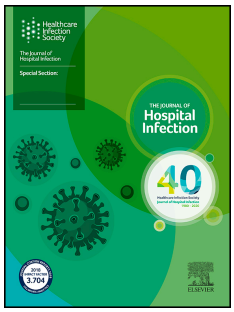

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Disinfection efficacy and safety of 222-nm UVC compared with 254-nm UVC: Systematic review and meta-analysis

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Summary

Background: Some studies have indicated disinfection with 222-nm Ultraviolet C (UVC) is more effective than that with 254-nm UVC. However, other studies reported the opposite findings. Moreover, additional studies have reported that 222-nm UVC exposure is safe for the skin and eyes. This study aimed to identify and quantitatively synthesize all studies evaluating the disinfection efficacy and safety of 222-nm UVC compared with 254-nm UVC.

Methods: We conducted a systematic review and meta-analysis. We searched Web of Science, SCOPUS, Medline, Ovid Embase, and the Cochrane Library through November 2024 for studies that evaluated the disinfection efficacy and safety of 222-nm UVC compared with 254-nm UVC.

Results: We identified 25 eligible publications including 15 publications providing data only on the efficacy, 7 only on the safety, and the remaining 3 on both efficacy and safety. The pooled odds ratio for studies comparing the efficacy of 222-nm UVC with that of 254-nm UVC was 1.382 (95% CI: 1.153-1.656, n=18 publications with 87 studies), indicating that 222-nm UVC is more effective for disinfection. The pooled risk difference for studies evaluating the safety of 222-nm UVC radiation was -0.211 (95% CI: -0.245,-0.177; n=10 publications with 29 studies), which indicates that the proportion of normal cells producing cyclobutane pyrimidine dimers via 222-nm UVC is 21.1% less than that via 254-nm.

Conclusion: Compared with 254-nm UVC, 222-nm UVC not only exhibits comparable or potentially superior efficacy in disinfecting diverse microorganisms but also causes less DNA damage to the mammalian cells.

Keywords: efficacy; safety; 222-nm; ultraviolet C; meta-analysis

Introduction

Ultraviolet C (UVC) light exposure is one of the most common techniques which is well known to elicit highly germicidal effects [1], and UVC irradiation at 254-nm has been widely used. Recently, far-UVC at 222-nm has been of great interest for pathogen inactivation, since the current evidence suggests that 222-nm UVC exhibits hardly any harmful effect on human skin and inactivates a broad spectrum of microorganisms [2,3]. Nevertheless, some studies have shown that 222-nm UVC exposure induces neither DNA damage nor epidermal lesions [4,5], and others have indicated that 222-nm UVC exposure results in DNA damage and transcriptional changes in mammalian cells [6].

Several studies have also compared the disinfection efficacy of 254-nm and 222-nm UVC and have shown varying results. Marcus et al. [7] reported greater photoinactivation of bacterial spores, UV-resistant vegetative bacteria and mould spores at 222 nm than at 254 nm. Similarly, Zhang and colleagues [8] suggested that compared with 254-nm UV, 222-nm UVC irradiation showed a comparable disinfection effect on airborne microorganisms. However, Narita et al.[9] reported that the fungicidal effect of 222-nm UVC on fungal spores and hyphae was weaker than that of 254-nm UVC. In addition, another study revealed that 254-nm UVC is more efficient than 222-nm UVC in inactivating SARS-CoV-2 present in human saliva [10].

Considering that quantitative syntheses of these studies may provide evidence on the disinfection efficacy and safety of 222-nm UVC and help to elucidate the odds ratios (ORs) or risk differences (RDs), this study aims to quantitatively synthesize the findings of all studies that evaluated the disinfection efficacy and safety of 222-nm UVC compared with 254-nm UVC and intends to perform two meta-analyses: one summarizing studies evaluating the disinfection efficacy of 222-nm UVC compared with 254-nm UVC, and the other exploring the safety of 222-nm UVC for mammalian cells

in comparison with 254-nm in order to provide information for future research and disinfection applications of 222-nm UVC.

Methods

Reporting Standards

The present meta-analysis complied with the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11].

Eligibility criteria

In accordance with the inclusion criteria outlined by the Patient Population or Problem, Intervention, Outcomes (PICO) framework [12], the selection process for studies involved the following requirements: (a) application of 222-nm UVC as part of the intervention; (b) evaluation of the disinfection efficacy against various types of microorganisms or the safety; (c) comparison of 222-nm UVC with 254-nm; and (d) inclusion of quantitative outcomes for evaluating the disinfection efficacy (the inactivation ratio or logs of cell reduction) or for safety. Studies written in English or Chinese and of any publication type were considered for inclusion.

Studies were excluded if they did not provide documented exposure to 222-nm UVC, did not encompass an evaluation of disinfection efficacy or safety, did not involve comparisons between 222-nm UV and 254-nm UVC exposure, or did not present quantitative outcomes for evaluating disinfection efficacy or safety. Commentaries, editorials, and review articles without primary data were also excluded.

Data Sources

A systematic search was conducted across the Web of Science, SCOPUS, Medline, Ovid Embase, and Cochrane Library databases. The search strategy incorporated MeSH terms pertaining to "ultraviolet".

The complete search strategy for each database can be found in E-Table 1 of the Supplementary Information. The last search was performed on November 18, 2024. Furthermore, all the references of the included publications were reviewed.

Study Selection

Duplicate references were omitted. Two reviewers independently screened all titles and abstracts, and full-text examination was carried out for records that were deemed eligible for inclusion by either reviewer. In cases where conflicts arose, a third research member was consulted to facilitate discussion and reach a consensus.

Data Extraction

A form was formulated in compliance with the data extraction template offered by the Cochrane Consumers and Communication Review Group. Subsequently, the form was subjected to a pilot test involving ten randomly selected eligible articles, and appropriate modifications and enhancements were made. For the studies evaluating disinfection efficacy, the form included the year of publication, first author's name, country of study, type of microorganisms, medium of microorganisms, UV radiation dosage, and logs of cell reduction. For the studies evaluating the safety of 222-nm UV radiation, the form included the publication year, first author's name, country of study, medium, exposure time, UV radiation dosage and proportion of cyclobutane pyrimidine dimers (CPD)-positive cells. The data were independently extracted by the two reviewers using the same form, and discrepancies were resolved through deliberation with another research member. If some essential information was not presented in the original publications, efforts were made to acquire the data by emailing the corresponding authors.

Quality Assessment

The quality of each individual study was evaluated using the Risk of Bias in Non-randomized

Studies—of Interventions (ROBINS-I) tool[13]. Assessment was conducted on seven domains based on signalling questions: bias due to confounding, bias in selection of participants into study, bias in classification of interventions, bias due to departure from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. Based on the answers to the signalling questions, each domain was classified as follows: low, moderate, serious, or critical risk of bias or no information. The overall risk of bias was defined by combining the results of the seven domains. If any of the seven domains were judged as serious or critical risk, the study was classified as exhibiting an overall serious or critical risk, respectively. The risk of bias was independently assessed by two reviewers, and any inconsistencies were resolved through discussion with an additional member of the research team.

To assessment of the overall quality (certainty) of the evidence included in the meta-analysis, we adopted the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, taking into consideration all relevant GRADE domains: methodological limitations, inconsistency, imprecision, indirectness, and publication bias.

Data Synthesis

Data analyses were performed using Stata Version 18.0 (Stata Corporation, College Station, Texas, USA), with the odds ratio (OR) and risk difference (RD) employed as measures of effect size.

The heterogeneity across studies was evaluated using the I^2 statistic [14], with values of 50% or higher indicating substantial heterogeneity and values of 75% or higher indicating very high heterogeneity. Considering the microbial heterogeneity observed, we used a random effects model to calculate the summary estimate of each risk ratio and hazard ratio, along with 95% confidence intervals (CIs). We employed meta-analyses and forest plots to analyse the data. Furthermore, forest plots and

Begg's tests were utilized to investigate publication bias. To explore potential sources of heterogeneity, multiple meta-regression and subgroup analyses were performed with predetermined study-level characteristics, such as the country in which the study was conducted, type of microorganisms, and medium of the microorganisms. To assess the robustness of the results, sensitivity analyses were conducted to assess whether excluding studies with a high risk of bias influenced the estimated effect or heterogeneity of the outcome.

Results

Study selection

The searches identified a combined sum of 787 citations, comprising 112 from Medline, 264 from Embase Ovid, 143 from Web of Science, 264 from SCOPUS, and 4 from the Cochrane Library. Subsequently, a total of 453 duplicate citations were eliminated. After the initial screening of titles and abstracts, we were able to identify 71 potentially eligible publications. Subsequently, an endeavour was made to obtain the complete texts of each candidate study for a more comprehensive evaluation, but the full text was unavailable for 5 articles. We excluded a total of 5 articles that were not original research, 31articles that were not compared with 254-nm, and 30 articles that failed to provide information regarding the inactivation ratio or logs of cell reduction (E-Table 2). Therefore, 25 publications were included, with 15 providing data only on the disinfection efficacy, 7 providing data only on the safety, and the remaining 3 providing data on both efficacy and safety [2,15,16] (Figure 1). No eligible studies were found in the reference sections of the included publications.

Study characteristics

1. The 18 articles on the disinfection efficacy of 222-nm UVC compared with 254-nm UVC

Our meta-analysis included 18 publications [2,7,8,10,15-28] (representing 87 studies published

from 2006 [7] to 2024 [23]) evaluating the efficacy of 222-nm in comparison to 254-nm. Table 1 presents the data collection form template and the extracted data of each study.

1.1 Study quality

The details of the quality assessment are presented in E-Table 3. Owing to large inconsistencies, studies evaluating the disinfection efficacy of 222-nm UVC compared with that of 254-nm UVC have exhibited a moderate quality of evidence. E-Table 4 provides the GRADE evidence profile.

1.2 Evidence Synthesis

Disinfection efficacy of 222-nm UVC compared with 254-nm UVC

Significant heterogeneity was observed among studies (P<0.001, I^2=99.9%), with individual effect sizes ranging from 0.025 (95% CI: 0.024-0.027) to 37.036 (95% CI: 31.110-44.091). The meta-analysis yielded an overall effect size of 1.382 (95% CI: 1.153-1.656), which is illustrated in Figure 2. Additionally, the funnel plots (Figure 3) revealed no significant evidence of publication bias across studies (Begg's test P=0.002; Egger's test P=0.002).

1.3 Meta-Regression and Subgroup Analysis

We investigated a multiple regression model with each possible source of heterogeneity (I^2 _res=99.83%, adjusted R^2 =11.32%; I^2_res indicates residual variation due to heterogeneity) and found that the country of study (P=0.001) was the potential sources of heterogeneity (Table 2). The studies conducted in Africa, Asia and America exhibited greater combined effect sizes. Moreover, subgroup analyses were undertaken to ascertain the factors contributing to heterogeneity, and a statistically significant interaction was identified (P for interaction<0.001) favouring the *L. monocytogene*s and *SARS-CoV-2* as the species of the microorganisms.

1.4 Sensitivity analyses

The exclusion of any individual study did not change the overall effect size, which ranged from 1.330 (95% CI: 1.111-1.592) to 1.445 (95% CI: 1.249-1.672). This indicates that our results have a high degree of robustness.

2. The 10 articles providing data on the disinfection safety of 222-nm UVC

Our meta-analysis included 10 publications [2,15,16,29-35] representing 29 studies from 2017 [2] to 2024 [35] evaluating the disinfection safety of 222-nm UVC radiation. Table 3 presents the data collection form template and the extracted data of each study.

2.1 Study quality

The details of the quality assessment are presented in E-Table 3. The studies exhibited a moderate quality of evidence due to serious inconsistency (E-Table 4).

2.2 Evidence Synthesis

Significant heterogeneity was observed among studies (P<0.001, I^2=100.0%), with individual effect sizes ranging from -0.625 (95% CI: -0.635, -0.614) to -0.033 (95% CI: -0.035, -0.032). The meta-analysis yielded an overall effect size of -0.211 (95% CI: -0.245, -0.177), which is illustrated in Figure 4. Additionally, the funnel plots (Figure 5) revealed no significant evidence of publication bias across studies (Begg's test P<0.001; Egger's test P<0.001).

2.3 Meta-regression and Subgroup Analysis

Subgroup analyses were performed to determine the factors contributing to heterogeneity (Table 4), and a statistically significant interaction was identified; these analyses were performed in different countries (P for interaction=0.002), with different medium of microorganisms (P for interaction<0.001), and with various exposure time (P for interaction=0.004). These studies conducted in America with mouse skin and human skin models, and with exposure time ≥24h exhibited less

combined effect sizes, which means greater difference between CPD% of 222nm and that of 254-nm. Moreover, we investigated a multiple regression model with each possible source of heterogeneity (I^2 _res=99.92%, adjusted R^2 =17.06%).

2.4 Sensitivity analyses

The exclusion of any individual study, ranging from -0.197 (95% CI: -0.228, -0.165) to -0.218 (95% CI:-0.253, -0.183) did not alter the overall effect size, which suggests that the results exhibit a high level of robustness.

Discussion

Principal Findings

The results obtained from the current meta-analysis suggest that the disinfection efficacy of 222-nm UVC surpasses that of 254-nm UVC (OR: 1.382, 95% CI: 1.153-1.656). The findings of our study revealed that the disinfection efficacy of 222-nm UVC is 1.382 times greater than that of 254-nm UVC. Moreover, the results also show that the safety of 222-nm UVC surpasses that of 254-nm UVC (RD: -0.211, 95% CI: -0.245, -0.177), which indicates that the proportion of normal cells producing CPD via 222-nm UVC is 21.1% less than that via 254-nm UVC at the same irradiation dose.

Despite the significant heterogeneity present in our two meta-analyses, these differences can be partially explained by meta-regression and subgroup analyses. For the meta-analysis of disinfection efficacy, the large heterogeneity observed in the findings could be attributed to variances in the country in which the study was conducted and the specific microorganism types investigated. Moreover, studies carried out in Africa, Asia and America exhibited greater effect sizes than those conducted in Europe. We also observed that studies involving *SARS-CoV-2* and *Bacillus subtilis* spores exhibited

considerably larger effect sizes than those involving alternative microorganisms. Similarly, significant differences were also observed in a previous investigation from the *Proceedings of the 2nd International Congress on Ultraviolet Technology*, in which the efficacy of inactivating *Bacillus subtilis* was nearly twice as pronounced when exposed to 222-nm UVC as when it was exposed to 254-nm UVC, in contrast to the findings for vegetative bacteria of the same strains [36]. This can be partially attributed to the comparatively higher resistance exhibited by bacillus spores, as one might expect, in comparison to the majority of microorganisms [37].

Our results found 222-nm UVC exhibits comparable efficacy to 254-nm in disinfecting diverse microorganisms, which aligns with the findings of David J. Brenner who reported the effectiveness of 222-nm UVC against multiple common pathogens [38]. The mechanism responsible for the comparable disinfection efficacy of 222-nm UVC to that of 254-nm UVC has yet to be determined [17]. Nonetheless, various mechanisms of protein damage can presumably be responsible for the inactivation of microorganisms. First, in the initial study conducted by Clauß and Grotjohann in 2008, it was observed that the photodegradation of proteins and the inactivation of enzymes were significantly enhanced when exposed to the 222-nm UVC, as compared to the 254-nm UVC [39]. In addition, Abdallah et al. indicated that the integrity of the bacterial membrane could be very important for evaluating the disinfection efficacy of 222-nm UVC irradiation because UV light at a wavelength of 222-nm exhibits a specific propensity for the degradation of bacterial outer membrane proteins [40]. Furthermore, according to a study conducted by Yin et al. in 2015, it was observed that the disinfection efficacy of 222-nm UVC was significantly greater than that of 254-nm UVC, which can be attributed to the detrimental effects of 222-nm UVC on the cell envelope [41].

However, for the meta-analysis of safety, the large heterogeneity observed in the findings could be

attributed to variances in the medium of the microorganisms and the exposure time. Furthermore, we also observed that studies with human skin models and mouse skin exhibited considerably less effect sizes than those with rabbits. We found that effect sizes were significantly less for studies with exposure time of ≥24h, which means greater difference between the CPD% of 222nm and that of 254nm. The establishment of the mechanism responsible for the superior safety of 222-nm UVC in comparison to that of 254-nm UVC may be due to the limited penetration of far-UVC in biological samples[2]: due to the strong absorbance in biological materials, far-UVC light cannot penetrate even the outer (non-living) layers of human skin or eye; however, because bacteria and viruses are of micrometer or smaller dimensions, far-UVC can penetrate and inactivate them [42].

The disinfection efficacy of far-UVC (222-nm) is influenced by several critical factors, including the speed of reaction, duration of exposure, distance from the source, environmental conditions, and so on. The speed of reaction or inactivation rate of 222-nm UVC was found by G.G. Matafonova et al. to vary significantly across different bacterial species, including *Bacillus cereus, Bacillus subtilis, Escherichia coli* O157:H7, *Staphylococcus aureus* and *Streptococcus pyogenes* [43]. Second, Hiroki Kitagawa MD found that duration of exposure is another key factor, as the viral titre of *SARS-CoV-2* was reduced on a plastic plate over the irradiation time of 222-nm UVC [44]. Third, distance from the far-UVC source also plays a significant role, as the intensity of far-UVC decreases with distance. Last, the environmental factors, such as humidity, temperature, ventilation air flows, and air quality, can affect the effectiveness of far-UVC [45]. However, the absence of standardized testing protocols poses a challenge for comparing results across studies. Regulatory agencies, such as the Environmental Protection Agency (EPA), have emphasized the need for standardized methods to ensure the safe and effective commercial application of UV technologies [46].

Several companies like Lumenlabs of China [47], Ushio Inc. of Japan [48, 49],and Vive, R-Zero Systems of USA [50] have developed 222-nm UVC lamps for public spaces, and their 222-nm UVC products have been explored and implemented in both clinical and public settings to prevent cross-transmission of pathogens. Firstly, in Beijing Tiantan Hospital of China, the upper-room 222-nm UVC radiation air sterilizers were installed at a height of 2.3–2.6m from the ground in the observation room, computed tomography (CT) scanning room, rescue room and consulting room of the emergency department. The study found 222-nm UVC could effectively reduce the total number of airborne bacterial colonies and improve the environment, and the continuous using of it is helpful for keeping the air safe and clean [47]. Secondly, in Shimane University Hospital of Japan, a prospective observational study involved a 36-month follow-up of physicians working in an ophthalmic examination room equipped with 222-nm UVC. Results indicated no significant changes in ocular examinations and no delayed side effects, suggesting no clinically significant ocular hazards associated with prolonged exposure to 222-nm UVC under real-world conditions [48].Thirdly, a study in USA examined human exposure to air contaminants under the 222-nm UVC system operation in an office, which revealed that the ceiling-mounted 222-nm UVC lamp reduces human exposure to airborne pathogens by up to 80% [49]. What's more, a study in Japan indicated that a 222-nm ultraviolet disinfection device with a motion sensor installed in a shared bathrooms reduced the aerobic bacteria surface contamination of the bathroom [51]. In addition, in a study of India, UVC-based devices were used for the sanitization of air through heating, ventilation and air conditioning systems in closed spaces, which showed that the use of UVC radiation could result in the reduction of the risk of infection in occupied spaces by up to 90% [52].

Some studies have suggested that 222-nm could be an alternative to 254-nm. Ha J and his

294 colleagues' study indicated that the 222-nm UVC surface disinfecting system can be applied as an
295 alternative to conventional LP Hg lamp treatment by the dairy industry [17]. A review in 2022
296 suggests that 222-nm KrCl would be an alternative to conventional 254-nm lamps for achieving target
297 removal levels of both pathogens and contaminants of emerging concern in potable water reuse [53].
298 However, the researchers in Norway installed 222nm UVC lamp in a frequently used elevator, but no
299 significant differences were found in the microbial content between the control elevator and the UV-
300 lamp elevator, which suggests that the 222-nm UVC requires a longer time to kill the bacteria, while
301 the people traffic were continuously re-contaminating the elevators [54]. Therefore, whether 222-nm
302 UVC can serve as a viable alternative to 254-nm UVC remains an open question, necessitating further
303 research to comprehensively evaluate its efficacy, safety, and practical applications. What's more,
304 while 222-nm UVC shows potential as a supplementary tool for hospital decontamination, the evidence
305 regarding its applicability to human wounds during surgical procedures remains inconclusive and
306 warrants further investigation [55].
307
308 **Strengths and Limitations**
309 There are several strengths to the present study. First, the evaluation of the disinfection efficacy and
310 safety of 222-nm UVC is timely and pertinent for researchers, manufacturers, and users. Second, we
311 intentionally conducted two meta-analyses regarding both the efficacy and safety of 222-nm UVC
312 compared with 254-nm, allowing us to include all potentially relevant studies. Third, we conducted a
313 comprehensive search across multiple scholarly databases, including not only Web of Science and
314 SCOPUS which include academic journals covering natural sciences, engineering technology, social
315 sciences, art, humanities and other fields, but also the Cochrane Library which includes grey literature

for relevant studies published up until November, 2024. Moreover, we ensured that every step of the review and extraction process was executed independently and in duplicate.

However, it is important to acknowledge that the present study also encompasses certain noteworthy limitations. First, it is plausible that pertinent scholarly articles were overlooked, such as those that cannot be acquired with the full text, thus resulting in a potential element of selection bias. Second, despite our thorough search of the Cochrane Library, it is possible that relevant grey literature in alternative databases might have been missed. Third, although the review and extraction processes were conducted independently and in duplicate, it is important to acknowledge that the outcomes were still susceptible to subjectivity and reliance on the article reports rather than a direct evaluation of the studies. Fourth, despite the reliability of the ROBINS-I tool, there exists a potential for reviewer bias attributable to the subjective nature of the reviewers. In addition, despite our subgroup analyses revealing discrepancies in the study's geographical location, diversity of microorganisms, exposure time, and cultivation medium used, the substantial heterogeneity observed across the studies poses a challenge in extrapolating the findings to a broader context. Moreover, we did not assess potential sources of heterogeneity, such as the speed of reaction, duration of exposure, distance from the source, environmental conditions, and so on. Our study lacks standardized testing conditions for comparing the efficacy of different UV wavelengths, which may affect the generalizability of our findings. Finally, the analysis was not registered on PROSPERO and the review protocol was not prepared.

Implications

Our research has significant implications for both scientific investigations and practical applications of 222-nm UVC in disinfection processes. Although our conclusions may be weakened by the large heterogeneity among studies, the results of our review and meta-analyses indicate that, compared with

254-nm UVC, 222-nm UVC not only exhibits comparable or potentially superior efficacy in disinfecting diverse microorganisms but also causes less DNA damage to the mammalian cells.

The pooled estimates of the meta-analysis on efficacy suggested that the disinfection efficacy of 222-nm UVC is greater than that of 254-nm UVC. However, although no significant reporting bias was found, the quality of evidence was deemed to be moderate owing to the substantial heterogeneity observed among the included studies. Thus, further research is required to determine with confidence whether 222-nm UVC is more effective than 254-nm UVC for disinfection. Pooled estimates calculated during our meta-analysis on safety indicated that 222-nm UVC caused less DNA damage to the mammalian cells than 254-nm UVC. Large heterogeneity was observed among the included studies, resulting in evidence of moderate quality, suggesting that further research is likely to change the estimate. In addition, further research is necessary to comprehensively evaluate the efficacy, safety, and practical applications of 222-nm UVC in real-world settings, as its potential to serve as a viable alternative to 254-nm UVC remains an open question. What's more, the applicability of 222-nm UVC for use on human wounds during surgical procedures remains an area requiring further investigation. Finally, future research should prioritize the development and adoption of standardized testing protocols to enable consistent and reliable evaluations of UV efficacy.

Conclusion

The findings of the present study demonstrated that, compared with 254-nm UVC, 222-nm UVC not only exhibits comparable or potentially superior efficacy in disinfecting diverse microorganisms but also causes less DNA damage to mammalian cells.

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Competing interests

The authors declare that they have no conflicts of interest.

Ethics

Not required.

Author contributions

QL and XYW performed the review, extraction, and data analysis. In case of conflicts, LJX was consulted to facilitate discussion and achieve consensus. XYW prepared the Introduction section of the first draft, and QL prepared the remaining parts of the paper. YYW, FG, LJX, YZF, LJ, XYW, and QL contributed to manuscript revision. All authors have read and approved the final manuscript.

Tables

Table 1. Description of included studies on efficacy of 222-nm UVC compared with 254-nm

384 Table 2. Meta-Regression and Subgroup Analysis of studies on efficacy of 222-nm UVC

385 Table 3. Description of included studies on safety of 222-nm UVC compared with 254-nm

386 Table 4. Meta-Regression and Subgroup Analysis of studies on safety of 222-nm UVC

387

388 **Figure legends**

389 Figure 1. Study selection process

390 Figure 2. Forest plot of studies on the efficacy of 222-nm UVC

391 Figure 3. Funnel plot of studies on the efficacy of 222-nm UVC

392 Figure 4. Forest plot of studies on the safety of 222-nm UVC

393 Figure 5. Funnel plot of studies on the safety of 222-nm UVC

394

395 **The supplemental information contains E-Table 1-4 and PRISMA 2020 check**

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Table 1. Description of included studies on efficacy of 222-nm UVC compared with 254-nm

No. Of Paper	No. Of study	Author, year	Data source	Medium of microorganisms	Type of microorganisms	222nm UVC		254nm UVC	
						UV fluence1 （mJ/cm²）	Logs of cell reduction 1	UV fluence2 （mJ/cm² ）	Logs of cell reduction 2
1	1	Buonanno,2017(1)	USA	Mammalian skin	MRSA	10	3.3	10	2.9
	2	Buonanno,2017(2)	USA	Mammalian skin	MRSA	30	4.6	30	4
	3	Buonanno,2017(3)	USA	Mammalian skin	MRSA	50	5.2	50	4.3
2	4	Kang,2019(1)	Korea	seed	E.coli	87	0.85	87	0.7
	5	Kang,2019(2)	Korea	seed	E.coli	174	1.77	174	1.16
	6	Kang,2019(3)	Korea	seed	E.coli	261	2.77	261	1.43
	7	Kang,2019(4)	Korea	seed	S. Typhimurium	87	1.22	87	0.75
	8	Kang,2019(5)	Korea	seed	S. Typhimurium	174	2.27	174	1.15
	9	Kang,2019(6)	Korea	seed	S. Typhimurium	261	3.04	261	1.85
3	10	Ha,2016(1)	Korea	sliced cheese surfaces	E. coli	0.87	2.46	0.87	1.26
	11	Ha,2016(2)	Korea	sliced cheese surfaces	E. coli	1.74	4	1.74	2.18
	12	Ha,2016(3)	Korea	sliced cheese surfaces	E. coli	2.61	4.66	2.64	3.34

	13	Ha,2016(4)	Korea	sliced cheese surfaces	S. Typhimurium	0.87	1.99	0.87	0.64
	14	Ha,2016(5)	Korea	sliced cheese surfaces	S. Typhimurium	1.74	3.55	1.74	1.63
	15	Ha,2016(6)	Korea	sliced cheese surfaces	S. Typhimurium	2.61	4.86	2.61	2.45
	16	Ha,2016(7)	Korea	sliced cheese surfaces	L. monocytogenes	0.87	2.01	0.87	0.41
	17	Ha,2016(8)	Korea	sliced cheese surfaces	L. monocytogenes	1.74	3.04	1.74	1.21
	18	Ha,2016(9)	Korea	sliced cheese surfaces	L. monocytogenes	2.61	4.58	2.61	2.02
4	19	Li,2023(1)	China	water	Ms2	12	4.5	12	1
	20	Li,2023(2)	China	water	E. coli	12	5	12	2.5
	21	Li,2023(3)	China	water	S. aureus	12	3.5	12	3
5	22	Ma,2021(1)	USA	thin-film buffered aqueous solution	SARS-CoV-2	1	1.2	1	0.5
	23	Ma,2021(2)	USA	thin-film buffered aqueous solution	SARS-CoV-2	2	2.4	2	2.4
	24	Ma,2021(3)	USA	thin-film buffered	SARS-CoV-2	3	3.5	3	2.1

				aqueous solution					
	25	Ma,2021(4)	USA	thin-film buffered aqueous solution	SARS-CoV-2	4	3.5	4	3.2
6	26	Zhang,2022(1)	China	air	E. coli	0.164	0.7	0.164	0.66
	27	Zhang,2022(2)	China	air	P. alcaligenes,	0.164	1.1	0.164	1.12
	28	Zhang,2022(3)	China	air	S. epidermidis,	0.164	0.47	0.164	0.4
	29	Zhang,2022(4)	China	air	S. marcescens	0.164	0.9	0.164	0.78
	30	Zhang,2022(5)	China	air	Bacteriophage P22	0.164	0.43	0.164	0.4
7	31	Wang,2010(1)	Canada	aqueous suspensions	Bacillus subtilis Spores	10	0.5	10	0.1
	32	Wang,2010(2)	Canada	aqueous suspensions	Bacillus subtilis Spores	15	1.23	15	0.3
	33	Wang,2010(3)	Canada	aqueous suspensions	Bacillus subtilis Spores	20	1.95	20	0.65
	34	Wang,2010(4)	Canada	aqueous suspensions	Bacillus subtilis Spores	25	2.3	25	1.1
	35	Wang,2010(5)	Canada	aqueous suspensions	Bacillus subtilis Spores	35	2.8	35	1.8
	36	Wang,2010(6)	Canada	aqueous suspensions	Bacillus subtilis Spores	70	3.5	70	3.45
8	37	Clauß,2006(1)	Germany	suspension	Aspergillus niger	325	3	370	3

	38	Clauß,2006(2)	Germany	suspension	Penicillium expansum	42	3	49	3
	39	Clauß,2006(3)	Germany	suspension	Bacillus cereus	69	3	140	3
	40	Clauß,2006(4)	Germany	suspension	Clostridium pasteurianum	7.9	3	6.7	3
	41	Clauß,2006(5)	Germany	suspension	Thermoactinomyces vulgaris	46	3	115	3
	42	Clauß,2006(6)	Germany	suspension	Streptomyces griseus	20	3	154	3
	43	Clauß,2006(7)	Germany	suspension	Bacillus cereus	13.7	3	8.5	3
	44	Clauß,2006(8)	Germany	suspension	Deinococcus radiodurans	91	3	170	3
	45	Clauß,2006(9)	Germany	suspension	Arthrobacter nicotinovorans	17.7	3	12	3
	46	Clauß,2006(10)	Germany	suspension	Staphylococcus aureus	13.8	3	7.3	3
	47	Clauß,2006(11)	Germany	suspension	Pseudomonas aeruginosa	5.9	3	2.3	3
9	48	Ong,2022(1)	Singapore	Plates	hCoV-OC43	22	2.2	22	2
	49	Ong,2022(2)	Singapore	Plates	hCoV-229E	22	2	22	1
10	50	Sesti-Costa,2022(1)	Brazil	DMEM	SARS-CoV-2	9.4	4	5.6	4
	51	Sesti-Costa,2022(2)	Brazil	Saliva	SARS-CoV-2	277	4	7.0	4
11	52	Nishikawa, 2023(1)	Japan	plates	F. nucleatum	10	4	10	6
	53	Nishikawa, 2023(2)	Japan	plates	P. gingivalis	10	4.22	10	6

	54	Nishikawa, 2023(3)	Japan	plates	S. mutans	10	3.40	10	5
12	55	Schleusener, 2023(1)	Germany	human oral mucosa	MRSA	20	1.7	20	3.2
	56	Schleusener, 2023(2)	Germany	human oral mucosa	MRSA	40	3.8	40	5.7
	57	Schleusener, 2023(3)	Germany	human oral mucosa	MRSA	60	3.6	60	5.2
	58	Schleusener, 2023(4)	Germany	human oral mucosa	MRSA	80	3.1	80	5.9
13	59	Clauß, 2005(1)	Germany	plates	E. coli	10.6	4	6.9	4
	60	Clauß, 2005(2)	Germany	plates	Y. enterolytica	8.8	4	5.9	4
	61	Clauß, 2005(3)	Germany	plates	E. coli	16.1	4	18.2	4
	62	Clauß, 2005(4)	Germany	plates	Y. enterolytica	11.7	4	18	4
14	63	Sicher, 2024(1)	Germany	human epidermis equivalent models	MRSA	20	2.9	20	2.6
	64	Sicher, 2024(2)	Germany	human epidermis equivalent models	MRSA	40	3.1	40	3.6
	65	Sicher, 2024(3)	Germany	human epidermis equivalent models	MRSA	60	4.7	60	4.4

	66	Sicher, 2024(4)	Germany	human epidermis equivalent models	MRSA	80	4.5	80	4.1
	67	Sicher, 2024(5)	Germany	Nacl	MRSA	40	4.68	40	5.89
	68	Sicher, 2024(6)	Germany	artificial sweat (pH 8.4	MRSA	40	2.27	40	5.98
	69	Sicher, 2024(7)	Germany	Albumin 0.3%	MRSA	40	1.49	40	6.04
	70	Sicher, 2024(8)	Germany	artificial wound exudate	MRSA	40	1.46	40	5.79
	71	Sicher, 2024(9)	Germany	mucin 0.5%	MRSA	40	1.34	40	1.69
	72	Sicher, 2024(10)	Germany	Artificial saliva	MRSA	40	0.46	40	3.20
15	73	Lu, 2024(1)	Hong Kong, China	Bioaerosol	E. coli	1	21.93	1	25.09
	74	Lu, 2024(2)	Hong Kong, China	Bioaerosol	S. epidermidis	1	3.95	1	4.25
	75	Lu, 2024(3)	Hong Kong, China	Bioaerosol	S. enterica	1	4.97	1	5.73
	76	Lu, 2024(4)	Hong Kong, China	Bioaerosol	MS2	1	5.75	1	3.46
	77	Lu, 2024(5)	Hong Kong, China	Bioaerosol	P22	1	17.14	1	9.71
	78	Lu, 2024(6)	Hong Kong, China	Bioaerosol	Phi6	1	20.08	1	6.38
16	79	Monika, 2024(1)	India	plates	MS2	1	1.343	1	0.811
	80	Monika, 2024(2)	India	plates	Phi6	1	1.604	1	0.207

	81	Monika, 2024(3)	India	plates	M13	1	2.061	1	1.494
	82	Monika, 2024(4)	India	plates	T4	1	3.672	1	2.946
17	83	Gierke, 2024	Germany	plates	C. auris	4.3	1	6.1	1
18	84	Liang, 2021(1)	Taiwan,China	plates	SARS-CoV-2	0.035	0.33	4.25	1.17
	85	Liang, 2021(2)	Taiwan,China	plates	SARS-CoV-2	0.07	0.6	8.5	3.34
	86	Liang, 2021(3)	Taiwan,China	plates	SARS-CoV-2	0.14	1.83	17	6
	87	Liang, 2021(4)	Taiwan,China	plates	SARS-CoV-2	0.28	1.33	34	6

Table 2. Meta-Regression and Subgroup Analysis of studies on efficacy of 222-nm UVC

Subgroup	Interventions, n	Pooled effect sizes (95% CI)	Heterogeneity (I^2), *P*	Interaction, *P* [a]	Meta-regression	
					Coef.	*P*
All	87	1.382(1.153-1.656)	99.9%,p<0.001			
Country of study						
Asia	38	2.094(1.685,2.602)	99.6%,p<0.001	<0.001	-0.381	0.001
America	14	1.705(1.419,2.048)	99.0%,p<0.001			
Europe	31	0.711(0.509,0.993)	99.9%,p<0.001			
Africa	4	2.161(1.110,4.206)	99.2%,p<0.001			
Species of microorganisms						
MRSA	17	0.639(0.498,0.820)	99.8%,P<0.001	<0.001	0.352	0.381
E. coli	11	1.340(1.047,1.716)	99.2%,p<0.001			
SARS-CoV-2	10	2.938(0.678,12.722)	100.0%,p<0.001			
Bacillus subtilis Spores	6	2.410(1.562,3.718)	99.4%,p<0.001			
S. Typhimurium	6	2.023(1.745,2.344)	95.1%,p<0.001			
L. monocytogenes	3	3.020(2.054,4.440)	97.8%,p<0.001			
Ms2	3	2.316(1.119,4.792)	99.4%,p<0.001			
Others	31	1.236(0.972,1.573)	99.8%,p<0.001			
Medium of microorganisms						
Surface of solid	36	1.242(1.072,1.439)	99.6%,p<0.001	0.502	0.963	0.895
Liquid	40	1.573(1.082,2.287)	99.9%,p<0.001			
Air	11	1.235(0.920,1.658)	98.4%,p=0.847			

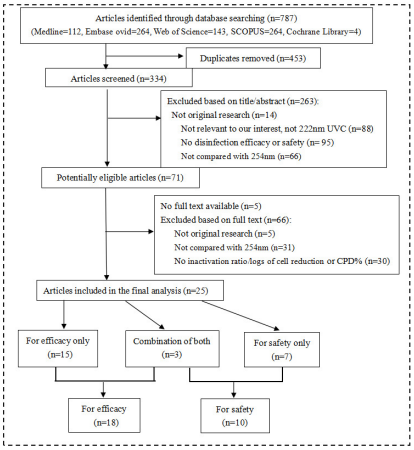
Table 3. Description of included studies on safety of 222-nm UVC compared with 254-nm

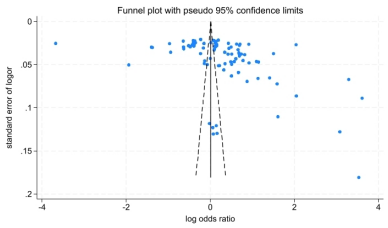
No. of Paper	No. of Study	Author, year	Data source	Medium of microorganisms	Exposure time	Study group (222nm)		Control group (254nm)	
						UV fluence1 (mJ/cm²)	CPD(%)	UV fluence2 (mJ/cm²)	CPD(%)
1	1	Buonanno,2017(1)	USA	mouse skin	48h	25	0	25	23
	2	Buonanno,2017(2)	USA	mouse skin	48h	50	0	50	40
	3	Buonanno,2017(3)	USA	mouse skin	48h	100	0	100	41
	4	Buonanno,2017(4)	USA	mouse skin	48h	150	0	150	48
2	5	Ponnaiya,2018(1)	USA	mouse skin	48h	40	1	40	82
	6	Ponnaiya,2018(2)	USA	mouse skin	48h	300	2	300	85
	7	Ponnaiya,2018(2)	USA	mouse skin	168h	40	1	40	32
	8	Ponnaiya,2018(2)	USA	mouse skin	168h	300	1	300	25
3	9	Narita,2017	Japan	mouse skin	1 h	150	0	150	58
4	10	Zwicker,2022(1)	Germany	human skin model	immediatly	150	10.7	150	44.2
	11	Zwicker,2022(2)	Germany	human skin model	24h	150	0	150	30.8
5	12	Narita,2018(1)	Japan	mouse skin	immediatly	75	0	75	37
	13	Narita,2018(2)	Japan	mouse skin	1h	75	0	75	31
	14	Narita,2018(3)	Japan	mouse skin	3h	75	0	75	28
	15	Narita,2018(4)	Japan	mouse skin	6h	75	0	75	21
	16	Narita,2018(5)	Japan	mouse skin	24h	75	0	75	13
6	17	Fukui, 2021(1)	Japan	rabbit fat	1h	500	5.6	500	47.5
	18	Fukui, 2021(2)	Japan	rabbit fascia	1h	500	2	500	51.8
	19	Fukui, 2021(3)	Japan	rabbit muscle	1h	500	2	500	36.5
	20	Fukui, 2021(4)	Japan	rabbit bone	1h	500	0.5	500	42.4

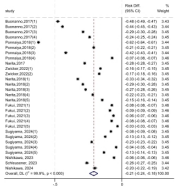
	21	Fukui, 2021(5)	Japan	rabbit cartilage	1h	500	0	500	17.3
7	22	Sugiyama, 2024(1)	Japan	small intestine of rat	0.28h	500	1.1	75	6.97
	23	Sugiyama, 2024(2)	Japan	Colon of rat	0.28h	500	1.27	75	10.99
	24	Sugiyama, 2024(3)	Japan	stomach of rat	0.28h	500	1.24	75	22.27
	25	Sugiyama, 2024(4)	Japan	liver of rat	0.28h	500	2.44	75	3.84
	26	Sugiyama, 2024(5)	Japan	spleen of rat	0.28h	500	1.74	75	12
8	27	Nishikawa, 2023	Japan	mice tongues	0.14h	1850	0	950	60.5
9	28	Schleusener, 2023	Germany	human oral mucosa	24	150	30	40	30
10	29	Nishikawa, 2024	Japan	Colon cancer cell line DLD-1	48h	30	3.37	30	13.1

Table 4. Meta-Regression and Subgroup Analysis of studies on safety of 222-nm UVC

Subgroup	Interventions, n	Pooled effect sizes (95% CI)	Heterogeneity (I^2), *P*	Interaction, *P* [a]	Meta-regression	
					Coef.	*P*
All	29	-0.211(-0.245,-0.177)	100.0%,p<0.001			
Country of study						
Asia	18	-0.153(-0.182, -0.124)	99.9%,p<0.001	0.002	-0.007	0.893
America	8	-0.348(-0.471,-0.225)	100.0%, p<0.001			
Europe	3	-0.197(-0.244,-0.150)	99.1%,p<0.001			
Medium of microorganisms						
Human skin model	4	-0.199(-0.238,-0.160)	98.7%,P<0.001	<0.001	-0.071	0.055
Mouse skin	20	-0.250(-0.308,-0.192)	100.0%, p=0.372			
Rabbit	5	-0.068(-0.091,-0.045)	99.8%,p<0.001			
Exposure time						
<1h	8	-0.145(-0.204,-0.087)	99.9%,P<0.001	0.004	0.052	0.360
1-24h	9	-0.156(-0.2199,-0.113)	99.9%,p<0.001			
⩾24h	12	-0.297(-0.382,-0.213)	99.9%,p<0.001			







NOTE: Weights are from random effects model; continuity correction applied to studies with zero cells