Health Protection Scotland

NHS National Services Scotland

Literature Review and Practice Recommendations: Existing and emerging technologies used for decontamination of the healthcare environment

Chlorine Dioxide

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Contents

Topic

The use of chlorine dioxide for decontamination of the healthcare environment and reusable non-invasive patient care equipment.

Background

There is strong scientific evidence that contaminated environmental surfaces contribute to the transmission of pathogens in healthcare settings.[1-4] As such, environmental decontamination has an important role to play in the prevention and control of healthcare associated infections.[1-4]

The National Infection Prevention and Control (IP&C) Manual[4] for NHSScotland currently outlines the following recommendations on agents for **routine environmental decontamination** within the Standard Infection Control Precautions (SICPs chapter 1), which are the basic measures intended to be applied by all staff, in all care settings, at all times, for all patients:

> *A fresh solution of general purpose neutral detergent in warm water is recommended for routine cleaning. This should be changed when dirty or at 15 minutes intervals or when changing tasks.*
>
> *Routine disinfection of the environment is not recommended. However, 1,000 parts per million available chlorine (ppm available chlorine (av.cl.)) should be used routinely on sanitary fittings.*[4]

The National IP&C Manual also makes recommendations on agents for environmental decontamination in the chapter outlining Transmission Based Precautions (TBPs), which are intended to be applied when caring for patients who are known to have or are suspected of having an infection.[4] The following recommendations are made in relation to **routine environmental decontamination** when applying TBPs:

*Patient isolation/cohort rooms/area must be decontaminated **at least daily** using either:*

- *a combined detergent/disinfectant solution at a dilution of 1,000ppm available chlorine; or*
- *a general purpose neutral detergent in a solution of warm water followed by disinfection solution of 1,000ppm av.cl.4*

In addition, the following recommendations are made in relation to **terminal cleaning** when applying TBPs:

> *The room should be decontaminated using either:*
>
> - *a combined detergent disinfectant solution at a dilution (1,000ppm av.cl.); or*
> - *a general purpose neutral detergent in a solution of warm water followed by disinfection solution of 1,000ppm av.cl.4*

Chlorine releasing agents are recommended for decontamination of sanitary fittings and for environmental decontamination under TBPs based on substantial evidence of their effectiveness against pathogens of HAI significance including norovirus and *C.difficile*.[5]

However, several issues and problems associated with the use of chlorine releasing agents such as corrosion of equipment and furnishings, release of toxic gas and respiratory irritation, has encouraged interest in alternative methods of decontamination.[6] There are numerous other existing technologies such as steam cleaners, and a growing list of novel technologies becoming available for decontamination of the healthcare environment.[7-9] Currently, these technologies have not been sufficiently assessed to advocate their use for environmental decontamination in NHSScotland. A review is required to assess the effectiveness of technologies of interest to the infection control community, to consider any practical and safety considerations related to their, and to explore the associated costs.

Aim

To review the evidence for using chlorine dioxide for decontamination of the healthcare environment and reusable non-invasive patient care equipment.

Objectives

- To provide a generic description of chlorine dioxide, including the proposed or actual mechanism of action and the procedure for use.
- To assess the scientific evidence for effectiveness of chlorine dioxide.
- To explore practical and safety considerations related to the use of chlorine dioxide.
- To explore the costs associated with chlorine dioxide.
- To produce a evidence sheet for chlorine dioxide to assist the Environmental Decontamination Steering Group in making practical recommendations on the use of chlorine dioxide for NHSScotland.

Research questions

The following research questions will be addressed for chlorine dioxide:

1. Is chlorine dioxide currently in use in UK healthcare settings?
2. What is the actual or proposed mechanism of action of chlorine dioxide?
3. What is the procedure for using chlorine dioxide?
4. What is the scientific evidence for effectiveness of chlorine dioxide for decontamination of the healthcare environment?
5. Are there any safety considerations associated with using chlorine dioxide in the healthcare setting?
6. Are there any practical or logistical considerations associated with using chlorine dioxide in the healthcare setting?
7. What costs are associated with using chlorine dioxide in the healthcare setting?
8. Has chlorine dioxide been assessed by the Rapid Review Panel?

Methodology

Search Strategy

The following databases and websites were searched to identify relevant academic and grey literature:

- MEDLINE
- CINAHL
- EMBASE
- NHS Evidence (http://www.evidence.nhs.uk/)
- Health Technology Assessment (HTA) Database (http://www.crd.york.ac.uk/CRDWeb/)
- Database of Abstracts of Reviews of Effects (DARE) (http://www.crd.york.ac.uk/CRDWeb/)
- National Patient Safety Agency (http://www.npsa.nhs.uk/)
- NICE (http://www.nice.org.uk/)
- MHRA (http://www.mhra.gov.uk/)
- Rapid Review Panel Reports Archive (http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/RapidReviewPanel/ReportsArchive/)

Search terms were developed and adapted to suit each database or website. Literature searches were run on 8/12/2015. See Appendix 1 for an example search run in the Medline database.

Exclusion criteria

Academic and grey literature was excluded from the review on the basis of the following exclusion criteria:

- Item was published before 2005
- Item was not in English
- Item does not concern chlorine dioxide (off topic)
- Item is an opinion piece or non-systematic review

Item does not present evidence compatible with the McDonald-Arduino evidentiary hierarchy[10]

- Study does not have a comparison in the form of standard cleaning methods

  N.B. If the study has used rigorous methodology and includes comparisons in the form of positive and negative controls or has been conducted as a before and after study it may be considered for inclusion. If these studies are included, then these limitations must be highlighted in the report.

Manufacturer information was not subject to the exclusion criteria outlined above, as it was sought primarily for information about the procedure for using the technology in question.

Screening

There was a two-stage process for screening the items returned from the literature searches. In the first stage, the title and abstract were screened against the exclusion criteria by the lead reviewer. Items that were not excluded at the screening stage progressed to the second screening stage. In the second stage of the screening process, the full text of remaining items was screened against the exclusion criteria by the lead reviewer. Items that were not excluded at the second screening stage were included in the review.

Critical appraisal

Critical appraisal of the studies included in this review and considered judgement of the evidence was carried out by the lead reviewer using SIGN methodology.[11] The McDonald-Arduino evidentiary hierarchy[10] was used as the framework for assessing the evidence, and was integrated into the critical appraisal process.

A number of studies used concentrations that were expressed in units such as mg/ml or as percentages. To enable easier comparisons to be made, all concentrations are converted to ppm.[12]

Results

The search found 350 articles. After the first stage of screening using the title and abstract this was reduced to 46 articles, and after stage 2 screening using the full text there were 16 articles that fulfilled the exclusion criteria and were critically appraised for inclusion in this review. All of these were experimental studies classed as level 3 evidence (non-analytic studies). Of these, 12 took place in laboratory settings,[13-24] 3 took place in hospitals[25-27] and 1 took place in an ambulance.[28]

Four studies [15;16;19;26] compared chlorine dioxide to **hypochlorite**:

- Chlorine dioxide **liquid disinfectant** (300ppm) was compared to microfibre and 1,000ppm hypochlorite in a hospital before and after study and showed *no difference in effectiveness*[26] in terms of the mean number of *Clostridium difficile* infections (CDIs), mean rate of infection or overall rate of environmental contamination. There was no mention within the studies if the microfibre used was disposable or reusable.
- Chlorine dioxide **liquid disinfectant** (500 and 1,000ppm) was compared to hypochlorite (2,500, 3,300 and 5,000ppm) and showed *similar levels of effectiveness*. In this study each disinfectant was tested against each organism individually and in a mixture. After a 5 min contact time, chlorine dioxide and hypochlorite were effective against *M. terrae, A. baumannii* and Hepatitis A virus. After a 20 min contact time, chlorine dioxide (1,000ppm) was only sporicidal if tested on spores individually but not when tested in mixture. However, at the 20 min contact time hypochlorite was sporicidal at all concentrations.[19]
- Chlorine dioxide **gas** (750ppmv) achieved 6 log reductions against *B. subtilis* spores after a 6 hour exposure compared with hypochlorite sprayed on (6,000–6,700ppm) which wasn't able to achieve this reduction after a 1 hour contact time in a laboratory experimental study. This *may indicate that chlorine dioxide was more effective than hypochlorite* but as the contact/exposure times were so different it is difficult to make this conclusion.[15] In addition sprays which are produced within the healthcare environment are not generally supported. This is due to the risk of contamination of the spray bottle and acting as a reservoir for transmission of microorganisms within the clinical environment.
- Nineteen chlorine dioxide and five hypochlorite **disinfectant solutions** (no concentrations provided) were compared in a laboratory experimental study and found that the eight products that achieved a 10^3 fold reduction in 1 minute under dirty conditions were all chlorine dioxide based. As no concentrations of any of the

products are provided, no useful conclusions can be made with regards to the relative effectiveness of the disinfectant solutions.[16]

Two studies compared chlorine dioxide to **hydrogen peroxide**: [21;24]

- Chlorine dioxide **gas** (10ppm) efficacy against spores was compared to vaporised hydrogen peroxide (290ppmv)[21] and found statistically similar efficacy of chlorine dioxide at spore loading levels of 1×10^6, $1 \times 10^7$and 1×10^8 at a >95% confidence level (p= 0.05). However, increasing the number of spores from 1×10^6 to 1×10^8 led to a significant *decrease in effectiveness* of VHP, and this decrease was statistically significant demonstrating that at higher spore loads chlorine dioxide was more effective than vaporised hydrogen peroxide.
- Chlorine dioxide **cleaning solution** (20,000ppm) was compared to 35,000ppm hydrogen peroxide[24] and found that effectiveness depended on the concentration and exposure time. Activated chlorine dioxide was *more effective than hydrogen peroxide at inactivating spores after 1 hour* (4 log reduction in spores compared to 1 log reduction with hydrogen peroxide). Hydrogen peroxide was able to inactivate the spores after 24 hours. Inactivated chlorine dioxide had no measurable effect.

One study compared chlorine dioxide to **hypochlorite and hydrogen peroxide**:[14]

- Chlorine dioxide **cleaning solution** (600ppm) was compared to hypochlorite (1000-5000ppm) and found that chlorine dioxide and hypochlorite at 1,000ppm needed 30 minutes to achieve the *same level of effectiveness* against spores. Increasing the hypochlorite concentration to 3,000ppm reduced the time required to 20 minutes, and increasing hypochlorite to 5,000ppm meant all spores could be inactivated in less than 10 minutes. Hydrogen peroxide at 70,000ppm inactivated all the spores in less than 13 minutes.

One study compared two **different chlorine dioxide generation methods** to each other:[20]

- Increasing the exposure time (30min, 1-10hrs) at each of the chlorine dioxide **gas** concentrations (500, 1,000, 1,500 and 3,000ppm) showed a *trend of reduction* in the number of viable spores recovered. This dose-response relationship demonstrates the spore sensitivity to the cumulative dose of chlorine dioxide gas rather than just the exposure time or concentration. The time required to reduce the number of recovered viable spores by 6 logs or more is a function of the *concentration of chlorine dioxide and exposure time*. Complete inactivation of spores required a chlorine dioxide dose of 1,500 to 3,000ppmv/h. This study demonstrated that

e**xposure time** is more critical than **concentration** of chlorine dioxide as long as the concentration is maintained within a target range.

Eight studies used **positive and negative controls** to increase the validity of the results.[13;17;18;22;23;25;27;28] It is worth noting that evidence from studies comparing chlorine dioxide to other cleaning methods is more useful in the formation of recommendations than evidence from studies that used positive and negative controls.

The three studies carried out in **hospital** settings are difficult to compare to each other as they do not show much consistency.

- One of the studies compared an existing cleaning regime of microfibre and 1,000ppm hypochlorite to a chlorine dioxide disinfectant[26] and found *no difference in the effectiveness* of the two cleaning regimes.
- The other two studies carried out in hospital settings used chlorine dioxide gas generated by the Minidox-M Decontamination System at concentrations of 350-385ppm and found that *chlorine dioxide gas was able to reduce bacterial loads by >6log*.[25;27]

Ten studies used chlorine dioxide as a **gas**[13;15;18;20-23;25;27;28] and all of these studies showed that chlorine dioxide gas was *effective* at reducing bacterial loads in a variety of settings and interventions, depending on the concentrations and exposure times used.

- One laboratory based study using chlorine dioxide **gas** (750ppmv) achieved 6 log reductions against *B. subtilis* spores after a 6 hour exposure compared with **hypochlorite** sprayed on (6,000–6,700ppm) which wasn't able to achieve this reduction after a 1 hour contact time in a laboratory experimental study.[15]
- One laboratory study compared the effectiveness of chlorine dioxide gas (10ppm) to hydrogen peroxide (290ppmv)[21] against spores and found chlorine dioxide to be effective at spore loading levels of 1×10^6, 1×10^7 and 1×10^8 at a >95% confidence level ($p = 0.05$).
- Two hospital based studies using chlorine dioxide gas (350-385ppm)[25;27] achieved >6log reductions against *Bacillus atrophaeus* spore strips, *A. baumannii*, *E. coli*, *E. faecalis*, *M. smegmatis* and *S. aureus*. However, the hospitals in these studies are representative of standard hospital rooms as they have additional safety measures not typically present.

- One study tested the effectiveness of chlorine dioxide gas (315-695ppm) in an ambulance[28] and found that only the highest concentration (695ppm) was able to inactivate the test organisms.
- One laboratory based study tested chlorine dioxide gas (800-830ppm)[18] against *B. subtilis* spores on different test surfaces and found it to be more effective on some surfaces than others with log reduction ranging from 1.80-6.64.
- One laboratory based study tested chlorine dioxide gas (500, 1,000, 1,500 and 3,000ppm)[20] against *B. anthracis* spores and found it to be effective depending on the concentration and exposure time used. Increasing the exposure time (30min, 1-10hrs) at each of the chlorine dioxide gas concentrations showed a *trend of reduction* in the number of viable spores recovered.
- One laboratory based study stated that chlorine dioxide gas (10,000ppm[13] was effective against *B. atropheus* spore strips but didn't provide detailed results, p values or confidence intervals.
- Two laboratory based studies tested the effectiveness of chlorine dioxide gas (500 and 1,000ppm) against fungi and fungal mycotoxins and found it effective against the fungi but not against the mycotoxins.

Six studies used chlorine dioxide based **liquid cleaning products**[14;16;17;19;24;26] and the results were much more varied.

- One study compared chlorine dioxide to hypochlorite[14] and found that hypochlorite was more effective at contact times less than 10 minutes whereas chlorine dioxide was only effective after 30minutes. However, it is worth noting that the chlorine dioxide concentrations used (600ppm free chlorine) were much lower than the hypochlorite concentrations (1,000-5,000ppm) and the authors suggest that higher concentrations may have led to a more sporicidal effect.
- One study compared a chlorine dioxide based liquid disinfectant (300ppm)[26] to 1,000ppm hypochlorite and found no significant difference in cleaning efficacy between them.
- One study compared 20,000ppm stabilised chlorine dioxide cleaning solution with 35,000ppm hydrogen peroxide solution and found that chlorine dioxide was only effective if it was activated using citric acid.[24]

- A study tested a chlorine dioxide solution (Vimoba at 2,500, 5,000 and 10,000ppm)[17] against spores and found that it was only effective if test materials were immersed in a solution but it wasn't effective as a spray. This would appear to be a serious limitation as it is much more likely in a practical setting that a cleaning product would be applied using a spray.
- One study used a chlorine dioxide based liquid disinfectant (500 and 1,000ppm) against a variety of bacteria, virus and spores and found that it was effective against the bacteria and virus after 5 minutes contact time but took 20 minutes to be effective against spores.[19]

2 of the studies took place in the UK,[16;26] 2 took place in Canada,[14;19] 1 took place in China[18] and 11 took place in USA.[13;15;17;20;22-25;27;28]

Only one study in this review[26] demonstrated **reduced pathogen transmission** by measuring the rates of *C. difficile* infection (CDI) before and after a hospital wide change in cleaning regimen to a chlorine dioxide-based product. This study found that changing to a chlorine dioxide-based cleaning regimen from a regimen using microfibre and hypochlorite at 1,000ppm did not significantly affect the rates of *C. difficile* environmental contamination or patient infection.[26] These results demonstrate that the chlorine dioxide based cleaning regimen used in this study was *as effective* as using microfibre and hypochlorite at 1,000ppm. It is not clear from the study if the microfibre used was reusable or disposable.

All the other studies in this review used environmental surface contamination either in a hospital or laboratory setting as outcome measures. It is not possible to quantify the link between environmental contamination and healthcare associated infection, so the potential impact of chlorine dioxide decontamination on HAIs is limited to the results from one study in this review.

Research Questions

1. Is chlorine dioxide currently in use in UK healthcare settings?

There is no mention of chlorine dioxide in the NHSScotland National Cleaning Services Specification,[29] the NHSScotland National Infection Prevention and Control Manual[4] or the HPS Standard Infection Control Precautions Literature Review of Routine Cleaning in the Environment in the Hospital Setting.[30]

The Association of Healthcare Cleaning Professionals (AHCP) Revised Healthcare Cleaning Manual,[31] and The National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual[32] have a section on dual function chlorine dioxide based cleaner/disinfectants under new technologies. They state that while these products are not widely used in UK healthcare premises, they are increasingly being used for terminal cleans and during infection outbreaks.

There are health boards in NHSScotland currently using chlorine dioxide products and other health boards considering using these products in the future.

2. What is the actual or proposed mechanism of action of chlorine dioxide?

Chlorine dioxide is considered to be a potent bactericidal, virucidal,[19] sporicidal and fungicidal agent, and is said to have two and a half times the oxidising power of chlorine.[24;33;34] Chlorine dioxide reacts with several cellular constituents, including the cell membrane of microbes. It works using oxidation, a process that breaks molecular bonds and "steals" electrons in order to combine with oxygen and produce an oxide product. Chlorine dioxide can attack several proteins simultaneously, and is able to alter the structure and function of proteins. This is how chlorine dioxide is able to affect very rapid death in bacteria and prevents them from mutating to a resistant form.[35]

The National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual[32] states that there is evidence that chlorine dioxide cleaning solutions are very efficient at the removal and inactivation of pathogens, and could play a role in reducing infection transmission in specific infections, such as *Clostridium difficile* where transmission may be linked to contaminated environments. Chlorine dioxide products have been shown to be effective against a wide range of microorganisms such as *Bacillus anthracis*, *Bacillus cereus*, *Clostridium perfringens* and *Legionella* species.[23;24]

3. What is the procedure for using chlorine dioxide?

Chlorine dioxide cleaning solution

The National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual[32] includes a chlorine dioxide cleaner comprising of two components kept apart in separate sections of a sachet. Manually squeezing the sachet allows the components to combine and make a solution which is able to clean and disinfect at a concentration of 125 parts per million. Chlorine dioxide is a more effective oxidant than chlorine therefore the concentration required is smaller than with hypochlorite products.

Friedline et al used an aqueous solution of 2% stabilized chlorine dioxide (Oxine®; Bio-Cide International, Inc., Norman, OK, USA). The product was activated by citric acid addition in a ratio of 0.2 g m/L of stabilized ClO2 solution without stirring for 30 minutes at room temperature, causing the formation of chlorine dioxide.[24]

Chlorine dioxide gas

Chlorine dioxide gas is a more effective decontaminant than its aqueous form as gases are able to penetrate porous surfaces, diffuse rapidly and are able to mix with air, allowing them to clean areas that are hard to clean manually.[28;36] Chlorine dioxide is unstable as a gas and is usually generated on site, either electrochemically or by reaction of sodium chlorite + chlorine gas, sodium hypochlorite + hydrogen chloride or sodium chlorate + peroxide and sulphuric acid.[24]

For the **wet process**, hydrochloric acid is reacted with sodium hypochlorite to generate chlorine, which reacts with sodium hypochlorite to produce Chlorine dioxide that can be stripped out of solution into an air stream moving through a column, generating chlorine dioxide gas (the method of Sabre Technical Services, LLC). In the **dry process**, chlorine gas is passed over a bed of sodium hypochlorite, resulting in generation of Chlorine dioxide gas (ClorDiSys Technology, ClorDiSys Solution, Inc).[15;20]

Lowe *et al.*[13;25;27;28] used the Minidox-M decontamination system which generates chlorine dioxide using a 2% mixture of chlorine gas cycled through cartridges containing sodium chlorite. The system monitors temperature, gas concentration, and exposure time to calculate exposure as ppm/hours. This system has a programmable five-phase decontamination protocol:

1) preconditioning phase increases relative humidity and monitors for leaks
2) conditioning phase maintains the target relative humidity (RH) for a specified time

3) charge phase injects chlorine dioxide gas into the room up to the target concentration (ppm)
4) exposure phase maintains the target concentration of chlorine dioxide to the specified exposure
5) aeration phase where Chlorine dioxide is removed from the decontamination area to 0 ppm[25;28]

Wilson et al dissolved one 6 g S-Tab 10 Aseptrol tablet (Engelhard, Jackson, MS) in 630 ml of sterile deionised water in a sealed bottle. Immediately after the tablet had dissolved (approximately 5 min), 157.5 ml was poured into a beaker with 472.5 ml sterile deionised water that was placed in the centre of the gas chamber. This resulted in a final concentration of 1000ppm chlorine dioxide gas per allotted space.[23]

4. What is the scientific evidence for effectiveness of chlorine dioxide for decontamination of the healthcare environment?

As detailed in the protocol, the McDonald-Arduino evidentiary hierarchy was used as the framework for assessing the evidence, and has been integrated into the critical appraisal process.[37]

Level V – Demonstration of reduced microbial pathogen acquisition (colonisation or infection) by patients via *non-outbreak* surveillance testing and clinical incidence:

Goldenberg *et al.*[26] conducted a hospital based before and after study investigating the prevalence of environmental contamination with *C. difficile* spores on hospital wards and the rates of *C. difficile* infection (CDI) before and after a hospital wide change in cleaning regimen to a **chlorine dioxide-based product**. The previous cleaning regimen involved the use of a microfibre system for routine cleaning and a chlorine releasing agent with 1000ppm chlorine for equipment and environments considered to be contaminated or potentially contaminated. Environmental samples were taken before the use of the new cleaning regimen and tested for the presence of *C. difficile*. CDI rates were measured using the mean number of CDIs per month and the mean number of CDIs per 1000 occupied bed days. There were no changes in antimicrobial prescribing polices, laboratory testing or infection control policies or practice during the study periods. The overall rate of **environmental contamination** did not differ significantly between the two periods of environmental sampling and the mean number of **CDIs** and **mean rate of infection** for both periods were not significantly different. In summary, the change to a chlorine dioxide-based cleaning

regimen did not significantly affect the rates of *C. difficile* environmental contamination or patient infection.

Level IV – Demonstration of reduced microbial pathogen acquisition (colonisation or infection) by patients via *outbreak* surveillance testing and clinical incidence:

No evidence identified.

Level III – Demonstration of in-use bioburden reduction that may be clinically relevant:

No evidence identified.

Level II – Demonstration of in-use bioburden reduction effectiveness:

Lowe *et al.*[25] evaluated the utility of chlorine dioxide **gas** to decontaminate a hospital room designed to provide comprehensive care for patients with highly infectious diseases. The inactivation levels of test organisms that were exposed to chlorine dioxide decontamination were compared to organisms that weren't exposed. Chlorine dioxide fumigation inactivated 116 of the 120 *B. atrophaeus* spore strips placed at 10 sites within the room over 6 decontamination trials. The gas was maintained at 350–385ppm with contact times of less than 4 hours. This demonstrates that chlorine dioxide is capable of reducing >6 log concentrations of bacterial organisms. However it is worth bearing in mind that this study took place in a specialised clinical facility to house highly infectious patients and uses safety measures typically used in biosafety level 3 laboratories such as negatively pressured rooms and corridors. This is not representative of a standard hospital room, making it difficult to generalise these results for all hospital based decontaminations.

Lowe *et al.*[28] evaluated the effectiveness of chlorine dioxide **gas** to decontaminate high concentrations of a variety of bacteria inside an ambulance by comparing the effect on organisms that were exposed to chlorine dioxide gas to unexposed organisms. Overall, chlorine dioxide at a concentration of 315ppm with 65% relative humidity (RH) failed to inactivate all five organisms. At a concentration of **695ppm** with 55% RH chlorine dioxide was able to completely inactivate *A. baumannii* and *M. smegmatis* vegetative cells but failed to achieve total inactivation of *B. anthracis* and *B. atrophaeus* spores as well as *S. aureus* vegetative cells located inside the closed cabinet. However this was a pilot study in a single ambulance so application of the results to other ambulances or other clinical environments may need additional factors to be considered.

Lowe *et al.*[27] evaluated the ability of chlorine dioxide **gas** to decontaminate pathogens known to cause healthcare-associated infections in a hospital room. Test organisms were

Acinetobacter baumannii, *Escherichia coli*, *Enterococcus faecalis*, *Mycobacterium smegmatis*, and *Staphylococcus aureus.* Chlorine dioxide concentrations of **351, 377, 379 and 385ppm** and relative humidities of 50% or 65% achieved complete inactivation of all the test organisms at all 10 placement sites throughout the hospital room. This resulted in a 7.4 log to 10.1 log reduction in viable counts. However, this study took place in the Nebraska Biocontainment Patient Care Unit which is not a good representative for a standard hospital room as it has additional safety measures not typically present in hospital rooms. As a result, these results may not apply in rooms that are not separately sealed and do not have the capability to rapidly evacuate gas if needed. This was a pilot study and a larger study would provide more robust results to validate the utility of gaseous chlorine dioxide in the healthcare setting.

Goldenberg *et al.*[26] conducted a hospital based before and after study investigating the prevalence of environmental contamination with *C. difficile* spores on hospital wards and the rates of *C. difficile* infection (CDI) before and after a hospital wide change in cleaning regimen to a chlorine dioxide-based product. The previous cleaning regimen involved the use of a microfibre system for routine cleaning and a chlorine releasing agent with 1,000 ppm chlorine for equipment and environments considered to be contaminated or potentially contaminated. Environmental samples were taken before the use of the new cleaning regimen and tested for the presence of *C. difficile*. CDI rates were measured using the mean number of CDIs per month and the mean number of CDIs per 1000 occupied bed days. There were no changes in antimicrobial prescribing polices, laboratory testing or infection control policies or practice during the study periods. The overall rate of **environmental contamination** did not differ significantly between the two periods of environmental sampling and the mean number of **CDIs** and **mean rate of infection** for both periods were not significantly different. In summary, as the change from using microfibre and 1,000ppm chlorine to a chlorine dioxide-based cleaning regimen did not significantly affect the rates of *C. difficile* environmental contamination or patient infection this demonstrates that the chlorine dioxide based cleaning regimen was *as effective* as using a chlorine releasing agent.

Level I – Laboratory demonstration of bioburden reduction efficacy:

Lowe *et al.*[13] conducted a study to develop and implement a laboratory decontamination protocol using chlorine dioxide **gas** with minimal disruption to building operations. Chlorine dioxide gas was able to completely inactivate *Bacillus atrophaeus* spore strips (median value of 10^6 spores). *B. atropheus* was used as a surrogate for the spore forming *B. anthracis.* This indicates a 6-log reduction of Bacillus spores relative to the controls. The use of positive

and negative controls increases the validity of the results. However, no detailed results, p values or confidence intervals were provided, making it difficult to compare the results of this study with other studies.

Perez *et al.*[14] conducted a study to identify disinfectants that could inactivate significant numbers of the spores of *C. difficile, Bacillus subtilis* and *Clostridium sporogenes* as these organisms are widely used in assessing the sporicidal potential of disinfectants. Acidified bleach (5,000 mg/L free chlorine- contains bleach, hard water and vinegar) and domestic bleach (5,000 mg/L free chlorine) could inactivate all the spores in ≤10 minutes. The accelerated hydrogen peroxide disinfectant (70,000 mg/l) inactivated all the spores in ≤13 minutes. Domestic bleach with 3000 mg/L free chlorine required up to 20 minutes to reduce the viability of the all the spores tested to undetectable levels. **Chlorine dioxide** (600 mg/L free chlorine) and **domestic bleach at 1,000 mg/L** free chlorine required up to 30 minutes to achieve the same level of activity. However, this study used chlorine dioxide with a concentration of 630 mg/L of free chlorine whereas the bleach products were used at concentrations of 1000-5000 mg/L free chlorine, hence a stronger solution of chlorine dioxide (e.g. 1000 mg/L free chlorine) may have had faster sporicidal activity.

Ryan *et al.*[15] investigated the decontamination effectiveness of chlorine dioxide **gas** compared to hypochlorite products by testing their ability to inactivate *Bacillus subtilis* spores (*Bacillus anthracis* surrogate) on test materials. Using chlorine dioxide gas, a greater than 6 log reduction was observed for all materials by 6 hours of fumigation at **750ppmv**. Using the pH adjusted bleach sprayed on; a 6 log reduction was not achieved within a 1 h contact time (this was the maximum contact time tested). Immersion in bleach solution resulted in significantly greater log reduction values compared to the results from the spray testing, however in a healthcare setting it is impractical for surfaces to be immersed in disinfectants and spraying of disinfectants would not be recommended in an inhabited environment. The use of appropriate non-pathogenic surrogates is necessary to conduct many of the applied studies without the safety restrictions necessitated when using fully virulent *B. anthracis*. However, surrogates do not always adequately predict the behaviour of the target species.

Speight *et al.*[16] tested 32 disinfectants against spores of *C. difficile* in a suspension test with contact times of 1 and 60 min in simulations of clean and dirty conditions to assess their ability to work even in the presence of organic matter that may affect cleaning ability. The disinfectants included chlorine dioxide **solutions** (n=19) and hypochlorite products (n=5) that were used at different dilutions. Only eight products achieved a 10^3 fold reduction in 1 min under dirty conditions, and all of them had chlorine dioxide as their active ingredient. None of the hypochlorite products tested in this study achieved adequate disinfection in the exposure

time in either clean or dirty conditions. However, a large limitation of this study is that the concentration of each of the products used was not provided and the methodology section only provided the levels of dilution. They were often provided as volumes of base and activator with no further information as to whether both of these consisted of the active ingredient. In addition, a 10^3 fold reduction of *C. difficile* is lower than many other decontamination studies have reported.

Chatuev *et al.*[17] tested the sporicidal potential of an aqueous chlorine dioxide **solution** to decontaminate stainless steel biosafety cabinet surfaces. *Bacillus anthracis* spores were used as the test organism. A 10 mg/ml solution of chlorine dioxide was able to reduce *B. anthracis* spore viability by 8 $\log_{10}$ to an undetectable number after a 3 min contact time. A 50% decrease in chlorine dioxide concentration to 5 mg/ml resulted in a 4.34 $\log_{10}$ reduction in spore viability. Reducing this to 2.5 mg/ml, the disinfectant potency was reduced proportionately to 1.57 $\log_{10}$. However, spraying or pipetting this solution onto the stainless steel work surface and spreading it out into a thin film resulted in a significant reduction in disinfectant potential, limiting the kill capacity to approximately 1 $\log_{10}$ in 3 min. The authors also found that preparing this chlorine dioxide solution in 5% bleach allowed it to remain stable for at least 7 days and improved its potency when used as a spray. This stability and potency of this chlorine dioxide liquid disinfectant was also tested, and the authors found that it was able to retain the capacity to kill 8 $\log_{10}$ of *B. anthracis* Sterne spores for up to 7 days as long as the 1litre bottles were at least three quarters full. This study took place in a biosafety cabinet, making it difficult to compare the results to a healthcare environment. In addition, it was most effective in a closed tube system and not very effective when used as a spray unless prepared in a hypochlorite solution. This is a key limitation, as in a practical setting a disinfectant would most likely be sprayed on rather than immersing surfaces with a disinfectant solution Li *et al.*[18] conducted a study to determine the sporicidal efficacy of chlorine dioxide **gas** on a variety of test surfaces and *B. subtilis* spores. Chlorine dioxide concentration ranged from 0.080% to 0.083% during the 3hr exposure period. The spore log reductions on the different materials ranged from 1.80 to 6.64. There was a statistically significant difference between the sporicidal efficacy of chlorine dioxide between the porous and nonporous materials at a >95% confidence interval. This study took place in a biosafety laboratory and despite the use of test materials that are commonly found in the hospital environment it would still be difficult to extrapolate the results to a healthcare environment.

Sabbah *et al.*[19] tested the efficacy of surface disinfectants-peracetic acid (500 and 1,000ppm), chlorine dioxide **solution** (500 and 1,000ppm) and domestic bleach (2,500, 3,300 and 5,000ppm) using a mixture or bacterial cells, spores and viruses (*Acinetobacter*

baumannii, *Mycobacterium terrae*, hepatitis A virus, and spores of *Geobacillus stearothermophilus).* After a 5 min contact time, chlorine dioxide (500 and 1,000ppm) was effective against *M. terrae* and *A.* baumannii (7.72-8.18 log_{10} reduction), was able to reduce the titre of Hepatitis A virus by 3.97-4.3log_{10} and was ineffective against the *Geobacillus stearothermophilus* spores. After 20min, chlorine dioxide was sporicidal at 1,000ppm when spores were tested alone but not in a mixture. After a 5min contact time, all the disinfectants met the criteria for *M. terrae* and *A.* baumannii. Only paracetic acid at 1,000ppm was effective against the spores. However, paracetic acid was ineffective against hepatitis A virus whereas the other disinfectants were able to reduce its titre to between 3.5 and 4 log_{10}. After a 20min contact time, paracetic acid and domestic bleach were sporicidal at all concentrations. Disinfectant testing with a single type of organism does not represent field conditions, so this study used a mixture of organisms with organic soil to simulate a real world situation. This was a small scale laboratory based study that would have more broad reaching conclusions if tested in a healthcare setting.

Rastogi *et al.*[20] compared the relative efficacy of chlorine dioxide **gas** generated by two generation systems, Sabre (wet system with gas generated in water) and ClorDiSys (dry system with gas generated in air) for the decontamination of six building interior surfaces contaminated with avirulent anthrax spores. There was no statistically significant difference in the efficacy of chlorine dioxide based on the method of generation at a 95% confidence level. The study found that the time required to reduce the number of viable spores by 6 logs or more is a function of the concentration of chlorine dioxide and exposure time (CT). Based on qualitative assessment, complete inactivation of bacterial indicators (BIs) required a chlorine dioxide dose of approximately 3,000ppmv/h. Quantitative assessment observed complete spore kill on BIs with a dose of 1,500 to 3,000ppmv-h of chlorine dioxide gas. Exposure time was found to be more critical than concentration of chlorine dioxide as long as the concentration was maintained within a target range. The use of lower chlorine dioxide concentrations could help avoid issues with material or equipment compatibility. This study took place in a laboratory and would provide more wide reaching results if it had taken place in a healthcare setting. Surrogate bacterial indicators were used instead of *B. anthracis.*

Rastogi *et al.*[21] compared the efficacy of chlorine dioxide **gas** and vaporous hydrogen peroxide (VHP) on three different levels of avirulent *B. anthracis* spores. Analysis of the data showed no statistically significant difference in the chlorine dioxide efficacy of spore killing on different materials at the three spore-loading levels (1×10^6, $1 \times 10^7$and 1×10^8) at a >95% confidence level (P= 0.05). However, increasing the number of spores per coupon from 1×10^6 to 1×10^8 led to a significant decrease in effectiveness of VHP, and this decrease was

statistically significant. Inclusion of 0.5% foetal bovine serum (to represent organic burden) with the spore preparation was found to have a negligible effect on either spore recovery or the efficacy of chlorine dioxide gas. However, increasing the amounts of serum bioburden to 2% or 5% resulted in decreased efficacy of chlorine dioxide gas and decreased spore recovery from building materials. In general, the mean spore recovery from different material surfaces ranged between 24-78% of the inoculated spores. There was no apparent correlation between spore recovery and the nature of the coupon material, i.e., porous or nonporous. Only one avirulent strain of *B. anthracis* was used in this study to test the effectiveness of chlorine dioxide gas, making it difficult to extrapolate these results to other microorganisms. The use of VHP as a comparator was limited to investigating the effects of three different spore loads of *B. anthracis*, and wasn't included for the rest of the study.

Wilson *et al.*[22] investigated the fungicidal effect of chlorine dioxide **gas** on four species of fungi: *Stachybotrys chartarum*, *Chaetomium globosum*, *Penicillium chrysogenum*, and *Cladosporium cladosporioides.* The results show that chlorine dioxide gas at concentrations of **500 and 1,000ppm** was successful in completely inhibiting growth of all the fungal species tested. This study focussed on four species of fungi that are commonly found in buildings with indoor air quality problems; however these fungi are not typically associated with healthcare associated infections.

Wilson *et al.*[23] tested the efficacy of chlorine dioxide **gas** against two potential fungal bioterrorism agents, the mycotoxins verrucarin A and roridin A. Chlorine dioxide gas was not able to inactivate either mycotoxin at any of the concentrations or exposure times tested. Conversely, chlorine dioxide was effective in solution, but these results are not included as decontamination of water is out with the remit of this review. The mycotoxins trichothecene mycotoxins verrucarin A and roridin A may be potential bioterrorism agents, but are not typically associated with healthcare associated infections.

Friedline *et al.*[24] investigated the effects of a stabilized chlorine dioxide based cleaning **solution** and a 3.5% hydrogen peroxide solution against spores of *B. pumilus* and *Bacillus subtilis*. Activated chlorine dioxide was effective at inactivating spores of both species of Bacillus. This efficacy was dependent both on chlorine dioxide concentration and duration of exposure. After exposure for 1 hour, activated chlorine dioxide demonstrated a 4-log reduction in viability compared to the control. The activated stabilised chlorine dioxide had sporicidal properties against *B. pumilus*; however, inactivated chlorine dioxide had no measureable effect. Hydrogen peroxide only produced a one order of magnitude of inactivation of *B. pumilus* compared to the control after 1 hour of exposure, but after 24 hours hydrogen peroxide killed nearly all the spores.

5. Are there any safety considerations associated with using chlorine dioxide in the healthcare setting?

Chlorine releasing agents are considered the cheapest and easiest environmental disinfection method. However, they have some limitations such as the release of irritating vapours and toxic gases which may affect the eyes and respiratory tracts of healthcare workers at high concentrations (e.g. 10,000 ppm available chlorine) and for this reason personal protective equipment (PPE) is recommended. Hypochlorite based products can be corrosive to various materials. In addition, the disinfection process must be performed manually-which can be time consuming and the quality of disinfection depends on the staff performing disinfection. This has led to an interest in alternative methods of decontamination.[6;38;39]

Chlorine dioxide is an environmentally preferred alternative to other chlorine releasing agents as the latter release undesirable pollutants such as dioxins and bio-accumulative toxic substances when they react with organic matter. In contrast, chlorine dioxide does not chlorinate organic material, eliminating the formation of trihalomethanes (THMs), haloacetic acids (HAAs) and other chlorinated organic compounds. As chlorine dioxide is a more effective oxidant than chlorine a lower concentration can be used, leading to lower environmental impact.[31;32;35]

Chlorine dioxide cleaning solution

The use of formulations at high concentrations to reduce contact times can be potentially hazardous to the user and materials treated. This means that workplace safety measures and personal protective equipment must be used.[14] The National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual[32] states that chlorine dioxide cleaning solutions do not produce irritant fumes to the same degree as hypochlorite products and may be less environmentally damaging than hypochlorite as they don't produce chlorinated products.

Chlorine dioxide gas

Lowe et al state that gaseous chlorine dioxide is a toxic compound that requires close monitoring of concentrations and adequate training in the technology and use of personal protective equipment (PPE) to limit the potential for occupational and environmental exposures.[25] Chlorine dioxide gas can be explosive when present at high concentrations (>10% in air) which prevents it being compressed or stored commercially.[33] This is in sharp contrast with Li et al who consider chlorine dioxide to be an environment-friendly

bactericide.[18] Keward *et al.* report that some staff reported respiratory issues to occupational health after exposure to chlorine dioxide gas.[40]

In the United States of America, the Occupational Safety and Health Administration (OSHA) has a chlorine dioxide exposure limit of 0.1ppm, with a short term exposure limit of 0.3 ppm for no more than 15 minutes. Chlorine dioxide gas is a severe respiratory and eye irritant that can produce irritating effects in humans at concentration levels of 5 ppm.[28]

Lowe *et al.* highlight the importance of determining a safety perimeter prior to decontamination to ensure personnel safety, and the use of fit-tested personal protective equipment.[28] Lowe *et al.* report that in their study to decontaminate a BSL-3 lab using chlorine dioxide, personnel entering the lab wore personal protective equipment in accordance with the policies and procedures in place. Decontamination personnel were properly fit tested for each piece of respiratory protective equipment that they wore, including an N95 face-filtering disposable respirator, gown, disposable nitrile gloves, head covering, and shoe coverings. The decontamination personnel monitoring the process from outside the lab had full face respirators. The full face respirators were available for an emergency but were also worn by personnel during the decontamination procedure when a gas leak was identified from outside the room being decontaminated. At no time did decontamination personnel enter a room that was in the process of being decontaminated.[13]

Byrns *et al.* state that there were no reports of injuries or illnesses to either fumigation operators or patients in health care settings at the time they conducted their study. They also state that peer-reviewed literature did not contain much evidence of the routine monitoring of occupational and environmental exposures resulting from fumigation activities in health care settings.[41]

6. Are there any practical or logistical considerations associated with using chlorine dioxide in the healthcare setting?

One of the major challenges in all decontamination studies is the rate of recontamination of environmental surfaces after cleaning has taken place. The CDC does not recommend chemical fumigation for general infection control in routine patient care areas because of the prospect of recontamination and the lack of sufficient evidence that chemical fumigation has an impact on healthcare associated infections.[41]

Chlorine dioxide cleaning solution

Keward *et al.* found chlorine dioxide cleaning solutions easy to use (product required mixing of sachets, dilution and stirring) but found issues with staff compliance with cleaning

products. They also highlight the deterioration of the product over time if diluted and stored-it is not stable in solution and needs to be generated on site prior to use[42] and limited cleaning effect on some surfaces or equipment.[40]

Chlorine dioxide gas

The decision to use fumigation in occupied buildings must be given careful consideration as any breaches that lead to chlorine dioxide gas escaping could damage surfaces or have a negative impact on patients, visitors or staff exposed to the gas. The safest approach is to evacuate buildings before fumigation, however this could prove costly or may not be feasible if sufficient additional beds in other facilities are not available.[41]

Del Busto-Ramos *et al.* highlight the challenge of ensuring that adequate **levels** of chlorine dioxide reached all areas of the facility being decontaminated[34] but Lowe *et al.* found they were able to maintain chlorine dioxide concentrations due to the small size of the facility being decontaminated and the tight seal of building preventing gas from escaping.[13]

Lowe *et al.* discuss one of the limitations of using chlorine dioxide gas fumigation being the **time** involved in the process from initial preparation to ensuring decontamination has been successful. Some areas of the building had reduced air supply during the decontamination process and non decontamination personnel were not allowed access to areas adjacent to the lab during decontamination. The entire process took 29 days from initiation to completion, and prolonged availability of the gas generator allowed the process to be spread over multiple weeks to limit the impact on other building occupants but the authors acknowledge that this may not always be feasible.[13]

Another key factor in fumigation is the need to **seal** rooms being decontaminated to prevent chlorine dioxide gas from escaping. Gas detectors can be used to detect any leaks coming from a sealed space undergoing fumigation, allowing adjustments to be made to the seal. Lowe et al state that they detected leaks of gas <0.1ppm outside the hospital room being fumigated, however tape reinforcement from the exterior of the hospital room eliminated the detection. No gas was detected on the floor below the hospital room being decontaminated, in the adjacent rooms, or more than several feet beyond the taped doors. The odour threshold used for ClO2 is approximately 0.1 ppm, allowing another level of detection.[25]

7. What costs are associated with using chlorine dioxide in the healthcare setting?

The National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual[32] states that chlorine dioxide disinfectants are currently more expensive than some hypochlorite

products, however few of the studies in this review included information on the costs involved.

Byrns *et al.* discuss the importance of determining the total cost of using chlorine dioxide as a decontaminant, and state that cost assessments should consider more than the cost of chlorine dioxide generation systems and should include the cost of environmental monitoring. Another factor to consider in cost calculations is the fumigation time needed, as long fumigation times could affect room turnover rates and potentially lead to a significant burden on room availability in hospitals.[41]

Decontaminating a whole hospital as opposed to a hospital ward has very different cost implications. Davies *et al.* discuss the decontamination of a hospital in USA which was contaminated with mould and the contents of the hospital had to be removed before the building was covered with a tarpaulin and then fumigated with chlorine dioxide for 24 hours at a cost of $25 million in 2011.[33]

8. Has chlorine dioxide been assessed by the Rapid Review Panel?

The Rapid Review Panel (RRP) is a panel of UK experts established by the Department of Health to review technologies with potential to help in the prevention and control of HAI.[43] To date no chlorine dioxide based products have been assessed by the Rapid Review Panel.

Discussion

Whilst there is some evidence demonstrating the effectiveness of chlorine dioxide as a gas or cleaning solution, there have been insufficient high level studies undertaken. All the studies included in this review are level 3 evidence and only one study uses pathogen transmission as an outcome measure instead of environmental contamination meaning that only the results from this study can be used to assess the potential impact of chlorine dioxide on healthcare associated infections.

Chlorine dioxide: evidence of effectiveness as a gas or a cleaning product

- There is evidence from ten studies (**level 3 evidence**) that chlorine dioxide **gas**[13;15;18;20-23;25;27;28] was ***effective*** at reducing bacterial loads in a variety of settings and interventions, depending on the concentrations and exposure times used. Two of these studies took place in hospitals, one took place in an ambulance and seven took place in laboratories.
- The two hospital based studies (**level 3 evidence**) demonstrated that chlorine dioxide **gas** at concentrations of 350-385ppm was able to reduce bacterial loads by >6log.[25;27]
- There is evidence from four studies (**level 3 evidence**)that chlorine dioxide **cleaning products** were ***only effective*** at reducing organism contamination under the following conditions:
    - After a 30 minute contact time[14]
    - If test materials were immersed in a chlorine dioxide solution[17]
    - After a 20 minute contact time to inactivate spores compared to 5 minutes for bacteria and viruses[19]
    - Only effective if activated using citric acid.[24]

Chlorine dioxide compared to hypochlorite

- There is evidence from one hospital based study (**level 3 evidence**) that compared cleaning with microfibre and 1,000ppm hypochlorite to chlorine dioxide cleaning solution (300ppm)[26] and demonstrated ***similar levels of effectiveness*** in terms of the mean number of CDIs, mean rate of infection or overall rate of environmental contamination.
- There is evidence from one laboratory based study (**level 3 evidence**) that chlorine dioxide liquid disinfectant (500 and 1,000ppm) and hypochlorite (2,500, 3,300 and

5,000ppm) showed ***similar levels of effectiveness*** against test bacteria, with hypochlorite having stronger sporicidal activity.[19]

- There is evidence from one laboratory based study (**level 3 evidence**) comparing chlorine dioxide cleaning solution (600ppm) to hypochlorite (1000-5000ppm) and found that chlorine dioxide and hypochlorite at 1,000ppm had the ***same level of sporicidal activity at 30 minutes***, but increasing the hypochlorite concentration to 3,000 or 5,000ppm allowed it to be sporicidal in as little as 10 minutes.[14]
- There is **inconclusive evidence** from one laboratory based study (**level 3 evidence**) comparing chlorine dioxide gas (750ppmv) with hypochlorite (6,000–6,700 ppm). Although it showed chlorine dioxide achieving 6 log reductions against *B. subtilis* spores, chlorine dioxide had a 6 hour exposure whereas hypochlorite contact time was one hour. The authors don't explain the reasons for the different exposure times so although chlorine dioxide would appear to be more effective than hypochlorite in this study as the exposure times were so different this does not make for a reasonable comparison.[15] In addition the hypochlorite was used in a spray format which unless sprayed and wiped may not allow full contact with the surface to be cleaned. Additionally sprays are not advocated within the clinical environment especially those which have to be reconstituted on site. Such sprays risk the refillable bottles becoming a reservoir for infection.
- There is **inconclusive evidence** from one laboratory based study (**level 3 evidence**) comparing chlorine dioxide and hypochlorite cleaning solutions as although the products achieving 10^3 fold reductions were all chlorine dioxide based, no concentrations were provided making it difficult to draw any meaningful conclusions with regards to the relative effectiveness of the disinfectant solutions.[16]

Three level 3 studies showed that chlorine dioxide was at least as effective as using hypochlorite, with hypochlorite being a stronger sporicidal agent.

Chlorine dioxide compared to hydrogen peroxide

- There is evidence from one laboratory based study (**level 3 evidence**) that chlorine dioxide gas (10ppm) and vaporised hydrogen peroxide (290ppmv)[21] had ***similar levels of effectiveness*** at spore loading levels of 1×10^6. However, increasing the spore load to 1×10^8 led to a significant *decrease in effectiveness* of hydrogen peroxide compared to chlorine dioxide.

- There is evidence from one laboratory based study (**level 3 evidence**) comparing chlorine dioxide cleaning solution (20,000ppm) to 35,000ppm hydrogen peroxide[24] that found effectiveness depended on the concentration and exposure times used. ***Activated chlorine dioxide was more effective than hydrogen peroxide at inactivating spores after 1 hour*** (4 log reduction in spores compared to 1 log reduction with hydrogen peroxide). However, inactivated chlorine dioxide had no measurable effect.
- There is evidence from one laboratory based study (**level 3 evidence**) comparing chlorine dioxide cleaning solution (600ppm) hydrogen peroxide at 70,000ppm and showed that *hydrogen peroxide was more effective than chlorine dioxide* as it inactivated all the spores in less than 13 minutes.[14]

Conclusion

The limited low level evidence on this topic (**all level 3**) assessing the effectiveness of chlorine dioxide may reflect the fact that it is challenging to undertake well designed studies to explore the effectiveness of cleaning methodologies in the healthcare setting due to practical considerations. It may also reflect the fact that environmental decontamination in healthcare has not been considered a priority area for research. All of the studies included in the review are subject to methodological limitations to a greater or lesser extent, which limit the conclusions that can be drawn from them. Many of the outcomes measured in the studies included in this review are of limited use as they only demonstrate reduced burden in-use or in a laboratory setting which is less useful than demonstrating reduced infections or clinical incidence. However, such studies would also probably be more costly and difficult to conduct.

Of the studies that have been identified in this review, there are only a few comparing the effectiveness of chlorine dioxide with other cleaning methods such as hypochlorite or hydrogen peroxide. Of these, three level 3 studies showed that chlorine dioxide was at least as effective as using hypochlorite, with hypochlorite being a stronger sporicidal agent.

Many of the studies are either before and after studies, compare different concentrations or exposure levels of chlorine dioxide or are laboratory based studies using positive and negative controls. Whilst the use of these controls provides some validity to the results, it does not provide results that are as clinically relevant as comparison to other cleaning methods in a healthcare setting.

It is important to consider that the effectiveness of cleaning depends not only on the cleaning product being used but also on appropriate use of the product and effective implementation of the cleaning protocol by all staff undertaking cleaning. It is possible that the Hawthorne Effect may have led to improved adherence to cleaning protocols by staff who modified their behaviour because they were aware that their cleaning behaviour was being observed.

The introduction of any novel decontamination technology should be used as part of a coordinated and structured infection control intervention and it is essential that recommendations by the local infection control team are followed. There may be circumstances where it is appropriate to use alternative decontamination technologies to supplement but not replace standard cleaning and disinfection methods, such as fumigation of a ward following an outbreak. Cleaning using traditional methods according to cleaning protocols is likely to be far more effective than the inappropriate use of any new decontamination technology.[33]

Fumigation in health care facilities and other related institutions should be limited to those instances where the benefits clearly exceed the risks of human exposure or environmental damage. Decontamination of an unoccupied building following a bioterrorism incident would meet this criterion. In situations where the building is occupied and the potential for recontamination is high, the benefits of fumigation do not appear to exceed the risks. Before fumigation is considered, simpler and safer approaches such as enhanced cleaning should be considered.[41]

As the costs of chlorine dioxide gaseous decontamination can be substantially greater than the costs of standard terminal cleaning by housekeeping personnel, additional studies are required to determine the cost-effectiveness of chlorine dioxide and to identify when and where it should be used. The time taken to empty and seal rooms or wards, the requirement to test for residual chemicals and delays in reopening wards should all be balanced against any additional microbial reduction that it can offer.[33]

Recommendations for practice

This review makes the following recommendations based on an assessment of the extant scientific literature on chlorine dioxide products.

If NHS boards use chlorine dioxide products for decontamination of the healthcare environment and patient care equipment, the following must be considered:

- There is no evidence to consider the use of chlorine dioxide products (gas) as an alternative to routine cleaning of the healthcare environment or reusable communal patient related equipment.
  (Grade D recommendation)
- Chlorine gas decontamination methods should not be used for routine cleaning purposes. They should only be considered where a risk to public health has been identified i.e. bioterrorism or highly infectious diseases.
  (Grade D recommendation)
- Where chlorine dioxide gas is to be considered for decontamination of the healthcare environment it must be undertaken following strict adherence to the manufacturers or external contractors instructions.
  (Good Practice Point)
- Chlorine dioxide solution (300ppm) can be considered as an alternative to hypochlorite products at 1000ppm for terminal/isolation/deep cleaning. Whilst it is recognised that the graded evidence for chlorine dioxide solution is low quality, HPS acknowledges that some health boards within NHSScotland are currently using chlorine dioxide products for this purpose.
  (Grade D recommendation)
- The choice of chlorine dioxide disinfectant should be cross checked with the manufacturers' instructions to determine if a detergent clean is required pre disinfection.
  (Good Practice Point)

Implications for research

This review identified several gaps in the literature in relation to chlorine dioxide. Many of the studies could not be included in this review as they did not have a suitable comparison. Future studies assessing the clinical effectiveness of chlorine dioxide for decontamination should include suitable comparisons to allow the results to be transferable into clinical practice. There are a number of different chlorine dioxide products available and this makes it difficult to draw meaningful conclusions based on the studies included in this review. There is insufficient data on the cost of implementing these products to enable cost-benefit analyses to be undertaken.

Appendix 1: Medline Search

Ovid MEDLINE(R) 1946 to present with daily update

AND

Ovid MEDLINE(R) In-process & other non-indexed citations

Search dates

08/12/2015

Search terms

AND

1 (all "OR")	2 (all "OR")
Chlorine compounds/ Chlorine dioxide.mp	Sterilization/ Decontamination/ Disinfection/ Housekeeping, Hospital/ Clean*.mp

Limits

English language

Publication Year 2005-current

Results: 207

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