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Review Article

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222-nm UVC light as a skin-safe solution to antimicrobial resistance in acute hospital settings with a particular focus on methicillin-resistant *Staphylococcus aureus* and surgical site infections: a review

Alexis Panzures*

Institutional affiliation: University of St Andrews, St Andrews, Fife KY16 9TF, UK

*Corresponding author. School of Medicine, University of St Andrews, North Haugh, St Andrews, Fife KY16 9TF, UK. E-mail: ap318@st-andrews.ac.uk

Abstract

The increasing burden of antimicrobial resistance necessitates a novel approach to disinfect multidrug resistant pathogens. Conventional 254-nm ultraviolet-C (UVC) light shows high germicidal efficacy against bacteria. However, it induces pyrimidine dimerization in exposed human skin with carcinogenic potential. Recent developments suggest 222-nm UVC light can be used to disinfect bacteria and cause less harm to human DNA. This new technology can be used to disinfect healthcare-associated infections and more specifically surgical site infections (SSIs). This includes but is not limited to methicillin-resistant *Staphylococcus aureus* (MR*SA*), *P. aeruginosa*, *C. difficile*, *E. coli*, and other aerobic bacteria. This thorough review of scarce literature assesses the germicidal efficacy and skin safety of 222-nm UVC light with a particular focus on its clinical applications to MR*SA* and SSIs. The study reviews a variety of experimental models, including *in vivo* and *in vitro* cell cultures, live human skin, human skin models, mice skin, and rabbit skin. The potential for long-term eradication of bacteria and efficacy against specific pathogens is appraised. This paper focuses on the methods and models used in past and present research to determine the efficacy and safety of 222-nm UVC in the acute hospital setting with a focus on MR*SA* and its applicability to SSIs.

Keywords: UV light, surgical site infection, MR*SA*, skin, disinfection

Introduction

Increasing misuse of antimicrobials in the last two decades has caused one of the greatest threats to global patient health, known as antimicrobial resistance (AMR) (Ferri et al. 2015). Specifically, the frequent overuse of antibiotics in clinics has caused increased antibiotic resistance genes amongst human pathogens such as methicillin-resistant *Staphylococcus aureus* (MR*SA*) (Wencewicz 2019). MR*SA* toxins and immune-modulatory gene products create the epidemiological challenge of treating complex MR*SA* strains globally (Klein et al. 2021).

Hospital-acquired infections (HAIs) are secondary infections leading to poor outcomes in hospital patients and are often associated with surgical sites (Boey and Kiss 2017). Surgical site infections (SSIs) are a large cause for patient mortality and morbidity in postsurgical care (Young and Khadaroo 2014). The risk of SSIs with multidrug resistant (MDR) pathogens is remarkable. Mengesha et al. (2014) determined 82.92% of isolates in postsurgical wound infections were MDR pathogens. Similarly, *S. aureus* was the most common SSI pathogen in hospital cases with 39.2% of *S. aureus* isolates resistant to methicillin (Salmanov et al. 2019). It is known that enhanced terminal disinfection of contaminated healthcare environments with UVC light decreases the risk of acquiring these AMR pathogens (Anderson et al. 2017). These findings encourage further inquiry into the role of UVC light as a germicide in the clinical environment.

In recent years, 254 nm near-UVC light has been used as an effective hospital room decontaminant; however, it is known to be carcinogenic and cataractogenic (Rutala and Weber 2015, Welch et al. 2018). While conventional low-pressure mercury-vapor 254-nm UVC is an effective disinfectant technique in hospitals for medical equipment, exposure in the clinical setting places human health in danger of erythema and skin cancers (Gharbi et al. 2020). The challenge in targeted implementation of UVC light is the ability to use it in an occupied space (Buonanno et al. 2020). The krypton–chloride (KrCl) excimer lamp is a far-UVC light operating at the 222 nm wavelength (Ponnaiya et al. 2018). With similar penetrance of bacterial cells to 254-nm UVC, 222-nm UVC shows less penetrance of mammalian skin cell barriers (Buonanno et al. 2017). It cannot penetrate the outer non-living layer of the human skin, however it is strongly absorbed in bacteria and viruses (Welch et al. 2018). Additional higher penetrating photons in non-peak transmissions can cause erythema and DNA photodamage (Buonanno et al. 2021). A lamp may be equipped with a bandpass filter to improve spectral purity by reducing transmissions outside 222 nm.

Germicidal efficacy of 222-nm UVC refers to its ability to eradicate certain pathogens. A variety of factors influence the germicidal efficacy of this novel technology, including the dose of radiation, the wavelength of radiation, degree of exposure, and sensitivity of the microorganism to UVC light (Reed 2010, Rutala and Weber 2015). The germicidal efficacy is evaluated by comparing log reductions in bacterial counts before and

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after irradiation and a total reduction refers to complete sterilization.

The use of germicidal UVC in hospital settings is often disputed by its safety for use on human skin. In the outermost protective layer of the skin, keratinocyte differentiation forms the terminal corneocyte and provides mechanical strength in the stratum corneum matrix (Gutowska-Owsiak et al. 2020). Reduced integrity of this barrier allows for subsequent damage to innate defences. Thus, the amounts of DNA photodamage adducts *cyclobutane pyrimidine dimers* (CPDs) and *DNA 6–4 photoproducts* (6–4PPs) induced in keratinocytes are common measurements of skin safety in this review. CPDs and 6–4PPs are quantified by enzyme-linked immunosorbent assay (ELISA), immunohistological analysis (IHC), or high-performance liquid chromatography (HPLC), and mass spectrometry. Conventional 254 nm technology is shown to form CPDs, which cause erythema and carcinogenesis (Hessling et al. 2021). Near-UVC also negatively impacts the upward migration of keratinocytes which causes biomechanical photoaging by structural degradation (Narita et al. 2018a, Lipsky and German 2019). UVC of wavelength 222 nm is conversely shown to have no notable effect on the natural migration of keratinocytes (Narita et al. 2018a).

Preventing AMR can be accomplished by eliminating the persistent overuse and exploitation of antibiotics with antimicrobial stewardship (AS). AS uses a conscientious approach to consuming and prescribing antibiotics for drug treatment and is shown to decrease AMR and increase positive patient outcomes when used with concurrent hygiene policy (Septimus 2018). A recent study by Maeda et al. (2012) showed that UVC at sublethal doses did not affect the minimum inhibitory concentration (MIC) of antibiotics. As such, AS may be redefined globally to prioritise access to antibiotic therapy for lower income communities (Buckel et al. 2018). AS is one of the global community's most powerful tools in reshaping AMR. UVC of wavelength 222 nm in healthcare policy may optimise bacterial eradication while minimising antibiotic use.

AIMS

This paper investigates the use of 222-nm UVC light to eradicate pathogens on patient skin, hospital surfaces, and tools with a particular focus on MR*SA*. The aims of the paper are:

1) To evaluate and compare the germicidal efficacy of 222-nm UVC light against MR*SA*, *P. aeruginosa*, *C. difficile*, *E. coli*, and other aerobic bacteria.
2) To evaluate the safety concerns of 222-nm UVC light on human skin.
3) To determine the role of 222-nm UVC in AMR with a focus on treating SSIs.

Literature search

Online databases Ovid MEDLINE(R) and Embase were searched in November 2022. The databases were searched for keywords and titles using the terms *UVC*, *far-UVC*, and *222* in several combinations with *skin*, *safety*, *germicide*, *germicidal*, *disinfection*, and *MRSA*.

The review included studies that used 222-nm UVC; studies that irradiated the pathogenic organisms MR*SA*, *P. aeruginosa*, *E. coli*, *C. difficile*, and aerobic bacteria from hospital settings; and studies that tested skin safety; *ex vivo*, *in vivo*, and *in vitro* studies; mammalian skin and mammalian skin models; and exploratory laboratory research, exploratory clinical trials, pilot studies, and hybrid studies. The review excluded studies that did not emit principally at the 222-nm UVC wavelength; studies that only irradiated corneas; reviews, abstracts, letters, editorials, and opinions; and articles that did not address the aims previously identified. The Preferred Reporting Items for Systematic Reviews (PRISMA) method was used to select studies in the literature review (see Fig. 1) (Page et al. 2021).

Results

Experimental properties

Each study was categorized and assessed according to experimental model and design, technology used, and method of CPD quantification (if applicable). In this review, normal skin was defined as intact and wounded skin was either ulcerated or experimentally incised. The papers were first appraised for the experimental specimen. Of the 15 papers, 5 used cell culture plates (Buonanno et al. 2017, Narita et al. 2020, Taylor et al. 2020, Kaiki et al. 2021, Ivanova et al. 2022), 5 used normal animal skin (Narita et al. 2018a, b, Yamano et al. 2020, Yamano et al. 2021, Narita et al. 2022), 3 used wounded animal skin (Ponnaiya et al. 2018, Narita et al. 2018a, Fukui et al. 2022), 2 used normal human skin (Woods et al. 2015, Fukui et al. 2020), 1 used wounded human skin (Goh et al. 2021), and 2 used human skin models (Buonanno et al. 2017, Ivanova et al. 2022) (see Fig. 2).

The papers were appraised for the KrCl lamp used. In total, six different lamps were used across the 15 papers. Two papers used CARE222 (Ushio Inc., Tokyo, Japan) (Taylor et al. 2020, Kaiki et al. 2021), 1 used an unidentified model by High Current Electronics Institute (Tomsk, Russia) (Buonanno et al. 2017), 1 used a MED-UV prototype (GME, Germany) (Ivanova et al. 2022), 9 used SafeZoneUVC (Ushio Inc., Tokyo, Japan) (Narita et al. 2018a,b, Fukui et al. 2020, Narita et al. 2020, Yamano et al. 2020, Goh et al. 2021, Yamano et al. 2021, Fukui et al. 2022, Narita et al. 2022), 1 used Sterilray (Sterilray Health Innovations, Dover, New Hampshire, NH, USA) (Woods et al. 2015), and 1 used an unidentified prototype model by Ushio (Ushio Inc., Tokyo, Japan) (Ponnaiya et al. 2018). The studies were further analyzed by the absence or addition of a bandpass filter. A total of nine studies used a bandpass filter (Buonanno et al. 2017, Narita et al. 2018a, b, Narita et al. 2020, Yamano et al. 2020, Yamano et al. 2021, Fukui et al. 2022, Ivanova et al. 2022, Narita et al. 2022) and five studies did not report using a bandpass filter (Woods et al. 2015, Ponnaiya et al. 2018, Fukui et al. 2020, Taylor et al. 2020, Goh et al. 2021, Kaiki et al. 2021) (see Fig. 3).

It was unclear whether Ponnaiya et al. (2018) used a bandpass filter as the study did not explicitly describe a bandpass filter. As a pilot study, Woods et al. (2015) used a neutral density filter that eliminated ≥250 nm emissions. On the other hand, some studies evaluated the effects of spectral purity with more than one bandpass filter (Yamano et al. 2020, Yamano et al. 2021, Ivanova et al. 2022). Some studies only reported a built-in optical filter (Fukui et al. 2020, Goh et al. 2021, Kaiki et al. 2021, Fukui et al. 2022). The optical filter in the CARE222 device (Ushio Inc., Tokyo, Japan) reduced emissions to 200–230 nm. The optical filter in the SafeZone UVC device (Ushio Inc., Tokyo, Japan) reported to filter ≥230 nm.

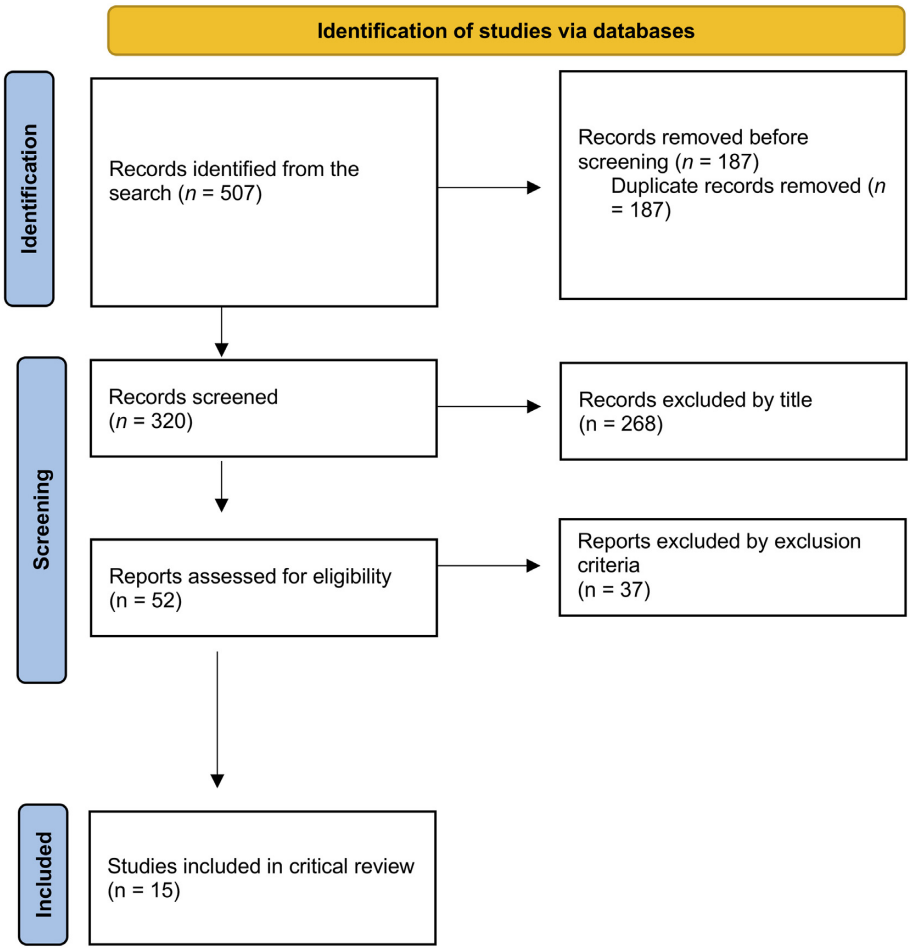

Figure 1. PRISMA flow diagram of the literature search. A total of 507 papers were identified by keywords and titles via Embase (196) and Ovid MEDLINE(R) (311); 187 duplicate papers were removed with a preference for Embase; 320 papers were screened; 268 papers were excluded by title; 52 papers were scrutinized against inclusion and exclusion criteria; 37 papers were excluded; 15 papers were included in this review. [PRISMA template sourced from: Page et al. (2021)].

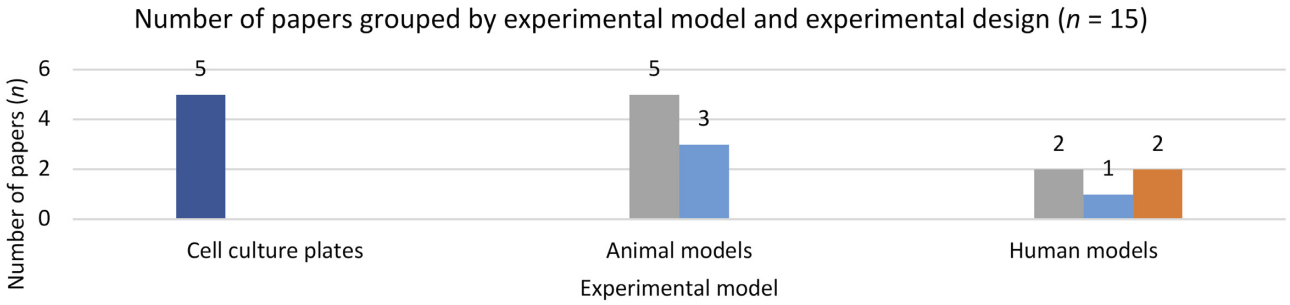

Figure 2. Results grouped by experimental model and experimental design ($n = 15$). Results grouped by experimental model and experimental design ($n = 15$). Each group shows the experimental model(s) described in Material and method section of each paper. Each bar represents the number of experimental designs per experimental model, including cell cultures (dark blue), normal skin (gray), wounded skin (light blue), and skin models (orange) were graphed. *Cell cultures (dark blue), normal skin (gray), wounded skin (light blue),* and *skin models (orange).*

Some studies reported spectral purity of emissions with a spectrometer (Woods et al. 2015, Buonanno et al. 2017, Ponnaiya et al. 2018, Yamano et al. 2020, Yamano et al. 2021, Ivanova et al. 2022, Narita et al. 2022).

Next, the principal method of CPD quantification in skin safety analysis was appraised. In total, 10 papers quantified CPD in skin. Two studies used ELISA (Fukui et al. 2020, Ivanova et al. 2022) and eight studies used IHC (Woods et al. 2015, Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018b, Yamano et al. 2020, Yamano et al. 2021, Fukui et al. 2022, Narita et al. 2022) (see Fig. 4). Ivanova et al. (2022) used both ELISA to detect CPDs and IHC to determine the depth of 222-nm UVC penetrance. Taylor et al. (2020) evaluated DNA photodamage using HPLC and mass spectrometry

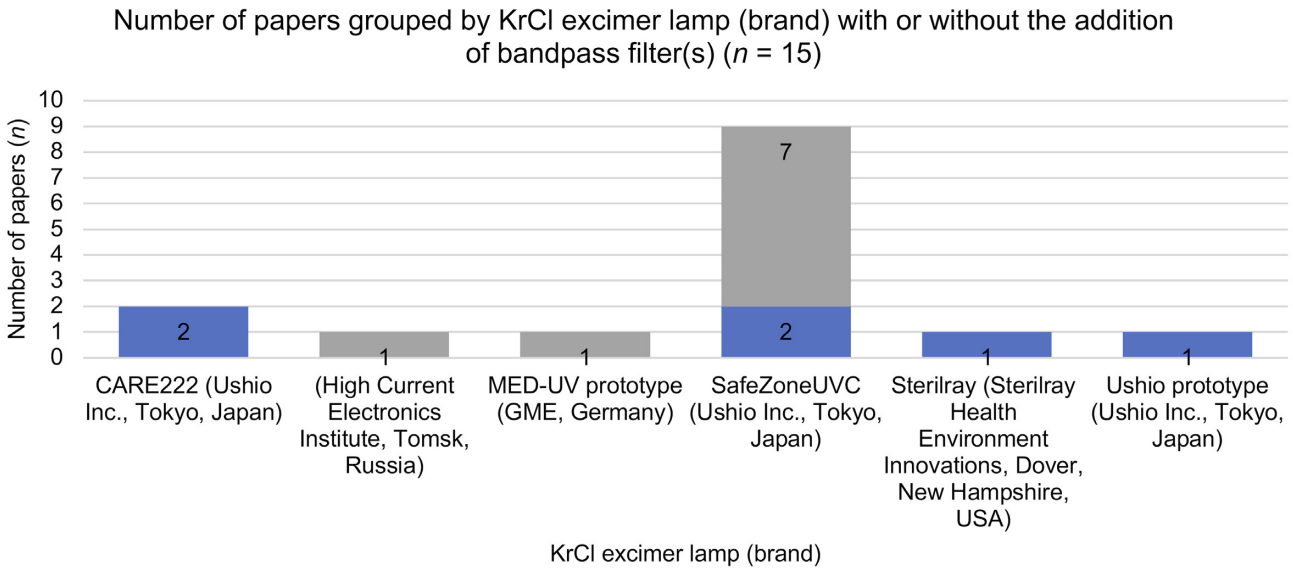

Figure 3. Results grouped by KrCl excimer lamp with or without the addition of a bandpass filter ($n = 15$). Each bar represents the number of papers per KrCl excimer lamp. The brand is included in parentheses. The addition of bandpass filter(s) is represented by a gray bar; without bandpass filter(s) is represented by a blue bar. Six lamps and four brands were included in this review: CARE222 (Ushio Inc., Tokyo Japan), KrCl lamp (High Current Electronics Institute, Tomsk, Russia), MED-UV prototype (GME, Germany), SafeZoneUVC (Ushio Inc., Tokyo, Japan), Sterilray (Sterilray Health Environment Innovations, Dover, New Hampshire, USA), Ushio prototype (Ushio Inc., Tokyo, Japan). *The addition of bandpass filter(s) is represented by a gray bar, without bandpass filter(s) is represented by a blue bar.*

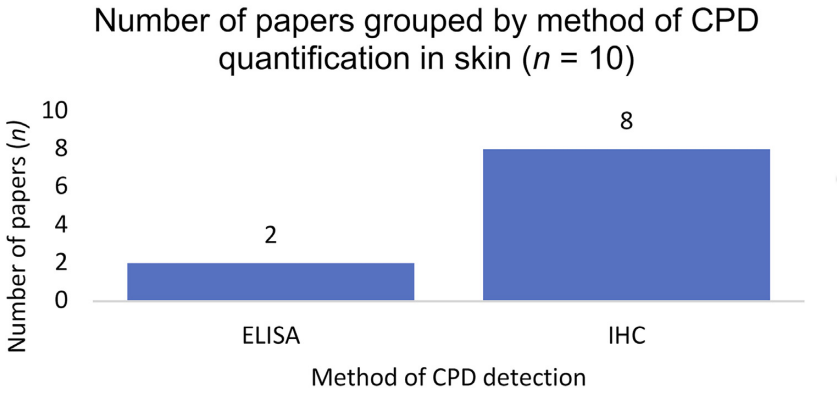

Figure 4. Results grouped by method of CPD quantification in skin ($n = 10$). Each bar represents the number of papers that used ELISA or immunohistochemistry (IHC) as the primary mode of CPD detection in skin following 222-nm UVC exposure.

after DNA hydrolysis in bacterial cells and spores, however this was not relevant to skin safety.

Germicidal efficacy

Of the 15 papers, 9 evaluated germicidal efficacy in cell cultures, human skin, human skin models, and mice skin (Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018a, Fukui et al. 2020, Narita et al. 2020, Taylor et al. 2020, Goh et al. 2021, Kaiki et al. 2021, Ivanova et al. 2022). Of the 15 papers, 7 papers evaluated the germicidal efficacy of 222-nm UVC against MRSA (Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018a, b, Taylor et al. 2020, Goh et al. 2021, Kaiki et al. 2021) (see Table 1).

Three papers evaluated the initial reduction of bacteria and subsequent growth of bacteria following irradiation (Ponnaiya et al. 2018, Narita et al. 2018a, Fukui et al. 2020) (see Table 2).

Four papers evaluated the germicidal efficacy of 222-nm UVC against other common HAI bacteria, including *P. aeruginosa*, *C. difficile* (including endospores), and *E. coli* (Narita et al. 2020, Taylor et al. 2020, Goh et al. 2021, Ivanova et al. 2022) (see Table 3).

Three papers evaluated the germicidal efficacy of 222-nm UVC light in the hospital setting (Fukui et al. 2020, Goh et al. 2021, Kaiki et al. 2021) (see Table 4).

Skin safety

Of the 15 papers, 10 evaluated skin safety of 222-nm UVC (Woods et al. 2015, Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018b, Fukui et al. 2020, Yamano et al.

Table 1. Log reduction of MR*SA* in cell cultures, human skin, and mice skin following irradiation with 222-nm UVC light.

Paper	Experimental model	Irradiation dose (mJ cm^{-2})	Method of quantification	Units	MR*SA* count before irradiation	MR*SA* count after irradiation	Reduction of MR*SA*
Buonanno et al.(2017)	Cell culture plates	~2	CC	CFU			0.7 log
		~3	CC	CFU			1.6 log
		~5	CC	CFU			2.5 log
		~9	CC	CFU			3.3 log
		~18	CC	CFU			3.9log
		~25	CC	CFU			4.5 log
		~50	CC	CFU			4.1 log
		~100	CC	CFU			4.4 log
		~150	CC	CFU			4.7 log
Goh et al. (2021)	Live human skin—pressure ulcers	540	MR	%	100	5	95%
‡Kaiki et al. (2021)	Cell culture plates	9	CC	CFU			2.91 log
‡‡Kaiki et al. (2021)		15	CC	CFU			3.95 log
‡‡‡Kaiki et al. (2021)		30	CC	CFU			4.86 log
‡‡‡‡Kaiki et al. (2021)		60	CC	CFU			5.41 log
Narita et al. (2018a)	Live mice normal—mouse skin (BALB/c)	75	CC	CFU	4.5 log	<2.8 log	1.7 log
		150	CC	CFU	4.5 log	2.7 log	1.8 log
		450	CC	CFU	4.5 log	2.5 log	2.0 log
	Live mice—dorsal skin wounds (BALB/c)	75	CC	CFU	3.9 log	3.0 log	0. 9 log
		150	CC	CFU	4.0 log	2.8 log	1.2 log
		750	CC	CFU	4.6 log	3.2 log	1.4 log
		1500	CC	CFU	4.6 log	3.2 log	1.4 log
Narita et al. (2020)	Cell culture plates	6	CC	CFU	1×10^7		~4 log
		12	CC	CFU	1×10^7	ND	1×10^7 (Total)
†Ponnaiya et al. (2018)	Live mice—dorsal skin wounds (SKH1-Elite strain 477)	40	CC	CFU g^{-1}	$\sim 3.5 \times 10^6$	$\sim 1.5 \times 10^6$	0.4 log
		300	CC	CFU g^{-1}	$\sim 3.5 \times 10^6$	$\sim 0.5 \times 10^6$	0.8 log
††Ponnaiya et al. (2018)		40	CC	CFU g^{-1}	$\sim 2.0 \times 10^5$	$\sim 0.2 \times 10^5$	1.0 log
		300	CC	CFU g^{-1}	$\sim 2.0 \times 10^5$	~0	$\sim 2.0 \times 10^5$ (Total)
°Taylor et al. (2020)	Cell culture plates	~850	SF	%	100	~0.001	>99%
°°Taylor et al. (2020)		~850	SF	%	100	~0.01	>99%

Seven (7) papers evaluated the log reduction of MR*SA* in cell cultures, human skin, and mice skin. For each paper, Table 1 highlights the experimental model (strain), irradiation dose (mJ cm^{-2}), method of bacteria quantification, units of bacteria quantification, MR*SA* count before irradiation, MR*SA* count after irradiation, and overall reduction of MR*SA*. CC = counting colonies; MR = median reduction; CFU = colony forming units; ND = not detected; SF = surviving fraction. °MR*SA* in the stationary phase. °°MR*SA* in the log phase. †Measured two (2) days following irradiation. ††Measured seven (7) days following irradiation. ‡1.5 mins of irradiation. ‡‡2.5 mins of irradiation. ‡‡‡5 mins of irradiation. ‡‡‡‡10 mins of irradiation.

2020, Yamano et al. 2021, Fukui et al. 2022, Ivanova et al. 2022, Narita et al. 2022) (see Table 5).

Discussion

Germicidal efficacy

The efficacy of 222-nm UVC light is determined by its ability to eradicate bacteria. The current gold standard method of quantifying viable bacteria in a sample is the CFU assay, which involves counting bacterial colonies following inoculation (Hazan et al. 2012). Irradiated samples are compared to non-irradiated samples. The methods of quantification are shown as MR (median reduction), CC (counting colonies), SF (surviving fraction), and SV (spore viability); the units used are shown as CFU (colony forming units), and percentage (%). Tables 1–3 show the log reduction of MR*SA*, *P. aeruginosa*, *C. difficile*, *E. coli,* and other aerobic bacteria. Seven studies evaluated the germicidal efficacy of 222-nm UVC against MRSA (Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018a, Taylor et al. 2020, Goh et al. 2021, Kaiki et al. 2021).

MR*SA in vitro*

Four studies evaluated the log reduction of MR*SA* in cell cultures over a range of irradiation doses (Buonanno et al. 2017, Narita et al. 2020, Taylor et al. 2020, Kaiki et al. 2021). Buonanno et al. (2017) designed a hybrid experimental study to observe *in vitro* MR*SA* irradiation in cell cultures and premutagenic DNA lesions on a 3D Human Skin Model (EpiDerm-FT, MatTek Corp., Ashland, MA, USA), and *in vivo* skin damage on SKH1-Elite strain 477 mice. The *in vitro* study irradiated the MR*SA* USA 300 strain common in community infections with a KrCl lamp (High Current Electronics Institute, Tomsk, Russia) with optical spectrometry revealing

Table 2. Log reduction of MR*SA* and skin swab cultures and at various times following irradiation with 222-nm UVC light in human skin and mice skin.

Paper	Experimental model	Bacteria	Irradiation dose (mJ cm^{-2})	Method of quantification (units)	Bacteria count before irradiation or in non-irradiated samples	Time(s) of measurement after irradiation	Bacteria count after irradiation
Fukui et al. 2020	Live human skin back	Skin swab cultures	500	CC (CFU)	7.21	5 min	0.05
						30 min	0.79
Narita et al. 2018a	Live mice skin dorsal skin wounds (BALB/c)	MR*SA*	75	CC (CFU)	3.9 log	Immediately	3.0 log
					6.5 log	1 day	5.7 log
					6.1 log	3 days	6.0 log
					6.8 log	5 days	6.1 log
					5.7 log	8 days	5.6 log
					4.2 log	12 days	4.2 log
			150	CC (CFU)	4.0 log	Immediately	2.8 log
					6.7 log	1 day	6.2 log
					7.0 log	3 days	6.3 log
					7.3 log	5 days	6.8 log
					5.2 log	8 days	4.7 log
					4.3 log	12 days	3.2 log
			750	CC (CFU)	4.6 log	Immediately	3.2 log
					6.0 log	1 day	4.8 log
			1500	CC (CFU)	4.6 log	Immediately	3.2 log
					6.3 log	1 day	5.5 log
Ponnaiya et al. 2018	Live mice skin dorsal skin wound (SKH1-Elite strain 477)	MR*SA*	40	CC (CFU)	~3.5 × 10^6	2 days	~1.5 × 10^6
				Infected samples (%)			100.0%
					~2.0 × 10^5	7 days	~0.2 × 10^5 50.0%
			300	CC (CFU)	~3.5 × 10^6	2 days	~0.5 × 10^6 66.7%
				Infected samples (%)			
					~2.0 × 10^5	7 days	~0 0.0%

Three (3) papers evaluated the log reduction of MR*SA* or skin swab cultures in human skin and mice skin. For each paper, Table 2 highlights the experimental model (strain), bacteria, irradiation dose (mJ cm^{-2}), method of bacteria quantification (units of bacteria quantification), bacteria count before irradiation or in non-irradiated samples at each time interval, time of measurement after irradiation, and bacteria remaining in the irradiated sample at each time interval. CC = counting colonies; CC = counting colonies; MR = median reduction; CFU = colony forming units; and ND = not detected.

~237 to ~258 nm emissions. Thus, the device was equipped with a custom bandpass filter. CFU on tryptic soy agar plates were counted the following day relative to sham-irradiated plates. MR*SA* was reduced by 0.7 to 4.7 log at doses of ~2 to ~150 mJ cm^{-2}, respectively. Remarkably, a plateau in log reduction occurred following a 4.5 log reduction at 25 mJ cm^{-2} (Buonanno et al. 2017). This study observed that 222 nm eradicates bacteria nearly as effectively as 254 nm at higher fluences.

Similarly, Kaiki et al. (2021) included an *in vitro* experimental study to irradiate MR*SA*. The study determined the rates of MR*SA* contamination on hospital mobile phones, reduction of MR*SA* in cell cultures, and reduction of aerobic bacteria on mobile phones following irradiation. Unlike Buonanno et al. (2017), the study did not enumerate bacteria immediately postirradiation and rather cultured bacteria in blood agar. The study found a 2.91 to 5.41 log reduction of MR*SA* cultures at 9 to 60 mJ cm^{-2} and similarly demonstrated a 4.86 log reduction at 30 mJ cm^{-2} (see Table 2). However, the study used the CARE222 lamp (Ushio Inc., Tokyo, Japan) equipped with an optical filter that only restricted emissions to 200–230 nm (Kaiki et al. 2021). The experiment did demonstrate a greater ~5.41 log reduction at 60 mJ cm^{-2}. It is suspected the greater range of emissions range accounted for this improved outcome.

Another *in vitro* study was conducted by Narita et al. (2020) to irradiate various microbial pathogens, including an MR*SA* clinical isolate. Cultures were irradiated with a custom bandpass-filtered 222 nm SafeZoneUVC device and grown on tryptic soy broth (Ushio Inc., Tokyo, Japan) (Narita et al. 2020). The study similarly recorded a high log reduction and low fluences with total reduction occurring at only 12 mJ cm^{-2} (Narita et al. 2020).

Taylor et al. (2020) also conducted an *in-vitro* investigation of MR*SA* strain 43 300 in the stationary and log phases to determine bacterial viability after 222-nm UVC irradiation. Similar to Kaiki et al. (2021), the experiment used the CARE222 Kr-Cl excimer lamp (Ushio America, Cypress, California) which allowed ≤1% of outputs above 235 nm, including the conventional 254 nm wavelength (Taylor et al. 2020). The two strains showed a >99% reduction in MR*SA* cultures (see Table 1) (Taylor et al. 2020). Interestingly, MR*SA*

Table 3. Log reduction of *P. aeruginosa*, *C. difficile*, and *E. coli* following irradiation with 222-nm UVC light in cell culture plates and human skin.

Paper number	Experimental model	Bacteria	Irradiation dose (mJ cm^{-2})	Method of quantification	Units used	Bacteria count before irradiation	Bacteria count after irradiation	Reduction of bacteria
Goh et al. (2021)	Live human skin—pressure ulcers	*P. aeruginosa*	540	MR	%	100	7.4	93%
		*C. difficile**	540	MR	%	100	0	>99%
		E. coli	540	MR	%	100	50	50%
Ivanova et al. (2022)	Cell culture plates	*E. coli*	12	CC	%	100	0.1	~4.4 log (99.9%)
			50	CC	%	100	0.001	~6.5 log (99.999%)
			100	CC	%	100	0.001	~6.5 log (99.999%)
			500	CC	%	100	0.001	~6.5 log (99.999%)
Narita et al. (2020)	Cell culture plates	*P. aeruginosa*	6	CC	CFU	5×10^6		~3 log
			12	CC	CFU	5×10^6		~4 log
			24	CC	CFU	5×10^6	ND	5×10^6 (Total)
		*C. difficile***	10	CC	CFU	5×10^5		~1 log
			20	CC	CFU	5×10^5		~2 log
			30	CC	CFU	5×10^5		~3 log
			40	CC	CFU	5×10^5		~3 log
			50	CC	CFU	5×10^5	ND	5×10^5 (Total)
		*E. coli****	6	CC	CFU	5×10^6		~2 log
			12	CC	CFU	5×10^6		~4 log
			24	CC	CFU	5×10^6	ND	5×10^6 (Total)
Taylor et al. (2020)	Cell culture plates	*C. difficile***	425	SV	%	100	0.1	>99%

Four (4) papers evaluated the log reduction of *P. aeruginosa*, *C. difficile* (including endospores), and *E. coli* in cell cultures and human skin. For each paper, Table 3 highlights the experimental model, bacteria, irradiation dose (mJ cm^{-2}), method of bacteria quantification, units of bacteria quantification, bacteria count before irradiation, bacteria count after irradiation, and overall reduction of bacteria. CC = counting colonies; CFU = colony forming units; MR = median reduction; ND = not detected; and SV = spore viability. *Clostridium species. **Clostoridiodes difficile* (endospores). ***Enterohaemorrhagic *E. coli* (EHEC).

Table 4. Log reduction of MR*SA*, *P. aeruginosa*, *C. difficile*, *E. coli*, and other aerobic bacteria following irradiation with 222-nm UVC light in the hospital setting, including human skin and hospital phones.

Paper	Experimental model	Bacteria	Irradiation dose (mJ cm^{-2})	Method of quantification	Units used	Bacterial count before irradiation	Bacterial count after irradiation	Reduction of bacteria
*Fukui et al. (2020)	Live human skin—back		500	CC	CFU	7.21	0.05	7.16
** Fukui et al. (2020)	Live human skin—back		500	CC	CFU	7.21	0.79	6.42
Goh et al. (2021)	Live human skin—pressure ulcers	MR*SA*	540	MR	%	100	5	95%
	Live human skin—pressure ulcers	*P. aeruginosa*	540	MR	%	100	7.4	93%
	Live human skin—pressure ulcers	*C. difficile*	540	MR	%	100	0	>99%
	Live human skin—pressure ulcers	*E. coli*	540	MR	%	100	50	50%
Kaiki et al. (2021)	Hospital phone—back side	Aerobic bacteria	9	CC	CFU	554	33	1.2 log
	Hospital phone—front keypad	Aerobic bacteria	9	CC	CFU	587	39	1.2 log

Three (3) papers evaluated the log reduction of MR*SA*, *P. aeruginosa*, *C. difficile*, *E. coli*, and other aerobic bacteria in the hospital setting. For each paper, Table 4 highlights the experimental model, bacteria, irradiation dose (mJ cm^{-2}), method of bacteria quantification, units of bacteria quantification, bacteria count before irradiation, bacteria count after irradiation, and overall reduction of bacteria. Fukui et al. (2020) did not report specific bacteria irradiated. *Measurements taken after 5 mins. **Measurements taken after 30 mins. Measurement taken after 1.5 mins.

cultures in the log phase exhibited a 10-fold greater reduction when compared to cells in the stationary phase (Taylor et al. 2020). UVC of wavelength 222 nm may be less effective in clinical practice in the stationary phase which leaves viable cells to grow on a surface or skin. It is speculated that similar or greater germicidal efficacy is achieved at lower fluences in cell cultures (Buonanno et al. 2017, Narita et al. 2020, Kaiki et al. 2021).

MR*SA in vivo*

This review focuses particularly on the clinical application of 222-nm UVC in SSIs. Three studies analyzed the effects of MR*SA* irradiation in wounds (Ponnaiya et al. 2018, Narita et al. 2018a, Goh et al. 2021) (see Table 2). Narita et al. (2018a) conducted the first *in vivo* experiment evaluating log reductions of MR*SA* 834 in normal and wounded BALB/c mice skin immediately and at various time intervals following irradiation. The study used SafeZoneUVC (Ushio Inc., Tokyo, Japan) with a custom bandpass filter. Remarkably, Narita et al. (2018a) demonstrated an immediate 1.7 log reduction at only 75 mJ cm^{-2} in normal mouse skin, however the maximum fluence of 1500 mJ cm^{-2} was required to generate a 1.4 log reduction in wounded skin (see Table 2). In samples with the greatest immediate log reductions, 2.5 log and 2.8 log CFU remained in the normal and wounded mice, respectively. UVC may not target bacteria shaded by the sulci of the skin in the wounded mice leaving viable cells with the potential to grow during and postsurgery (Rutala and Weber 2015). The viable bacteria counts were observed to peak at both 75 and 150 mJ cm^{-2} in wounds five days following irradiation. This was characteristically followed by a reduction then plateau in irradiated bacteria counts comparable to initial counts (see Table 2). Interestingly, the control specimens paralleled this reestablishment of bacteria count equilibrium. Thus, the remaining MR*SA* was shown to analogously grow and infect irradiated and non-irradiated wounds over specific time intervals.

Ponnaiya et al. (2018) incised and inoculated only wounded dorsal skin of live SKH1-Elite strain 477 mice. The *in vivo* study used a Kr-Cl excimer lamp (Ushio Inc., Tokyo, Japan) with a built-in optical filter, although the spectral range of emissions is unclear. Ponnaiya et al. (2018) conducted CFU assay at two and seven days postirradiation with 40 and 300 mJ cm^{-2} fluences. Like Buonanno et al. (2017), MR*SA* USA 300 was irradiated to emulate surgical wound infection control of common clinical pathogens (Ponnaiya et al. 2018). Ponnaiya et al. (2018) demonstrated a similar peak at two days and plateau at seven days using 40 mJ cm^{-2} (see Table 2). Contrary to Narita et al. (2018a), the study achieved complete sterilization using only 300 mJ cm^{-2} at seven days. While it was speculated that MR*SA* 300 and 834 may have different UV susceptibility, Buonanno et al. (2017) did not irradiate MR*SA* USA 300 cell cultures greater than 150 mJ cm^{-2} for empirical comparison. Thus, it is unclear how Ponnaiya et al. (2018) exhibited decreased bacterial viability when measured at this time interval. These studies suggest two key findings. (1) MR*SA* can grow in both irradiated and non-irradiated wounds. Bacteria undergo a rapid growth phase then re-establish an equilibrium postirradiation and this trend simultaneously occurs in non-irradiated bacteria; and (2) this may necessitate a higher irradiation dose and constant bathing for long-term MR*SA* decontamination.

Table 5. DNA damage photoproducts CPD and 6–4PPs following irradiation with 222-nm UVC light in human skin, human skin models, mice skin, and rabbit skin.

Paper	Experimental model	Number of subjects (if applicable)	Irradiation dose (mJ cm^{-2})	Presence of CPD detected following irradiation	Presence of 6–4PP following irradiation
Buonanno et al. (2017)	Human skin model (EpiDerm-FT)		25	0% induced in keratinocytes	0% induced in keratinocytes
			100	0% induced in keratinocytes	0% induced CPDs in keratinocytes
			145	0% induced in keratinocytes	0% induced CPDs in keratinocytes
	Live mice (SKH1-Elite strain 477)		157	0% induced in keratinocytes	0% induced in keratinocytes
Fukui et al. (2020)	Live human skin	19	500	0.25 absorbance at the 492 nm wavelength	
Fukui et al. (2022)	Live rabbit—incised back, thigh, and knee		500	2.0% CPD positive cells in fascia; 5.6 in fat; 2.0 in muscle; 0.5 in bone; 0.0 in articular cartilage immediately after irradiation 2.0 in fat 24 hours after irradiation	
*Ivanova et al. (2022)	Human skin model (Episkin)		100	2 ng ml^{-1}	
			500	14 ng ml^{-1}	
			500 (x3)	12 ng ml^{-1}	
**Ivanova et al. (2022)			100	1.5 ng ml^{-1}	
			500	5 ng ml^{-1}	
			500 (x3)	2 ng ml^{-1}	
***Ivanova et al. 2022			100	1.5 ng ml^{-1}	
			500	3 ng ml^{-1}	
			500 (x3)	1 ng ml^{-1}	
Narita et al. (2018b)	Live mice—normal dorsal skin (Hos Hr-1)		450	ND	
*Narita et al. (2022)	Live mice—normal dorsal skin (Hos Hr-1)	1	10	0% CPD positive cells per high power field (x400)	
		1	15	0.75% CPD positive cells per high power field (x400) ($P < 0.05$)	
		1	20	0.25% CPD positive cells per high power field (x400)	
		1	50	7.1% CPD positive cells per high power field (x400) ($P < 0.01$)	
		1	150	11.0% CPD positive cells per high power field (x400) ($P < 0.01$)	
		1	300	27.3% CPD positive cells per high power field (x400) ($P < 0.01$)	
**Narita et al. (2022)		1	150	0.25% CPD positive cells per high power field (x400)	
		1	300	0.63% CPD positive cells per high power field (x400)	
Ponnaiya et al. (2018)	Live mice—dorsal skin wound (SKH1-Elite strain 477)		40	No significant increase	
			300	No significant increase	

Table 5. Continued

Paper	Experimental model	Number of subjects (if applicable)	Irradiation dose (mJ cm^{-2})	Presence of CPD detected following irradiation	Presence of 6–4PP following irradiation
Woods et al. (2015)	Live human skin	1	63	Present in majority of suprabasal keratinocytes	
		1	63	Present in small to moderate numbers of keratinocytes	
		2	101	Present in moderate numbers of suprabasal keratinocytes; present in small numbers of basal keratinocytes	
°Yamano et al. (2020)	Live mice—skin normal dorsal skin (WT)		100	Not present	
			500	Present	
			10 000	Present	
	Live mice skin—normal dorsal skin (Xpa-KO)		100	Not present	
			500	Present	
			10 000	Present	
°°Yamano et al. (2020)	Live mice skin—normal dorsal skin (WT)		10 000	Present	
	Live mice skin—normal dorsal skin (Xpa-KO)		10 000	Present	
Yamano et al. (2021)	Live mice skin—normal dorsal skin (Hos:HR-1)		1 500	4% CPD positive cells/all epidermal cells	

Ten (10) papers evaluated the induction of CPD and/or 6–4PPs in human skin, human skin models, mice skin, and rabbit skin. For each paper, Table 5 highlights the experimental model (strain), number of subjects (if applicable), irradiation dose (mJ cm^{-2}), presence of CPDs, and presence of 6–4PPs following irradiation. Buonanno et al. (2017), Fukui et al. (2022), Narita et al. (2022), Yamano et al. (2021) report CPDs as percentage induced either in keratinocytes or in all epidermal cells in the magnified field. Fukui et al. (2020) reports CPDs as a matter of absorbance at the 492 nm wavelength which parallels the presence of CPDs. Narita et al. (2018b), Woods et al. (2015) and Yamano et al. (2020) report CPDs as a matter of presence or detection. Ponnaiya et al. (2018) reports CPDs as a matter of significant increase. Ivanova et al. (2022) reports CPDs as ng ml^{-1}. Ivanova et al. (2022) irradiated with 500 mJ cm^{-2} twice per number of spectral filters. The first experiment used one (1) session of 500 mJ cm^{-2} irradiation therapy; the second experiment used three (3) sessions of 500 mJ cm^{-2} irradiation therapy with 4-hour intervals in between each session denoted as '(x3)' (Ivanova et al. 2022). Ponnaiya et al. (2018) measurements skin damage two and seven days after irradiation with the same qualitative and quantitative results. ND = not detected. *Irradiation without a 222 nm spectral filter. **Irradiation with one (1) 222 nm spectral filter. ***Irradiation without two (2) 222 nm spectral filters. °Irradiator A with one (1) custom bandpass filter °°Irradiator B with three (3) stacked bandpass filters.

Goh et al. (2021) was the only study to conduct a clinical trial on human wounds. Stage 2 or 3 pressure ulcers (PUs) were irradiated with the SafeZoneUVC device (Ushio Inc., Tokyo, Japan) with a built-in optical filter. Four patients with MR*SA* underwent 90 sec of 540 mJ cm^{-2} irradiation for a total of 13 sessions. CFU from wound culture swabs were counted pre- and post-UV. However, the study lacked a control and recruited few patients. Despite a relatively high irradiation dose and multiple exposures, a median 5% of the initial MR*SA* bacteria remained on the skin (Goh et al. 2021). Contrasting mice models, variability in temperature, sterility, wound dimensions, and individual patient factors may account for a generalisable reduced log reduction of MR*SA* in human wounds. Furthermore, the study reported the device was hand-held (Goh et al. 2021). This subjection to human error may have led to poorer irradiation of deeper sulci. The study further demonstrated that infection by multiple species and greater CFU counts in the PUs led to poorer bacterial penetrance of 222 nm UVC light (Goh et al. 2021). Thus, it is necessary to determine an efficacious radiation dose for both experimentally and clinically imperfect conditions.

P. Aeruginosa, C. Difficile, and *E. Coli*

Similar to MR*SA*, *P. aeruginosa*, *C. difficile*, and *E. coli* exhibit increasing antibiotic resistance. *P. aeruginosa* shows great resistance to B-lactams, aminoglycosides, and quinolones (Pang et al. 2019). Similarly, emergent strains of *C. difficile* show reduced susceptibility to numerous antibiotics (Spigaglia 2015). *E. coli* also shows increased resistance to cephalosporins and the rise in MDR *E. coli* causes great concern for treatment globally (Wu et al. 2021). Four studies evaluated the germicidal efficacy of 222-nm UVC against one or more of *P. aeruginosa*, *C. difficile* (including endospores), and *E. coli* (Narita et al. 2020, Taylor et al. 2020, Goh et al. 2021, Ivanova et al. 2022). In addition to MR*SA*, Goh et al. (2021) also studied 222-nm UVC irradiation of other bacteria in PUs, including *P. aeruginosa* and *C. difficile* with the protocol previously described. The study reported a total reduction in *C. difficile* at 540 mJ cm^{-2} and was less efficacious against *P. aeruginosa* and *E. coli* (see Table 3) (Goh et al. 2021). Additionally, *Clostridium* was treated in only two patients; *P. aeruginosa* in three patients; and *E. coli* in nine patients (Goh et al. 2021).

Narita et al. (2020) used the study design previously described to evaluate *P. aeruginosa*, *C. difficile*, and *E. coli* in cell cultures. Narita et al. (2020) exhibited total reduction of *C. difficile* at only 50 mJ cm^{-2}. As expected, sterilization of the organisms occurred at low fluences in laboratory conditions. The study achieved complete sterilization of all organisms at fluences $\leq$50 mJ cm^{-2}. Similar to results from Goh et al. (2021), *P. aeruginosa* and *E. coli* required a higher fluence for complete sterilization (see Table 3).

The study by Taylor et al. (2020) achieved complete sterilization of *C. difficile* spores at 425 mJ cm^{-2}. Considering the laboratory conditions described, this is particularly unsurprising. This study is consistent with other findings suggesting 222-nm UVC has greater potency when used to eradicate vegetative cells (*P. aeruginosa* and *E. coli*) when compared to bacterial endospores (*C. difficile*) (Narita et al. 2020). Taylor et al. (2020) also explored how DPA loss mutations impacted resistance to 222-nm UVC. *C. difficile* lacking *spoVF* and *spoVA* operons, and the *sleB* gene showed decreased spore viability compared to the wild-type (WT) strain at similar fluences (Taylor et al. 2020). Mutational diversity of protective components either increased or decreased susceptibility to 222-nm UVC. No other literature in this review considered mutagenesis in this manner. Although promising in laboratory conditions, certain bacteria and patient factors in the acute hospital setting pose challenges to complete sterilization.

The study by Ivanova et al. (2022) used a MED-UV prototype lamp (GME, Germany) with two custom bandpass filters to irradiate *E. coli* in Mueller-Hinton agar plates, as this demonstrated the greatest skin-protective effects discussed later in this review. At this improved spectral purity, the study showed a 4.4 log reduction at only 12 mJ cm^{-2} and a 6.5 log reduction at $\geq$50 mJ cm^{-2} in *E. coli* (Ivanova et al. 2022). Interestingly, the irradiation dose required to eliminate 99.9% of the bacteria was consistent at 12 mJ cm^{-2} across both papers that evaluated *E. coli* in cell cultures (Narita et al. 2020, Ivanova et al. 2022). Equipping UVC devices with a bandpass filter may still allow sufficient antimicrobial effects while improving skin safety in the clinical setting.

Hospital disinfection and decontamination

There are few studies that consider the impressive germicidal effects of 222-nm UVC in a clinical manner. Three studies investigated disinfection and decontamination in hospitals (Fukui et al. 2020, Goh et al. 2021, Kaiki et al. 2021) (see Table 4).

In addition to *in vitro* MR*SA* irradiation, Kaiki et al. (2021) measured aerobic bacteria from hospital phones before and after irradiation with this CARE222 device (Ushio Inc., Tokyo, Japan). The bacteria were irradiated at 9 mJ cm^{-2} for 1.5 mins and were enumerated with trypticase soy agar (TSA) with lecithin and polysorbate RODAC contact plates (Kaiki et al. 2021). The irradiation reduced the colonies obtained from phones by 1.2 log CFU. When compared with current literature, 222-nm UVC may be more effective in reducing bacteria than chemical disinfectants in similar clinical conditions (Singh et al. 2010).

Goh et al. (2021) was the only clinical trial that evaluated bacterial reduction in wounded human skin with the method previously described. Similar to Kaiki et al. (2021), the study did not achieve complete sterilization of PUs infected with an MR*SA* clinical pathogen (Goh et al. 2021). Remarkably, Goh et al. (2021) demonstrated similar and greater log reductions in three of the four irradiated pathogens despite wounded skin sulci. However, the study included Stage 2 and 3 PUs and had no control over antibiotic use in patients (Goh et al. 2021). This may have reduced bacterial diversity on the patients' microbiome and allowed only resistant pathogens to flourish (Xu and Li 2019, Jo et al. 2021).

Fukui et al. (2020) contrarily irradiated normal skin on the backs of 20 healthy volunteers using a handheld SafeZoneUVC device (Ushio Inc., Tokyo, Japan) with a custom bandpass filter that restricted emissions to 200–230 nm. Pre- and post-UVC skin swabs were cultured in soybean casein digest agar and underwent membrane filtration and then colonies were determined macroscopically. The samples were not paralleled by controls and 1 result was accidentally discarded. Similar to Narita et al. (2018a) and Ponnaiya et al. (2018), the study evaluated log growth over time intervals (see Table 4). Bacteria reduced by > 99% at 5 mins post-UVC (Fukui et al. 2020). Bacteria increased over 15-fold and to ~89% of the pre-UVC value after only 25 mins ($P = 0.0007$)

(Fukui et al. 2020). It is possible that 222-nm UVC may be a useful adjunct to hospital decontamination however there is inconclusive evidence regarding its applicability to human wounds in surgery. This finding is consistent with a recent review that suggested UV is most pertinent as a germicide in routine disinfection in operating rooms (Scott et al. 2022).

Skin safety

Conventional 254-nm UVC devices are known to produce CPDs and 6–4PPs (Pfeifer and Besaratinia 2012). This study aimed to determine whether germicidal 222-nm UVC could cause less harm to human skin. The detection of DNA photodamage products often used IHC and ELISA. In IHC analysis, cultures are stained, magnified, and enumerated under a microscope in various visual fields. In ELISA analysis, dilutions are generally assayed in four steps: coating (with an antigen or antibody), blocking, detection (with a colored substrate), and final read, typically with a phosphate-buffered saline (PBS) buffer and detergent in between each step (Alhajj and Farhana 2022). In this review, 10 papers assessed skin damage (Woods et al. 2015, Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018b, Fukui et al. 2020, Yamano et al. 2020, Yamano et al. 2021, Fukui et al. 2022, Ivanova et al. 2022, Narita et al. 2022).

Two papers looked at live human skin (Woods et al. 2015, Fukui et al. 2020). The study by Woods et al. (2015) assessed skin safety in four patients. At irradiation doses of 63 and 101 mJ cm^{-2}, CPDs were detected in basal keratinocytes and in suprabasal keratinocytes of the latter dose (see Table 5) (Woods et al. 2015). As the first trial of its kind, the pilot study used a Sterilray device (Sterilray Health Environment Innovations, Dover, New Hampshire, NH, USA) designed for equipment sterilization with a neutral density filter (Woods et al. 2015). Unlike newer studies and technologies, 3% of emissions were ≥250 nm (Woods et al. 2015). This may be responsible for the presence of CPDs in this skin irradiation.

With the method described previously, Fukui et al. (2020) measured CPDs in live human skin in 19 subjects at 500 mJ cm^{-2}. The CPD counts were measured by ELISA and the irradiated region was statistically significantly higher than the non-irradiated region (Fukui et al. 2020). Similar to Woods *et al.* (2015), irradiation was conducted on healthy patient skin. It is speculated that newer technology with fewer off-peak transmissions would account for improved skin safety. These discrepancies may also be due to a higher fluence and an increased number of subjects.

Two papers used human skin models to simulate irradiation in the clinical setting (Buonanno et al. 2017, Ivanova et al. 2022). Buonanno et al. (2017) conducted an *in vitro* study on the multi-layered 3D human skin model EpiDerm-FT (MatTek Corp., Ashland, MA, USA) to mimic the physiological response of an epidermis and dermis. The paper used a KrCl lamp (High Current Electronics Institute, Tomsk, Russia) and a custom bandpass filter (Buonanno et al. 2017). The study reported 0% CPDs and 6–4PPs induced in keratinocytes at 25–145 mJ cm^{-2} (Buonanno et al. 2017). However, the paper used immunohistochemical (IHC) analysis to evaluate DNA damage (Buonanno et al. 2017).

The use and efficacy of bandpass filters helped to evaluate the impact of spectral purity on 222 nm as a germicide and skin-safe technology. Ivanova et al. (2022) compared the effects of spectral purity on human skin and also used a 3D human skin model. However, the model was composed of human skin reconstructs (Episkin, Lyon, France) cultured in a T-skin medium (Ivanova et al. 2022). The model was irradiated *in vitro* with the MED-UV prototype lamp (GME, Germany). The addition of one filter was reported to reduce off-peak 230–240 nm and 240–260 nm transmissions to 1.0% and 1.18%, respectively; two filters reduced 230–240 nm and 240–260 nm transmissions to 0.45% and 0.116%, respectively (Ivanova et al. 2022). One filter and two filters were found to significantly reduce CPD formation at a fluence of 500 mJ cm^{-2} (Ivanova et al. 2022). However, there was no significant difference in CPD formation between one and two filters for all fluences which may suggest redundancy of more than one filter (Ivanova et al. 2022). ELISA detected CPDs at all fluences and IHC was used to determine the depth of UVC penetration (see Table 5) (Ivanova et al. 2022). It is speculated that IHC used in Buonanno et al. (2017) is objectively less sensitive quantitatively when compared to ELISA which may account for undetected levels of premutagenic lesions. The vitality of the models is also expected to differently affect keratinocyte responses.

Seven papers used live animal skin to evaluate mammalian skin safety in pathogen-free laboratory conditions (Buonanno et al. 2017, Ponnaiya et al. 2018, Narita et al. 2018b, Yamano et al. 2020, Yamano et al. 2021, Fukui et al. 2022, Narita et al. 2022). Buonanno et al. (2017) included an *in-vivo* experiment to evaluate skin safety of 222 nm in SKH1-Elite strain 477 mice known to show a similar physiological response to UV as humans. Normal unwounded skin was irradiated with 222 nm and found 0% CPD and 6–4PPs induced in keratinocytes at 157 mJ cm^{-2} (Buonanno et al. 2017). Similar to its human skin analysis, IHC may not have been nearly as accurate as other assays.

Ponnaiya et al. (2018) similarly irradiated the SKH1-Elite strain 477 with the protocol previously described. The study likewise incorporated a bandpass filter and tissues underwent IHC analysis. Neither 40 or 300 mJ cm^{-2} induced a statistically significant increase in CPDs when measured two- and seven-days following irradiation (Ponnaiya et al. 2018).

Narita et al. (2018b) irradiated normal Hos Hr-1 mice with a custom bandpass-filtered SafeZoneUVC device (Ushio Inc., Tokyo, Japan) at 450 mJ cm^{-2} once daily for ten days. The study reports mounting the irradiator in a fixed position and a multilayer bandpass filter that remarkably reduced 230–360 nm irradiation to approximately one-ten-thousandth of 222 nm (Narita et al. 2018b). CPD-expressing cells were not detected with IHC analysis. Similar to Ponnaiya et al. (2018), the study collected samples one day following the last irradiation.

Fukui et al. (2022) was the only study to evaluate wounds in rabbits to emulate surgical site infections. The study used a bandpass-filtered SafeZoneUVC device (Ushio Inc., Tokyo, Japan) at 500 mJ cm^{-2}. Spectral emissions were restricted to 200–230 nm with a 222 nm maximum output (Fukui et al. 2022). An incision of the back, thigh and knee exposed fat, fascia, muscle, bone, and cartilage for IHC analysis. One-hour postirradiation, CPDs were insignificantly present in fascia, muscle, or bone and were not present in articular cartilage (see Table 5) (Fukui et al. 2022). However, CPDs were significantly present in fat likely due to different composition and lack of DNA damage protection mechanisms (Fukui et al. 2022). Consistent with the findings of Ponnaiya et al. (2018) and Narita et al. (2018b), the study found CPD-positive cells

in fat tissue reduced to insignificant levels 24 hours postirradiation. This may have permitted biological DNA damage repair activity. This suggests CPD induced by 222 nm in single and repeated irradiation may be reparable and not particularly harmful.

A study by Narita et al. (2022) evaluated the impact of spectral purity on normal Hos: Hr-1 mice skin. Akin to the study protocol by Narita et al. (2018b), a mounted SafeZoneUVC device (Ushio Inc., Tokyo, Japan) was equipped with a bandpass filter that reduced ≥230 nm emissions to ∼0.0001% of 222 nm (Narita et al. 2022). Each exposure was performed on one mouse and tissues underwent IHC analysis. Remarkably, irradiation without a bandpass filter statistically significantly induced 11.0% and 27.3% CPDs at 150 and 300 mJ cm^{-2}, respectively. However, irradiation with a bandpass filter statistically insignificantly induced 0.25% and 0.63% CPDs at the same respective fluences.

Similarly, Yamano et al. (2020) compared safety on normal skin between WT and Xpa-KO mice using the SafeZoneUVC device with one and three custom bandpass filter(s). One filter (irradiator A) accounted for 200–230 nm wavelength emissions, whereas three stacked filters (irradiator B) reduced 235 to 280 nm emissions to <1% (Yamano et al. 2020). IHC monoclonal antibodies were enumerated 3 hrs after irradiation. The group with only one bandpass filter revealed no CPDs at 100 mJ cm^{-2} and presence of CPDs in the upper epidermis at 500 mJ cm^{-2} in both genotypes (Yamano et al. 2020). The group with three bandpass filters showed present yet remarkably reduced CPDs at 10 000 mJ cm^{-2} (Yamano et al. 2020).

Yamano et al. (2021) irradiated Hos: Hr-1 mice skin with irradiator B as described above. Interestingly, the study only determined CPDs at the minimal perceptible response dose (MPRD) determined by visual inspection. The study found 4% CPD-positive cells 3 hrs at 1500 mJ cm^{-2}. Similarly, CPDs were only detected in the upper epidermal layer at this fluence. The reduction of CPDs by bandpass filters in mouse skin is consistent with the findings of Ivanova et al. (2022) in human skin. This means that 222-nm UVC alone is not responsible for DNA damage in skin irradiations.

Conclusion

The rapidly evolving AMR epidemic and prevalence of SSIs require novel approaches to reduce the global dangers of antibiotic overuse. 254-nm UVC is a recognised effective hospital decontaminant; however, it is not safe for use in human-occupied space. This review investigated 222-nm UVC as a skin-safe approach to hospital decontamination in the clinical setting and its applicability in decontaminating MR*SA* and SSIs. 15 papers were appraised for germicidal efficacy and/or skin safety. The study type, protocol, specimens, devices, conditions and handling, and analysis tools were considered for each paper.

It was generally agreed that MR*SA* and other common HAI pathogen decontamination was far greater *in vitro* in cell cultures when compared with live mammalian irradiation likely due to controlled pathogenic-free conditions and reduced variable factors. The selectivity of growth media and initial bacterial counts in cell cultures made comparison particularly difficult. UVC of wavelength 222 nm was shown to be efficacious in animals; however, even models with significant log reductions demonstrated remaining bacteria with potential for later growth and infection. Most papers evaluated bacteria immediately following irradiation and so it is unclear how effective 222-nm UVC may be in long-term sterilization of surgical sites. Additionally, literature surrounding germicidal efficacy in human wounds was scarce and literature in human surgical sites was not discovered by the author at the time of the search. It was speculated that handheld and fixed devices may have impacted the outcomes of various studies, however detailed information on device configuration was not consistent throughout the papers.

Many studies agreed that CPDs were induced by 222-nm UVC irradiation at levels that may be reparable and harmless to human skin. The presence of CPDs was vastly improved by the addition of bandpass filters that eliminated damaging wavelengths. The equipped device often exhibited similar germicidal efficacy even with this enhanced spectral purity. The assessment of skin safety was limited to the induction of CPDs in keratinocytes as few studies measured 6–4PPs, minimal erythema dose (MED), and skin thickness; however, the precise value of these measurements is unclear. Furthermore, it was speculated that discrepancies in CPD counts could be attributed to sensitivity of ELISA and IHC. A standardised implementation of a UV spectrometer to determine the proportion of off-peak transmissions and assays with higher sensitivity are recommended in future research.

This novel technology demonstrated remarkable reductions in bacteria and lower rates of DNA photodamage than conventional devices. Many studies suggested that the technology was a skin-safe decontaminant for use in an occupied hospital space. Its germicidal efficacy in experimental *in vitro* studies and skin safety in wound associated *in vivo* studies and clinical trials was promising, however a well-supported conclusion regarding its germicidal efficacy and skin safety in surgical sites cannot be drawn. Further research in the area with greater methodological standardization and specifically in human surgical wounds is recommended.

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Conflicts of interest

None declared.

Author contributions

Alexis Panzures (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing).

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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