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Health-based ingestion exposure guidelines for *Vibrio cholerae*: Technical basis for water reuse applications☆

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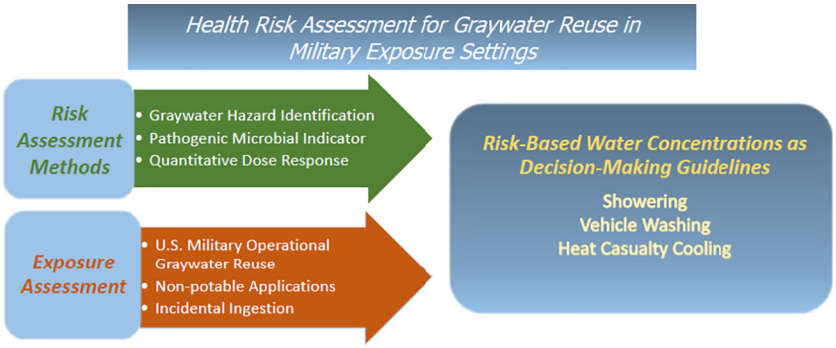
HIGHLIGHTS

- Generation of non-potable graywater reuse exposure guidelines for *Vibrio cholerae*.
- Dose-response modeling for diarrheal illness following *V. cholerae* exposure
- Novel risk-based water concentrations proposed for military graywater reuse applications.

GRAPHICAL ABSTRACT



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ABSTRACT

U.S. military and allied contingency operations are increasingly occurring in locations with limited, unstable or compromised fresh water supplies. Non-potable graywater reuse is currently under assessment as a viable means to increase mission sustainability while significantly reducing the resources, logistics and attack vulnerabilities posed by transport of fresh water. Development of health-based (non-potable) exposure guidelines for the potential microbial components of graywater would provide a logical and consistent human-health basis for water reuse strategies. Such health-based strategies will support not only improved water security for contingency operations, but also sustainable military operations.

Dose-response assessment of *Vibrio cholerae* based on adult human oral exposure data were coupled with operational water exposure scenario parameters common to numerous military activities, and then used to derive health risk-based water concentrations. The microbial risk assessment approach utilized oral human exposure *V. cholerae* dose studies in open literature. Selected studies focused on gastrointestinal illness associated with experimental infection by specific *V. cholerae* serogroups most often associated with epidemics and pandemics (O1 and O139). Nonlinear dose-response model analyses estimated *V. cholerae* effective doses (EDs) aligned with gastrointestinal illness severity categories characterized by diarrheal purge volume. The EDs and water exposure assumptions were used to derive Risk-Based Water Concentrations (CFU/100 mL) for mission-critical illness severity levels over a range of water use activities common to military operations.

Human dose-response studies, data and analyses indicate that ingestion exposures at the estimated ED_1 (50 CFU) are unlikely to be associated with diarrheal illness while ingestion exposures at the lower limit (200 CFU) of the

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estimated ED_{10} are not expected to result in a level of diarrheal illness associated with degraded individual capability. The current analysis indicates that the estimated ED_{20} (approximately 1000 CFU) represents initiation of a more advanced stage of diarrheal illness associated with clinical care.

1. Introduction

1.1. Background

Developing health-based exposure guidelines for waterborne gastrointestinal pathogens are an essential component to implementing sustainable water use and reuse practices that will be protective against illness caused by microbial pathogens. Such exposure guidelines are a source of increasing interest to communities and institutions that are evaluating water supply enhancement strategies that reduce both fresh water consumption as well as demand on septic treatment facilities (Ludwig, 2015; NAS, 2016; Church et al., 2015; Jahne et al., 2017; Schoen et al., 2017). Included among the many users evaluating these options is the U.S. Department of the Army, which is evaluating applications for fixed and contingency facilities as well as related operations (USAPHC, 2017; Umble, 2014; AEPI, 2011).

U.S. military and allied contingency operations are increasingly occurring in locations with limited, unstable or compromised fresh water supplies. Non-potable graywater reuse is currently under assessment as a viable means to increase mission sustainability while significantly reducing the resources, logistics and attack vulnerabilities posed by transport of fresh water (USAPHC, 2017; USAPHC, 2014a, 2014b). Water scarcities create military health vulnerabilities that could be mitigated in part by placing greater emphasis on sustainable practices that reduce potable and fresh water demand. Such practices include re-using graywater from sinks, showers and laundries for non-potable uses such as showering, laundry, heat-casualty cooling, and vehicle washing (USAPHC, 2014a, 2014b; Ferdinado, 2013; Church et al., 2015; Schoen and Garland, 2017; Barker et al., 2017). While it is known that potable-quality waters are not required for certain military operations such as dust suppression, fire-fighting and the washing of vehicles, there are, at present, no health-based or risk-based exposure guidelines for pathogenic components of graywater directly applicable to decision-making for non-potable use in the field (USAPHC, 2014a; USAPHC, 2017).

Gastrointestinal system infections and accompanying gastroenteritis are a significant cause of morbidity and degraded military operational effectiveness in active-duty components of the U.S. Armed Forces (MSMR, 2013a, 2013b; Rha et al., 2016; Hyams et al., 1991; Chapman et al., 2011; Arness et al., 2000). Thus, in any consideration of incidental ingestion of reused graywater, emphasis should be placed on microbes known to be responsible for incapacitating gastrointestinal illness and adverse performance effects. Such emphasis is the focus of this assessment.

Causative microbes potentially associated with gastrointestinal illness from incidental graywater ingestion include enteric bacteria and viruses as well as certain protozoans (Schoen and Garland, 2017). To build upon previous estimates of non-potable reuse water quality (Church et al., 2015; Schoen and Garland, 2017), the authors chose an example enteropathogenic microbe for which there are ample human data collected from well-conducted, open-literature challenge studies. In addition, the human subject data for the example microbe needed to be age-consistent with the active-duty composition of the U.S. Armed Forces. The selected microbe meeting those criteria is *Vibrio cholerae*, the causative pathogen of cholera, and a potential water contaminant of interest to the military (DA, 2010). As a waterborne disease primarily transmitted by ingestion of contaminated water and/or food, cholera generates military concern due to its swift and adverse health effects on exposed populations and the resulting potential for rapid mission impact (DA, 2010).

Further, this pathogen is considered a "Category B" bioterrorism organism of concern (DHHS/CDC, 2014a). Contamination with *V. cholerae* in food and water supplies is a high-consequence event for individual, unit, and installation health as well as for storm and disaster recovery (DA, 2005; DHHS/CDC, 2014b; Colwell, 1996). *V. cholerae* occurrence in water and other aquatic media could create a biosecurity issue that is worthy of detailed assessment (Casadevall and Relman, 2010).

1.2. Vibrio cholerae pathotypes and illness characteristics

Of the >200 *V. cholerae* serogroups, only the O1 and O139 serogroups are known to cause epidemic or pandemic cholera. Serogroup O1 has been associated with pandemics since 1899, serogroup O139 has been associated with pandemics since 1992, and both serogroups have been identified in recent cholera outbreaks (Colwell, 1996; UN, 2011; WHO, 2017). Serotyping has now been largely supplanted by combined genotypic and phenotypic analyses in determining pathogenic isolates of serogroups O1 and O139 (e.g., Hasan et al., 2012; Mutreja et al., 2011; Safa et al., 2009; Li et al., 2002). The present derivation of health-based exposure guidelines focuses only on dose-response data for the O1 and O139 serogroups.

V. cholerae O1 and O139 serogroups produce the cholera toxin (CT) that alters epithelial cell membrane permeability in the small intestine, resulting in an uncontrolled secretion of water and electrolytes into the large intestine and colon (Colwell, 2002; USAMRIID, 1998). Virulence is a function of intestinal colonization and adherence factors (Merrell et al., 2002; Kaper et al., 1995), which can enhance CT effects. Onset is usually abrupt and can be associated with vomiting. The American Public Health Association (APHA, 2008) indicates that, in most cases, infection is usually asymptomatic or can cause mild diarrhea. In symptomatic cases, severe purging results in rapid dehydration, acidosis, circulatory collapse, electrolyte imbalance, and renal failure, all of which can lead to shock and a swift death (Colwell, 2002; Ministry of Health and Population in Haiti/CDC, 2011; DHHS/CDC, 2014b). In severely dehydrated cases (cholera gravis; associated with passage of ≥1 L diarrheal feces/h) (Morris, 2011), death may occur within a few hours and the case-fatality rate may exceed 50% unless rehydration therapy is initiated (APHA, 2008; Ministry of Health and Population in Haiti/CDC, 2011).

Cholera is communicable and contagious as long as stools contain viable *V. cholerae* (considered "culture-positive"); this can occur several days post-recovery. Contagion takes place through personal contact with culture-positive stool material or fluids (common examples include inadequate management of body waste or unclean hands after toileting). A person who is in a "carrier state" appears well but remains infectious and can unintentionally transfer *V. cholerae* to food, contact surfaces, and sewer or septic systems for multiple months post-recovery (APHA, 2008; DA, 2010).

1.3. Study purpose

This paper introduces a health-based exposure guidelines derivation process specific to gastrointestinal illness resulting from single-event oral exposure to the candidate waterborne enteropathogen (*V. cholerae*). Data qualification processes and logic, diarrheal illness