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Disinfection of environmental surfaces and reusable patient care equipment is a fundamental infection prevention strategy that is proven to prevent transmission of healthcare associated infections (HAIs)¹. However, despite the knowledge and evidence-based guidelines addressing the importance of thorough environmental and equipment disinfection, outbreaks and HAIs continue to occur with regularity in the healthcare setting, costing healthcare facilities, patients, and the United States billions of dollars annually². This whitepaper will review the cost of HAIs, explore the most common causative pathogens of HAIs and the classification of pathogens relevant to the levels of disinfection, and define the Environmental Protection Agency's registration pathway for surface disinfectants. A case will be made for evaluating the quality of disinfectant kill claims to address the epidemiologically important pathogens (EIPs) responsible for the majority of HAIs and reported outbreaks as opposed to the quantity of claims cited by the manufacturer.

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Cost of Healthcare Associated Infections

There is a large amount of research that has been done on the cost of healthcare associated infections, in a variety of settings, ranging from a single acute care hospital to a system of Veterans Association (VA) hospitals. Zimlichman et al., found that the total costs for the five most common HAIs, which are: Central Line Associated Bloodstream Infections (CLABSI), Catheter Associated Urinary Tract Infections (CAUTI), Surgical Site Infections (SSI), Ventilator Associated Pneumonias (VAP), and *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI), amounted to 9.8 Billion dollars per year in attributable costs (2013)². CLABSIs were the most costly per episode, averaging \$45,814 per episode, while CAUTIs were the least costly, averaging only \$896 per episode². Due to the incidence of SSIs, these infections account for the biggest piece of attributable costs, or approximately 34% of the total annual attributable cost.

This data has been replicated in other settings for specific HAIs and/or specific pathogens. A study conducted in 129 VA hospitals found that when costs were compared between patients who developed an SSI versus those who did not, costs for patients with an SSI were an average of 1.43 times greater, with costs varying by the severity

of the SSI, with the cost per episode estimated around \$21,000³. Another study done in the VA hospital setting looked at the six month costs related to treating methicillin resistant (MRSA) and methicillin sensitive (MSSA) *Staphylococcus aureus* infections in 948 patients⁴. Not only did the researchers find that the costs to treat an MRSA infection were over twice the amount for treatment of an MSSA infection, they also found that the overall length of stay was longer for patients with an MRSA infection⁴.

When it comes to CLABSI, many cost studies have been done to quantify the true costs of these infections in various care settings and populations. Goudie and colleagues performed a case-control study in the pediatric population over three years that looked at the mean attributable cost and length of stay of patients who developed CLABSI versus those that did not⁵. They found that the cost to treat a patient that developed a CLABSI was approximately \$55,000, which aligns with the available national data. In addition, Goudie et al., also found that the average length of stay increased by 19 days when a pediatric patient developed a CLABSI⁵.

Societal costs are even greater when both financial and quality of life factors are considered. Marchetti and Rossiter calculated that indirect and direct costs of HAIs occurring in U.S. acute care hospitals accounted for \$147 billion dollars annually⁶. When considering HAIs that occur in other settings, such as skilled nursing facilities, dialysis centers, and ambulatory surgical centers, the total cost impact to the U.S. could easily double or triple.

Common Pathogens of Healthcare Associated Infections

By far, the most common pathogens that cause healthcare associated infections are bacteria^{7,8}. In a multi-state HAI point prevalence survey conducted in 183 hospitals, approximately 65% of the causative pathogens were bacterial⁸. In a separate study that examined the causative organism of all HAIs over one calendar year, 80% of all HAIs were caused by bacterial pathogens⁷. These results have been replicated repeatedly when looking at single units, hospitals, or hospital systems⁹.

When it comes to potential pathogenicity, not all bacteria are created equal, and certain bacteria are much more likely to cause infections in the acute care setting. The ESKAPE pathogens are a group of bacteria that are cited as the most common HAI pathogens. This group of bacteria includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species¹⁰. This group of EIPs is also much more likely to develop antimicrobial resistance,

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which can further enhance the pathogenicity and virulence of the bacteria. Increased virulence of the bacteria can contribute to poorer outcomes in patients with infections caused by multidrug resistant (MDR) strains of these bacteria versus non-MDR strains¹⁰. The aforementioned prevalence survey found that of the bacterial pathogens that caused HAIs, 34.3% were caused by the ESKAPE pathogens. These particular pathogens, along with other EIPs are the primary focus of disinfectant manufacturers when deciding kill claims for their product.

Outbreaks Associated with Environmental Transmission

There have been many outbreaks associated with the healthcare environment and the role it plays in transmission of HAIs. Some research has estimated that up to 40% of HAIs in the intensive care setting are caused by the contaminated hands of the healthcare worker, who acquired the pathogen from either the patient, environmental surface, or patient care equipment¹¹. Certain pathogens are much more likely to be the source of HAI outbreaks than others¹². In a historical review of all outbreaks investigated by the CDC from 1946 to 2005, researchers found that there were particular characteristics of pathogens that rendered them much more likely to be causative organisms of an outbreak¹³. Weber and colleagues further highlighted these ideal pathogen traits, which include the ability to live on environmental surfaces for an extended period of time, virulence after a period of time on a surface, ability to colonize patients, and potential resistance to a disinfectant¹². Additionally, Archibald and Jarvis found that of the greater than 100 investigations performed by the CDC in the 60 year period, 18% of the outbreaks were caused by multi-drug resistant organisms. The majority of these outbreaks occurred in the last decade of the study time frame examined¹³. This trend has continued to worsen with the increasing prevalence of multi-drug resistant organisms, highlighting the need for healthcare grade disinfectants to have kill claims that can mitigate the risk of outbreaks with these pathogens.

Depending on the type of environmental surface, EIPs such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *C. difficile* have the ability to live for weeks or months on these surfaces^{1,14}.

Environmental surfaces and patient care equipment have been repeatedly shown to be an excellent fomite or reservoir for organisms that cause HAIs¹. Depending on the type of environmental surface, EIPs such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *C. difficile* have

the ability to live for weeks or months on these surfaces^{1,14}. These pathogens also regularly contaminate patient care equipment through contaminated healthcare worker hands and inadequate disinfection of the equipment between patients. VRE is especially pathogenic, having been implicated in many outbreaks related to patient care equipment, as well as environmental surfaces¹⁵. Outbreaks can also be lengthy when the source of environmental contamination is not apparent¹⁶. These outbreaks again highlight the need for disinfectants to have the ability to kill the EIPs and prevent the continuation of pathogen transmission.

Disinfectant Testing and Validation Process

Healthcare grade disinfectants must undergo stringent testing to ensure they meet the necessary requirements that the EPA has imposed to achieve registration. In order to be considered a healthcare grade disinfectant, manufacturers must submit data proving that the disinfectant can kill a minimum of two specific organisms, *Staphylococcus aureus* and *Pseudomonas aeruginosa*¹⁷. If a manufacturer wants to have additional efficacy or kill claims, they must submit separate testing for each organism they wish to include on the registration label. Additionally, if the manufacturer is making a request for registration as an intermediate level disinfectant, which the majority of healthcare settings currently use, then efficacy testing must be submitted for *Mycobacterium bovis*, which is the surrogate pathogen for *Mycobacterium tuberculosis*¹⁸. A similar requirement applies to fungi as well; in order for a disinfectant to have a fungicidal claim, efficacy data must be submitted for *Trichophyton interdigitale* demonstrating a kill claim according to the specified testing parameters.

There are different sets of testing methodologies for a disinfectant wipe (towelette) versus a disinfectant spray, pour, or dilutable liquid. In the U.S., the EPA has specified the testing methodology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) that must be used and submitted in order for a disinfectant to gain approval. This strict testing methodology used for a towelette clearly defines the standard operating procedure and requires the manufacturer to meet stringent criteria to pass¹⁹. For healthcare grade disinfectants, the testing method for *Staphylococcus aureus* and *Pseudomonas aeruginosa* requires that multiple slides be inoculated with the specific pathogen. One slide is wiped back and forth three times, for a total of six passes, with the disinfectant towelette. The towelette is then unfolded once, exposing a new section of the towelette, and this process is repeated on a different slide, using the same towelette. The same towelette is used to wipe a total of 10 carrier slides¹⁹. The slides are then left undisturbed for the contact time specified by the manufacturer. The slide is then neutralized, and incubated for approximately 48 hours in a setting with a temperature range from 35-37 degrees Celsius. In all, 60 carrier slides must be inoculated and tested with the disinfectant towelette, with a range of 3-6 carrier slides out of 60, depending on the pathogen being tested, being

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allowed to have growth¹⁹. For each additional organism which the manufacturer would like to establish a kill claim, only 10 carrier slides are used for testing, with a requirement of no growth on all of the slides.

The testing methodology for liquid disinfectants uses the Association of Official Analytical Chemists (AOAC) Use Dilution method with no friction from a towelette. This testing methodology uses 60 stainless steel cylinders that have been inoculated with the specific pathogen²⁰. The cylinders are then placed in test tubes that contain the liquid disinfectant and are immersed in the disinfectant solution for the prescribed contact, or wet time. The cylinders are then removed from the solution, neutralized, and cultured onto media that is grown for 48 hours. If greater than the acceptable number of cultures is positive, which varies based on the specific pathogen tested, then the disinfectant fails the test²⁰. The testing methodology for a spray disinfectant is very similar to a liquid disinfectant with a few key differences²¹. Sprays are tested using slides that have been inoculated with the test organism. However, the slides are instead sprayed with the disinfectant and allowed to sit for the proposed contact time, before the slide is placed in a neutralized, nutrient broth and allowed to incubate for 48 hours. Disinfectant spray requirements to pass for each organism are even more stringent than the towelette, with none or only one slide being allowed to show growth, depending on how many slides are tested.

It is important to note that submitting a single kill claim registration can cost upwards of six figures, when factoring in testing time and registration fees. Additionally, once the federal EPA has accepted the kill claim registration, then it must be submitted to the California EPA organization for approval in addition to having the product label approved by each state. This entire process can take up to 18 months, during which, no changes to the product label or additional changes can be submitted until the approval process is complete. Therefore, many companies are very selective regarding the pathogens they test to ensure they are choosing those that are common in healthcare facilities and/or have the potential to cause an outbreak. In any case, whether spray, liquid or towelette, the stringent testing required by the EPA should instill a high degree of confidence among consumers that the disinfectant is efficacious against the organisms that are listed on the label.

Hierarchy of Pathogens and Kill Claims

The hierarchy of pathogens was first introduced by E.H. Spaulding in the late 1930's and was further refined in the 1950's into the well-known Spaulding Classification used today. Along with determining which pathogens were harder to kill than others, Dr. Spaulding also recommended levels of disinfection or sterilization that should be performed to kill or eradicate the potential pathogens on equipment

and surfaces²². Spaulding's vertical hierarchy still mostly holds true, but with the emergence and globalization of new pathogens such as *Ebolavirus* or *Candida auris*, necessary changes and additions have been made to the traditional hierarchy. Today, the new hierarchy of pathogens is still a vertical model, but is much more comprehensive, and includes additional levels for organisms such as prions and parasites²². This hierarchy, and further information, can be found in the CDC Guidelines for Disinfection and Sterilization for Healthcare Facilities²².

The consideration of hierarchy of pathogens is an essential component of any disinfectant selection process. One needs to take into account if the appropriate hierarchal level of organisms are killed to meet the facility's needs. The specific kill claims that are listed on the product are extremely important. The disinfectant should be able to kill the most common causative pathogens of HAIs and outbreaks in a user's facility. Seven vegetative bacteria species: *Staphylococcus aureus*, *Escherichia coli*, Coagulase-negative staphylococci, *Klebsiella (pneumoniae/oxytoca)*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Enterobacter* species cause approximately 65% of HAIs reported⁷. Therefore, at a minimum, there should be sufficient kill claims for these specific types of pathogens on the disinfectant label to ensure that adequate environmental and equipment disinfection is being achieved in the facility.

Confusion may exist among healthcare workers regarding disinfectant kill claims for some organisms in a hierarchical level and the absence of other organisms in the same level. The EPA does not allow disinfectant manufacturers to speak "off-label" about specific organisms that are not listed on the kill claims. However, one can theoretically infer using the hierarchy of pathogens provided in the CDC guidelines that since vegetative bacteria are fairly low on the hierarchy, if a disinfectant is efficacious on a higher level of pathogen, then the vegetative bacteria of concern would be killed²². In addition to vegetative bacteria, the facility also needs to consider what other non-bacterial kill claims are on the disinfectant label. As an example, if the facility has recently experienced an influenza outbreak, then choosing a disinfectant that has a kill claim for the influenza virus may be important. Additionally, if the facility is undergoing renovations, having a kill claim for *Aspergillus* may be important. The quantity of kill claims is not as important as the quality of the disinfectant to address the EIPs responsible for HAIs and outbreaks at the facility. For example, a disinfectant may have 100 kill claims, all vegetative bacteria, on the product label, however, another disinfectant may list 20 organisms which includes bacteria, fungi, viruses, and mycobacteria. Which disinfectant would be preferred? A low level with 100 bacterial kill claims, or an intermediate level with 20 kill claims that include mycobacteria?

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There have been calls for the EPA to reconsider how testing and registration of disinfectants is performed. A commentary by Rutala and Weber from 2004 proposed a disinfectant registration process based on a sampling of microorganisms from each level of the hierarchy, rather than having to test for each individual pathogen²³. These organisms would be chosen based on their epidemiologic importance, commercial availability, and relative safety for the testing process, among other attributes. The authors present a valid argument that if the disinfectant manufacturer can prove efficacy against these specific organisms in the hierarchy level, then they should be able to claim efficacy against all microorganism for that level. In addition, they also propose an effective process for how emerging pathogens would be placed into a hierarchy level, and how other potential challenges would be handled²³. Their proposed process would speed up EPA approval of disinfectants, as well as simplify understanding for users.

While level of disinfection and specific kill claims are important, there are many other attributes of a disinfectant that a facility should consider in the selection process. Rutala and colleagues highlight many of these qualities that include treatment time, compatibility on surfaces, ease of use, safety, and persistence of the disinfectant²⁴.

The facility also needs to take other questions into account, such as, does the facility only want to have one disinfectant for general and terminal cleaning? Or, does the facility want to have a disinfectant that has persistence for a period of time after cleaning? Many factors exist to consider when trying to select the appropriate disinfectant for a particular facility. However, there are helpful guides in the published literature that list additional qualities to consider and provide checklists that facilities can use when going through the disinfectant selection process^{22,24}.

Summary

Healthcare associated infections cause an undue burden on the U.S. healthcare system with costs in the billions of dollars annually. Thorough disinfection of environmental surfaces and reusable patient care equipment with an EPA-approved disinfectant is a core component of infection prevention in healthcare facilities as these surfaces and equipment harbor EIPs which are responsible for HAIs and outbreaks. Evaluating the quality of disinfectant kill claims to address the EIPs responsible for the majority of HAIs and reported outbreaks in the healthcare setting as opposed to the quantity of claims cited by the manufacturer will aid decision-making of the right disinfectant and promote patient safety.

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