradiation (Ku et al., 2017), these results are for the degradation of organics and are based on the time of irradiation rather than UV fluence. It has been mentioned previously that the UV fluence delivered cannot be simply assumed to be equivalent for pulse and continuous irradiation modes based on the irradiation time. Similarly, the impact of duty cycle on energy efficiency also needs to be considered in future investigations. Similarly, there is a lack of direct comparison of the E_{EO} required using different wavelength UV-LEDs. Such comparison is very important to correlate and compare the inactivation efficiency of different wavelengths with the energy requirements.

Ongoing developments will see substantial increase in the WPE of UV-LEDs and they are projected to be much more competitive with the LP mercury lamp systems. It is recommended that studies of the energy requirements for the inactivation of ARB and ARGs for different UV-LED wavelengths and operational conditions be undertaken in future. To date there has been no research on the energy required for different levels of inactivation of ARGs using UV-LEDs, and hence no comparative assessments with conventional UV lamp systems are available. Moreover, cost estimation has yet to be made for UV-LEDs for disinfection applications, but it is known that at the current stage they are not comparable (with respect to their output) to conventional LP mercury lamps.

7. Future of UV-LED technology

Significant improvements in external quantum efficiency (EQE) (ratio of the number of photons emitted from the LED to the number of electrons passing through the device) due to developments in crystal growth, chip processing, and packaging technologies, particularly for UVA-LEDs, have been made recently. For example, for 375 nm, EQE of up to 43.2% has been reported at an output power of 28.7 mW at 20 mA, and 30% for 365 nm (Muramoto et al., 2015). Likewise, the WPE of UVA-LEDs (365 nm) has improved markedly to 22.1% (Tien et al., 2017). The EQE of UV-LEDs decreases rapidly with increase in the molar fraction of aluminium content, i.e., as the wavelength decreases (Kneissl et al., 2011), hence the EQE and WPE of UVC-LEDs are much lower than for UVA-LEDs. Recent advancements for enhancing the EQE of UV-LEDs through improvements such as high-quality AlGaN epitaxial layers, transparent and reflective ohmic contacts, and light extraction have been reviewed by Park et al. (2017).

In the past decade, the EQE of UVC-LEDs has increased from <0.1% to >10% (Park et al., 2017). In 2015, the highest EQE in the 280–300 nm range was 14.3% (Chen et al., 2017; Hirayama et al., 2014). By enhancing the light extraction efficiency through additional features (a transparent AlGaN:Mg contact layer, a Rh mirror electrode, an AlN template on a patterned sapphire substrate, and encapsulation resin) a recent study reached EQE efficiency of 20.3% for 285 nm (Takayoshi et al., 2017). These modifications led to an increase of WPE from 2.2% to 5.7%. A corresponding increase in output power from 3.9 to 18.3 mW (20 mA) and from 9.3 mW to 44.2 mW (50 mA) was also reported.

As the output power has increased, the corresponding cost of UV-LEDs has decreased, primarily due to mass production (Muramoto et al., 2015). As mentioned earlier in Section 3, some UVA wavelengths are approaching the efficiency equivalent of blue LEDs (Galbraith, 2016). These improvements are happening along with an increase in the lifespan which is dependent on the wavelength of UV-LEDs (Chen et al., 2017). For example, 365 nm and 250 nm UV-LEDs have been reported to have a lifespan expectancy of 26,000 h and 2000 h, respectively (Chen et al., 2017). Similarly, from a lifetime of a few hundred hours in 2010, lifetime in excess of 10,000 h was reported in 2016 for 50 mW UVC-LED (285 nm) (Nikkiso, 2016). A much higher life expectancy of ~45,000 h (approximately 3-fold more than existing LP mercury lamps) was reported for 285 nm UV-LEDs (METAWATER, 2017). Ongoing cost reductions in UVC-LEDs are projected to result in taking over the UV curing market by 2019–2020 (Yole Development, 2016). These developments have widened the range of applications of UV-LEDs, and continuing improvements in their output power and energy efficiency, and reduction in cost, are expected to make this technology a competitive alternative to traditional UV systems.

In parallel with the increasing application of UV-LEDs for disinfection and oxidation of organic contaminants, their application for the inactivation of ARGs has started to emerge. It is recommended that particular focus be given to the advantages of the use of specific wavelengths, appropriate reactor design, and improving energy efficiency since the UV fluence will need to be markedly higher to inflict substantial DNA damage. Since UV lamps have mainly been used, with very few investigations using UV-LEDs for this purpose, and given that inactivation of ARGs requires a significantly higher fluence than bacterial disinfection, the energy efficiency becomes particularly important when using UV-LEDs.

Finally, the research questions related to the development of UV-LED reactors, fluence requirements and benchmarking UV fluence requirements for complete inactivation of ARGs vs disinfection remain to be addressed. One important area to facilitate widespread application of UV-LEDs that some recent studies have attempted to address is development of a standard protocol for comparison of the different wavelengths for disinfection and oxidation, for both UV-LED and UV lamp technology by Kheyrandish et al. (2017, 2018). The authors developed a protocol for accurate control and measurement of the output of UV-LEDs (Kheyrandish et al., 2017), and estimation of the UV fluence and calculation of various factors including petri factor, water factor, divergence factor, reflection factor, and collimation factor (Kheyrandish et al., 2018).

Despite the well-established nature of UV lamp technology, there is increasing interest in UV-LED technology given the advantages of LEDs over UV lamp-based systems. However, the competitiveness of UV-LEDs with conventional UV lamps needs to be demonstrated in terms of the advantages they provide through, for example, the combination of desired wavelengths and their potential synergistic effect, energy efficiency, and other operational advantages such as pulse vs continuous irradiation. Considering the different mechanisms involved in disinfection and damage to DNA, investigation of the effectiveness of the combination of low, intermediate, and higher wavelength UV-LEDs for direct and indirect damage looks promising.

8. Conclusions

Disinfection using UV irradiation with a particular focus on controlling antibiotic resistance is reviewed in relation to the potential of UV-LEDs as possible alternatives to UV lamps in future applications. UV-LEDs have emerged as a potentially competitive and promising alternative source of UV irradiation to conventional mercury lamps for disinfection. Although the current low output power of UV-LEDs and high cost are the main limitations to their application in water and wastewater treatment, significant developments in terms of wall plug efficiency, external quantum efficiency, and output power have been made over

the last few years. These developments, combined with improved reactor design, are expected to improve the overall viability of their application.

Increasing concern regarding the spread of antibiotic resistance bacteria (ARB) and genes (ARGs) further highlight the significant benefit of UV technology since LP mercury lamp-based UV irradiation has been used successfully to inactivate ARB and ARGs. However, the required UV fluence and therefore energy requirement to achieve an adequate level of DNA damage (i.e., to avoid environmental spread/transfer) could be very high, which limits the large-scale application of conventional UV lamps. Better understanding of the effectiveness of combinations of different wavelength UV-LEDs for efficient control of ARB and ARGs is required for developing the technology. Since most of the investigations have looked only at log inactivation of ARGs, it is important to understand how the log ARG inactivation correlates with different mechanisms of gene transfer with a view to determining the level of ARG inactivation required to achieve the desired level of treatment. These aspects need to be considered for UV irradiation in general and UV-LEDs in particular, since their use for controlling antibiotic resistance is limited. UV/chlorine and UV-based AOPs have been investigated less than direct UV photolysis, although they could offer several attractive advantages including enhanced inactivation of ARGs.

UV-based treatment processes could lead to selection for certain ARGs, resulting in potential transfer of antibiotic resistance to the environment. Further work on determining the appropriate conditions to avoid selection pressure is required, including benchmarking the UV fluence required to avoid selection pressure for various ARB and ARGs. Consequently, disinfection under different operational conditions such as wavelength, pulse irradiation and duty cycle need to be investigated. Further research on energy assessment and repair mechanisms, particularly with different combinations of UV-LED wavelengths, could give a better picture of the total inactivation potential of those combinations.

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