

Article

Determining the Efficacy, Safety and Suitability of Disinfectants to Prevent Emerging Infectious Disease Transmission

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Abstract: The scale of the 2014–2017 West African Ebola Virus Disease outbreak overwhelmed the international response capacity. This has led to inconsistencies in international guidance documents, particularly around chlorine disinfection of surfaces and hands to prevent transmission. To provide evidence for the disinfection recommendations, three research strands were conducted: (1) impacts of chlorine chemistry; (2) efficacy of surface cleaning recommendations; and (3) safety and efficacy of handwashing recommendations. Strand 1 research found that the compound chemistry of the chlorine source has an impact on the chlorine solution shelf-life (<1 day–30 days), with testing of chlorine solutions recommended to ensure accuracy. Strand 2 research found that surface cleaning with 0.5% chlorine solutions with a 15-min exposure time is efficacious in reducing transmission risk. Strand 3 research found that community handwashing with chlorine solutions is as safe and efficacious as handwashing with soap and water or sanitizer, which offers a benefit of reducing pathogens in the rinsing water. Using calcium hypochlorite as the chlorine source compound provided a particularly good performance in chemistry and handwashing studies. The research was successful at providing information to align with the inconsistent international guidelines. Further research is needed to proactively establish the efficacy, safety and suitability of disinfection for the seven viral pathogens that are considered likely to cause severe outbreaks with few/no medical countermeasures.

Keywords: disinfectants; efficacy; emerging infectious diseases; feasibility; safety

1. Introduction

During the 2014–2017 West African Ebola Virus Disease (EVD) outbreak, 493 of 500 healthcare providers (99%) and 550 of 550 patients (100%) who were surveyed reported that their body had been deliberately sprayed with 0.5% chlorine solution [1]. This is a denigrating, non-evidence based disinfection intervention that damages eyes, skin and lungs. This spraying occurred due to fear and lack of information, which highlights the need for improved recommendations for appropriate disinfection procedures in EVD response.

Disinfectants are critical for cleaning living and non-living surfaces and preventing the transmission of infectious diseases. The Centers for Disease Control and Prevention's (CDC) framework for preventing infectious disease transmission includes three elements: (1) public health fundamentals, including surveillance, laboratory detection and epidemiologic investigation; (2) high-impact interventions, including new vaccines, *strategies and tools for infection control* and treatment and other interventions to reduce zoonotic transmission; and (3) policies to prevent, detect and control infectious diseases [2].

One key *strategy for infection control* is cleaning, disinfection and sterilization [3]. According to CDC, cleaning is the “removal of visible soil (e.g., organic and inorganic material) from objects and surfaces and normally is accomplished manually or mechanically using water with detergents or enzymatic products”; disinfection “describes a process that eliminates many or all pathogenic microorganisms, except bacterial spores, on inanimate objects”; and sterilization “describes a process that destroys or eliminates all forms of microbial life”. Evidence-based recommendations on the preferred methods for cleaning (e.g., towels, soap), disinfecting (e.g., chlorine, quaternary ammonium compounds) and sterilizing (e.g., steam sterilization, liquid peracetic acid) have been largely established for well-resourced healthcare settings. However, there are currently two critical knowledge gaps on disinfection, including: (1) disinfectant efficacy against emerging infectious disease (EID) pathogens; and (2) disinfectant options for low-resource settings. The current EID pathogens (considered to be those that are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist) are: Crimean Congo Hemorrhagic Fever, EVD and Marburg, Lassa Fever, MERS and SARS coronavirus diseases and Nipah and Rift Valley Fever [4]. All of these diseases are caused by viral pathogens and all can cause outbreaks in low-resource settings.

Historically, the Doctors Without Borders (Médecins Sans Frontières, MSF) organization provided medical care in EVD outbreaks in collaboration with national governments. The 2008 MSF Filovirus hemorrhagic fever guideline recommends using 0.05% (500 mg/L) chlorine solutions to disinfect living things (people and hands) and 0.5% (5,000 mg/L) chlorine solutions to disinfect non-living things (surfaces, personal protective equipment and dead bodies) [5]. However, these recommendations were intended for Ebola Treatment Units (ETU) and there was no evidence provided that supports the recommendations. The scale and size of the West African EVD outbreak overwhelmed international response capacity, which led to: (1) MSF guidelines being widely expanded to community settings; and (2) the World Health Organization (WHO) and CDC also developing disinfection guidelines, based on expert consensus [5–7]. The inconsistencies between these guidance documents led to confusion in the response (Table 1).

Table 1. Inconsistencies in International EVD Chlorine Recommendations.

	MSF [5]	WHO [6]	CDC [7]
Chlorine Solution Type	HTH, recently changed to NaDCC	Not addressed	Not addressed
Chlorine Solution Testing	Not recommended	Not addressed	Not addressed
Surface Cleaning	Apply 0.5% chlorine for 15 min	Pre-clean, apply 0.5% chlorine for 10 min.	For hospitals: pre-clean, apply a “chemical disinfectant for non-enveloped viruses”. For households: cover spills, apply 0.5% chlorine for 15 min.
Handwashing	0.05% chlorine solution	Soap, sanitizer, avoid chlorine solution	Soap, sanitizer, avoid chlorine solution

Acronyms: MSF (Médecins Sans Frontières); WHO (World Health Organization); CDC (Centers for Disease Control and Prevention, HTH (calcium hypochlorite, high-test hypochlorite), NaDCC (sodium dichloroisocyanurate).

At Tufts University, we conducted laboratory, field and policy research to reduce the burden of infectious diseases. Furthermore, we are members of water, sanitation and hygiene emergency response groups. During and after the West African EVD outbreak, we conducted research, funded by the United States Agency for International Development’s Office of U.S. Foreign Disaster Assistance (USAID/OFDA), to answer the questions that responders were asking related to the inconsistencies between the MSF, WHO and CDC guidelines, including: (1) impacts of chlorine chemistry on shelf-life and solution testing; (2) efficacy of surface cleaning recommendations; and (3) safety and efficacy of handwashing recommendations. In this communication, we summarize the results of these three

research streams (which led to eight individual peer-reviewed manuscripts summarized herein) and propose future disinfection research for EID contexts.

2. Materials and Methods

2.1. EVD Research Thread #1: Chlorine Chemistry Methods

Chlorine solutions in emergencies are primarily made from the chlorine source compounds of powdered calcium hypochlorite (HTH), granular sodium dichloroisocyanurate (NaDCC) and liquid sodium hypochlorite (NaOCl). NaOCl solutions can be generated from an electrolysis of salt and water or diluted from high concentration solutions and pH-stabilized using caustic soda (sodium hydroxide). The MSF, CDC and WHO guidelines do not specify which chlorine source compound to use. As each source compound has drawbacks and benefits (Table 2), the responders select the most appropriate option for each context. For example, MSF now informally recommends NaDCC based on logistical and safety benefits. Additional relevant chlorine chemistry factors include pH, as a lower pH is associated with a shorter chlorine solution shelf-life (defined as the time until the solution degrades by 10%) and higher efficacy [8], and how to test chlorine solution concentration to ensure it is accurately 0.05% or 0.5%. MSF guidelines recommended making solutions daily using a reliable method and not testing the concentration daily; while WHO and CDC guidelines did not address testing (Table 1). It is important to note that while high concentration powders (HTH, NaDCC) are known to have longer shelf-lives than concentrated liquids (NaOCl), we tested the shelf-lives of the dilute solutions made with those concentrated powder and liquid products in this work.

Table 2. Benefits and Drawbacks of Disinfectants Used for Surfaces and Hands.

	Benefits	Drawbacks
Bar soap and water	Widely available Widely acceptable Low cost	Primary goal to remove, not inactivate Requires water
Alcohol Based Hand Sanitizer	Simple to use Portable	Not widely available Not widely acceptable Expensive
NaDCC (pH = 6)	Easy to ship (powder) Long shelf-life of powder Does not clog pipes Inexpensive	-
HTH (pH = 11)	Easy to ship (powder) Long shelf-life of powder Inexpensive	Clogs pipes Can be explosive
Stabilized NaOCl (pH = 11)	Can be locally produced Does not clog pipes	Shorter shelf-life of concentrate Difficult to ship
Generated NaOCl (pH = 9)	Can be produced on-site Does not clog pipes	Shorter shelf-life of concentrate Difficult to ship Quality control

Acronyms: NaDCC (sodium dichloroisocyanurate), HTH (calcium hypochlorite), NaOCl (sodium hypochlorite).

Shelf-life: We conducted 30-day shelf life experiments with 0.05% and 0.5% NaDCC, HTH and stabilized NaOCl in addition to generating NaOCl solutions at 25–35 °C.

Testing Methods: Fourteen commercially available methods to test 0.5% and 0.05% solutions were identified and assessed for: accuracy and precision in the laboratory setting; ease-of-use with volunteers; and cost using available data [9].

2.2. EVD Research Thread #2: Surface Cleaning Methods

To begin the surface cleaning work, four bacteriophages sharing characteristics with the Ebola virus were identified [10] and a surface disinfection experiment completed with the Ebola virus by Cook et al. in a Biosafety Level 4 laboratory was replicated [11,12]. After this, the testing matrix was developed that included various surface types that are relevant in emergency health responses (nitrile, heavy duty tarp, stainless steel); chlorine types (NaDCC, HTH, generated NaOCl, stabilized NaOCl); soil load (with and without); and factors that varied between the MSF, WHO and CDC recommendations, including exposure time (10, 15 min) and recommended pre-treatments (none, covering, wiping, covering/wiping) [13]. The bacteriophage that was most similar to the Ebola virus from the above study was left to dry for one hour on a disc with a surface diameter of 8 cm, disinfection was carried out with or without pre-treatment and the residual contamination on the disc was measured at the end of the exposure time.

2.3. EVD Research Thread #3: Handwashing Safety and Efficacy Methods

In the West African EVD outbreak, the recommendation to wash hands with 0.05% chlorine solution was widely extended beyond ETU settings to community settings. The MSF, CDC and WHO guidelines were inconsistent on whether it was safe (due to potential hand irritation that might increase transmission) or efficacious (due to chlorine demand of skin) to wash hands with 0.05% chlorine solution.

Safety: To assess safety, a randomized trial with 91 volunteers who washed their hands 10 times a day for 28 days was conducted [14]. Volunteers were assigned and used commercially-available bar soap and water; 70% ethanol hand sanitizer (referred herein as ‘sanitizer’ and equivalent “alcohol based hand sanitizer, ABHS”); or 0.05% chlorine solution created from HTH, NaDCC, generated NaOCl or stabilized NaOCl for handwashing. The outcomes included irritation as measured by the Hand Eczema Score Index (HECSI) (range 0–360), signs of transmission risk (e.g., cracking) and dermatitis diagnosis.

Efficacy: To assess the efficacy of handwashing methods, 18 volunteers’ hands were spiked on four separate trial days with a non-infectious BSL-1 *E. coli* or the selected BSL-1 surrogate from above, with and without soil load [15,16]. For each trial, the volunteers completed seven handwashing methods, including control (nothing); water only; soap and water; sanitizer; and HTH, NaDCC, generated NaOCl and pH-stabilized NaOCl solutions. After each washing, any remaining organisms were recovered from hands and rinsing water (if available) was collected and tested for remaining *E. coli* or selected bacteriophage.

3. Results

3.1. EVD Research Thread #1: Chlorine Chemistry

Shelf-life: NaDCC solutions (pH = 6) had a maximum shelf life of 2 days, generated NaOCl solutions (pH = 9) 6 days and HTH and stabilized NaOCl solutions (pH = 11) > 30 days [17]. Extrapolating to 40 °C using mathematical modeling, NaDCC solutions fell to a shelf-life of < 1 day, while other chlorine source compound solutions remained with shelf-lives of 5 days > 30 days.

Testing Method: Accuracy and precision were greatest in titration methods, followed by N,N-diethyl-p-phenylenediamine (DPD) color change dilution methods and test strips [9]. Conversely, titration was most expensive and hardest to use, while test strips were the least expensive and easiest to use. Results from most non-titration methods varied with solution pH, with the exception of one test strip.

Summary of Research Thread #1: Each chlorine source compound has benefits and drawbacks and it is recommended that responders choose the appropriate compound for their context, while ensuring chlorine solutions made from these source compounds are stored appropriately, used within their shelf-life, periodically tested by trained personnel using titration methods and tested daily with

pH-resistant test strips. For example, in a large ETU, NaDCC powder may be the most appropriate chlorine source compound as the solutions would be used within a few hours. In a small ETU making solutions once per day or a community setting where solutions are made once per week, HTH (if powder is stored appropriately to mitigate explosive risk) or NaOCl may be most appropriate.

3.2. EVD Research Thread #2: Surface Cleaning Results

After we replicated the surface disinfection experiment completed with the Ebola virus using each of the selected bacteriophages, Phi6 appeared slightly more resistant than the Ebola virus under the tested conditions and was thus identified as the most appropriate surrogate [12].

Across the entire test matrix, there was always a reduction of > 99.9% in Phi6 [13]. The results suggest that: (1) surface type influenced disinfection efficacy; (2) chlorine type and soil load did not impact disinfection efficacy when using 0.5% chlorine; (3) contact time did impact efficacy against Phi6; and (4) wiping or covering did not increase disinfection efficacy, but the latter could limit splashing.

Summary: Overall, a 15-min exposure to 0.5% chlorine (independently of chlorine type, surface, pre-cleaning practices and organic matter) was found to reduce surface contamination by an Ebola virus surrogate to non-detectable levels. These results are consistent with recent results from small-scale studies using the Ebola virus [18].

3.3. EVD Research Thread #3: Handwashing Safety and Efficacy Results

Safety: Although all groups experienced statistically significant increases in HECSI scores, these increases in irritation were not clinically relevant as the average HECSI score was only 9/360 after 28 days [14]. Subjects using sanitizer had the smallest increases, followed by higher pH chlorine solutions (HTH and stabilized NaOCl) as well as soap and water. Handwashing with soap and water was performed using bar soap intended for handwashing, following WHO-recommended handwashing guidelines. Although some individuals are especially sensitive to handwashing, these protocols were not expected to cause significant irritation in most people. The signs of irritation disrupting skin integrity, which are possibly related to higher transmission risk, were observed most frequently in subjects using soap and least frequently in those using sanitizer or HTH.

Efficacy: With *E. coli*, HTH performed most consistently well, with statistically significantly greater logarithmic reductions than other individual handwashing methods [16]. However, the magnitude of handwashing efficacy differences was small, suggesting that methods were similarly efficacious. With Phi6, no statistically significant differences were seen between controls and handwashing methods. One explanation for this is that mechanical action is the main removal mechanism for Phi6. Finally, chlorine-based handwashing methods resulted in statistically significantly less persistence of *E. coli* and Phi6 in rinsing water.

Summary: These safety and efficacy results indicate all handwashing methods were roughly equally efficacious in practice, although: (1) HTH in particular was consistently more safe and efficacious; and (2) chlorine solutions, as compared to soap and water and sanitizer, offer the benefit of reducing pathogen persistence in rinsing water. As all handwashing methods have benefits and drawbacks (Table 2), it is recommended that EVD responders and communities use whichever handwashing method(s) are most acceptable, available and feasible for handwashing, considering that chlorine solutions may offer a benefit in reducing transmission risk from rinsing water.

4. Discussion

In this work, it was found that: (1) chlorine source compound chemistry has an impact on the chlorine solution shelf-life, with solutions made from NaDCC having the shortest shelf life and solutions from HTH and NaOCl the longest; (2) testing of 0.05% and 0.5% chlorine solutions is recommended to ensure accuracy, particularly when solutions are not made continuously or daily; (3) surface cleaning with 0.5% solutions with a 15-min exposure time is efficacious at reducing (but not eliminating) transmission risk from the very low infectious dose Ebola virus; and (4) handwashing

with chlorine solutions is as safe and efficacious as handwashing with soap and water or sanitizer, which also offers a benefit of reducing pathogens in rinsing water. Across all studies, the chlorine source compound HTH performed particularly well, with chlorine solutions made from this product having the longest shelf-life, the least hand irritation and the highest handwashing efficacy. However, HTH has the operational challenges of being more explosive than NaDCC and having a precipitate form in mixing with water that can clog pipes. In well-maintained ETUs, this can be managed with appropriate training and maintenance. However, explosions did occur in ETUs that were managed by less experienced organizations in the West African outbreak, which poses a great risk to the health and safety of response personnel and patients (personal communication, available from authors to protect privacy). Additionally, the MSF guidelines were most often found to be both efficacious and achievable in the field, indicating that field experience provided solid guidelines in the absence of evidence and in this circumstance.

Overall, the work was successful at answering responder questions and providing information to align inconsistent international guidelines. Factors that led to this successful research included: (1) funding allocated with the knowledge that the results would most likely not be available for the current outbreak but for the next outbreak; and (2) collaborations with an interdisciplinary team, including researchers with expertise in laboratory testing and human subject trial design, clinicians and responders. One key lesson from this work is that partnering laboratories working with the Ebola virus (with small sample processing capacity) with laboratories using surrogates (with large sample processing capacity) is one mechanism to promote rapid response research in outbreaks. The main limitation of this work is that it was reactive, rather than proactive.

Future Research Needed

Between 1980 and 2013, 12,102 outbreaks of 215 human infectious diseases, including more than 44 million cases, were reported from 219 nations [19]. This statistic is substantial even when taking into account the improved capabilities to recognize and diagnosis outbreaks that occurred during this time. Although outbreaks are defined as an increase in the number of cases beyond expectations, human EIDs are further characterized by novelty. Diseases that have undergone recent evolutionary change, have been newly recognized or re-emerging, have entered the human population for the first time, have bioterrorism potential or are newly-developed antibiotic resistance are classified as EIDs.

EID introductions have risen significantly over time and these introductions are mostly zoonotic in nature [20]. The factors that have led to increases in EID introductions include environmental, social, political and economic changes [21,22]. Although the transmission pathways differ for the EID pathogens vary, many of these pathways can be interrupted and their transmission prevented by appropriate disinfection interventions. However, there is currently a knowledge gap on disinfection efficacy and safety for these EID pathogens, especially in low-resource settings. Research is needed to proactively (rather than retroactively) establish the efficacy, safety and suitability of cleaning, disinfection and sterilization practices. The research should systematically include the pathogen of interest and relevant surrogates (ensuring that the surrogates are representative of the pathogen by completing low-volume sampling of the pathogen and high-volume sampling of the surrogate), hands and surfaces and materials used in high and low-resource health facilities and communities, cleaning procedures, appropriate disinfectants and sterilizers and matrices that are representative of bodily fluids (blood, vomit, feces). Additionally, the research should include factors that are known to affect disinfection efficacy on viruses, including the presence or absence of an envelope, aggregation and relative humidity [23,24]. Finally, the capacity to rapidly conduct research in the event of a novel EID outbreak is needed and developing appropriate surrogates could help improve research responsiveness/capacity.

To facilitate this research, partnerships between responders, donors and researchers are necessary. Responders can voice questions and share field experience; researchers can design and conduct high-quality studies (including prioritizing timely, open-access publication); and donors can prioritize

funding this research before an outbreak or at the onset of an outbreak. The overall goal of this type of collaborative research is to advance the understanding of the efficacy, safety and suitability of disinfectants to reduce EID transmission, keep healthcare providers and community members safe and increase EID outbreak emergency preparedness.

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