Cost-Effectiveness of Multifaceted Built Environment Interventions for Reducing Transmission of Pathogenic Bacteria in Healthcare Facilities

Marietta M. Squire, MS¹, Takeru Igusa, PhD¹, Sauleh Siddiqui, PhD¹, Gareth K. Sessel, BM BCh, MSc², and Edward N. Squire Jr., MD, MPH³

Abstract

Objectives: The objective of this study is to determine the optimal allocation of budgets for pairs of alterations that reduce pathogenic bacterial transmission. Three alterations of the built environment are examined: handwashing stations (HW), relative humidity control (RH), and negatively pressured treatment rooms (NP). These interventions were evaluated to minimize total cost of healthcare-associated infections (HAIs), including medical and litigation costs. Background: HAIs are largely preventable but are difficult to control because of their multiple mechanisms of transmission. Moreover, the costs of HAIs and resulting mortality are increasing with the latest estimates at US$9.8 billion annually. Method: Using 6 years of longitudinal multidrug-resistant infection data, we simulated the transmission of pathogenic bacteria and the infection control efforts of the three alterations using Chamchod and Ruan’s model. We determined the optimal budget allocations among the alterations by representing them under Karush–Kuhn–Tucker conditions for this nonlinear optimization problem. Results: We examined 24 scenarios using three virulence levels across three facility sizes with varying budget levels. We found that in general, most of the budget is allocated to the NP or RH alterations in each intervention. At lower budgets, however, it was necessary to use the lower cost alterations, HW or RH. Conclusions: Mathematical optimization offers healthcare enterprise executives and engineers a tool to assist with the design of safer healthcare facilities within a fiscally constrained environment. Herein, models were developed for the optimal allocation of funds between HW, RH, and negatively pressured treatment rooms (NP) to best reduce HAIs. Specific strategies vary by facility size and virulence.

¹ Department of Civil Engineering, Johns Hopkins University, Baltimore, MD, USA
² Outreach Engineering NPC (non-profit company), Johannesburg, South Africa.
³ Moss Clinic, Fredericksburg, VA, USA

Corresponding Author:
Marietta M. Squire, MS, Department of Civil Engineering, Johns Hopkins University, 3400 N. Charles St., Baltimore, MD 21218, USA.
Email: marietta.squire@gmail.com
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Literature Review

Healthcare-Associated Infections

Healthcare-associated infections (HAIs) severely threaten hospitalized patients who are often highly susceptible to infection. The numbers are extremely high. On any given day, 1 in 25 (4%) of pediatric and adult hospitalized patients will have at least 1 HAI (Magill et al., 2014). Among those, 1 in 17 will die as a result (Klevens, 2007). Estimates of the annual number of HAIs in U.S. hospitals vary between 400,000 (Zadeh, Sadatsafavi, & Xue, 2015) and 1.7 million (Klevens et al., 2007). The estimated annual mortality in the United States ranges from 75,000 (Lee, 2014) to 99,000 (Klevens et al., 2007).

In 2013, the direct cost of these infections was US$9.8 billion (US$10.47 billion in 2017; Zimlichman et al., 2013). These HAIs had multiple causes: 33.7% from surgical site infections, 31.6% due to ventilator-associated pneumonia, 18.9% from central line–associated bloodstream infections, and the remaining 15.8% from Clostridium difficile and other pathogens (Zimlichman et al., 2013). HAIs prove most deadly among older adults and those with immune system suppression. Deeming such infections preventable, the Centers for Medicare and Medicaid Services have begun withholding payments for certain infections (Center for Medicare and Medicaid Service Hospital-Acquired Condition Reduction Program, 2018). It has been found that when including indirect costs, HAIs cost American society US$96 billion to US$147 billion each year (Marchetti & Rossiter, 2013).

Infections caused by three multidrug-resistant organisms (MDROs). MDROs, sometimes referred to as superbugs, are dreaded because they are the most difficult to treat. In this investigation, three groups of these MDROs were evaluated: methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and vancomycin-resistant *Enterococci* (VRE).

The first strains of MRSA were discovered in 1961 by a British investigator (Barber, 1961). The resistance of *Staphylococcus aureus* to methicillin has expanded to additional antibiotics (Nichols, 2017). In 1986, vancomycin-resistant *Enterococcus* spread rapidly throughout Europe and the United States (O’Driscoll & Crank, 2015; Uttley, Collins, Naidoo, & George, 1988). VRE infects vulnerable patients via surgical wounds and urinary tract catheters. It also causes colitis and endocarditis (Cerrud-Rodriguez, Alcaraz-Alvarez, Chiong, & Ahmed, 2017; Stevens & Edmond, 2005). Carbapenem-resistant species in the family, Enterobacteriaceae, CRE were first identified in November 2012 (Deen & Debbie, 2014). During the course of just 2 years, CRE spread across 42 states and 200 hospitals in the United States (Deen & Debbie, 2014).

Benchmark for infection control. Biocontainment labs and biocontainment units are the gold standard in infection control against “nightmare pathogens” such as the Ebola virus. Evaluation of hospital infection control within the context of these types of facilities provides an important frame of reference. Levels 3 and 4 biosafety labs (i.e., biocontainment labs) and treatment facilities for highly infectious patients (i.e., biocontainment units) have rigorous controls and expensive infrastructure. This infrastructure includes specialized HVAC systems, water decontamination, and chemical decontamination of personnel and equipment exiting hot (highly infectious) regions.

There is a spectrum of infection control efficacy, in which biocontainment units lie at the cost-prohibitive upper limit. Healthcare facilities must determine where on the spectrum they should position themselves and evaluate their infection control measures accordingly.

Three alterations of the built environment intended to reduce HAIs. While many efforts for infection
control have focused on hand hygiene, our interest is in the trade-offs between multiple candidate interventions; we considered the impact of pairs of the following three alterations in the built environment: handwashing stations (HW), controlled indoor air hydration (i.e., relative humidity control or RH), and negatively pressured treatment rooms (NP). Architects and engineers acknowledge the need for greater insight into the impact of infrastructure on patient safety (Eames, Tang, Li, Wilson, 2009; Hamilton, 2013). Close interactions between microbiologists, infection control experts, engineers, architects, and healthcare providers are critical to improve hospital design and thereby decrease HAIs (Eames et al., 2009).

Therefore, our article seeks to answer the following research questions:

1. What is the optimum resource allocation for implementation of the three candidate alterations in the built environment among healthcare facilities of varying sizes and budgets?
2. How effective is a pair of alterations at minimizing infections, when compared to another feasible pair for a specific scenario? The best case for each pair is used for these comparisons, in which resources are optimally allocated between the alterations in the pair.

Specifically, we investigated the cost–benefit analysis for each intervention (i.e., for each pair of alterations). The contribution of our study is a first-of-its-kind toolset that enables evidence-based decisions for the allocation of budgets to minimize HAIs. Furthermore, the toolset can be used to analyze multiple budgets, hospital sizes, and pathogens.

**Alteration #1: Handwashing measures.** In 1846, Ignaz Semmelweis first observed the relationship between infection and healthcare workers’ (HCW) failure to wash their hands (Davis, 2015). Even today, microorganisms may be transported by the unwashed hands of HCW and travel from one patient to another. Therefore, compliance with hand hygiene protocols remains a critical preventative measure in the avoidance of HAIs (Beggs, Shepherd, & Kerr, 2009).

Evidence to date shows that handwashing compliance is increased with convenient placement of hand gel dispensers (Cure & Van Enk, 2015). For example, a paper towel dispenser which automatically presents a paper towel to passers-by significantly increased handwashing compliance from 61.8% to 75.9% (Ford, Boyer, Menachemi, & Huerta, 2014).

Boyce, Potter-Bynoe, Chenevert, and King (1997) demonstrated that when treating MRSA patients, 65% of nurses’ scrubs and uniforms became contaminated with MRSA. This occurs during contact with colonized or MRSA-infected patients. Even without physical contact with MRSA-infected patients, 42% of nurses became contaminated from contact with contaminated surfaces in MRSA patients’ rooms (Boyce, Potter-Bynoe, Chenevert, & King, 1997). Frequent handwashing reduces person-to-person and environment-to-person transmission of MRSA and other bacteria.

**Alteration #2: Control of indoor air hydration in healthcare facilities.** Whereas handwashing is important for HAIs that are spread by direct contact, RH is important because it affects dispersion of bacteria-containing droplets that are aerosolized by coughing. Investigators found that CRE can be spread by direct contact with sinks (Crespo et al., 2004). VRE spreads by direct contact and through contact with contaminated surfaces. MRSA is spread by both of these routes and airborne transmission (Boswell & Fox, 2006; Shiomori, Miyamoto, & Makishima, 2001).

Flugge in 1897 evaluated the spread of infection via aerosols. He determined that droplets emitted from the nose and mouth contained bacteria (Eames et al., 2009).
et al., 2009). Wells showed in 1934 that droplet movement is dependent on droplet size (Wells, 1934; Tang, Li, Eames, Chan & Ridgway, 2006). In addition, Arundel, Sterling, Biggin, and Sterling (1986) demonstrated the control of indoor air hydration/relative humidity between 40% and 60% is effective at mitigating the transmission of pathogens through the air. Relative humidity (vapor equilibrium) impacts the droplet size and therefore the viability of the infectious microorganism. The mechanism is further described below.

During a cough, about 3,000 droplets are expelled from the airways at velocities up to 50 miles per hour (American Lung Association, 2018). Sneezes can reach speeds up to 100 miles per hour and can include up to 100,000 droplets (American Lung Association, 2018). MRSA’s diameter ranges in size from 0.5 to 0.7 μm (Haddadin, Fappiano, & Lipsett, 2002). The largest droplets, comprised of saliva and bacteria, settle quickly and are deposited on surfaces. The bacteria are then released as the droplets evaporate. Larger droplets settle on surfaces at shorter distances from the source, thereby reducing the area of the infectious zone (Tang et al., 2006).

Once the infectious droplet has settled, it can be effectively removed via surface cleaning. An RH between 40% and 60% is the optimum level both to reduce transmission of infection and to prevent mold formation (Arundel et al., 1986). The Department of Energy requires HEPA-filtration units to filter particulates greater than or equal to 0.3 μm (Biosafety in Microbiological and Biomedical Laboratories, 2009). HEPA filtration is known to trap particles down to at least 0.1 μm; MRSA droplets measure 0.5 μm (Biosafety in Microbiological and Biomedical Laboratories, 2009).

Negative pressure rooms exist to block the airborne egress of pathogens. During the 2003 Canadian outbreak of severe acute respiratory syndrome, 46 patients were successfully isolated using negative pressure rooms. The deployment of these isolation measures required augmented staffing, intense ancillary activity, and widespread collaboration within the facility (Loutfy et al., 2004).

Two years later, in 2006, the work by Boswell and Fox further supported the effectiveness of these measures, by demonstrating that HEPA-filtration blocked the airborne transmission of MRSA. Boswell and Fox (2006) demonstrated that HEPA filtration greatly and significantly reduces the prevalence of pathogenic bacterial infections within the rooms of highly infectious patients. These investigators placed agar plates in three private intensive care unit (ICU) rooms occupied by three patients with MRSA infections. Two of the three patients, considered to be “heavy shedders,” aerosolized enough MRSA to produce 5.0 colony-forming units per 10 hr of exposure. Placement of portable HEPA-filtration units in each room reduced contamination by 75%.
90%, and 96% (Boswell & Fox, 2006). In a 2007 review, Li’s conclusions also supported the effectiveness of negative pressure rooms as he identified multiple studies that demonstrated how ventilation in the built environment may be responsible for airborne transmission (Li et al., 2007).

Proposed tool to facilitate informed decision-making. The principal goal of this investigation was to quantify the relative effectiveness of multiple interventions (each consisting of a pair of alterations). The secondary goal was to optimize cost and effect for these interventions in various scenarios. Total cost consists of both the cost of the intervention and the cost of infection.

As far as we are aware, this is the first technique to analyze budget, pathogen virulence, and facility size concurrently. By using these models, hospital administrators can assess cost savings that occur as a by-product of implementing infection control measures. Informed decision-making bolsters patient safety, thereby facilitating an improved environment of care.

Method

Study Design and Facility Size

We considered three facility sizes with the following bed counts, for the treatment region of each facility: a 134-bed census count for large hospitals, a 56-bed count for medium hospitals, and a 13-bed count for small hospitals. Facility bed count is distributed between private, two-bed, three-bed, and six-bed rooms (see Supplement). We assumed the beds in the treatment region of this investigation are filled by highly immunocompromised patients, without time gaps.

Models. This investigation is based on Chamchod and Ruan’s (2012) baseline model of hospital infection rates. This model was expanded into cost-optimization models for each of the three alterations, HW, RH, and NP. The cost-optimization models simultaneously account for budgets, cost of infections, virulence of pathogen, and cost of the respective alterations. Given a limited budget, the investigation determines outcomes for each facility size.

We initially obtained 24 scenarios, which are summarized in Table 1. We used three virulence levels (VRE = 0.4, CRE = 0.22, MRSA = 0.08). We produced 6 scenarios for large hospitals with 3 virulence levels and 1 budgetary level ($600,000), 12 scenarios for medium hospitals (budgetary level of $180,000 and $250,000), and 6 scenarios for small hospitals (budgetary levels of $60,000).

Data. We used the longitudinal data from the MDRO Repository and Surveillance Network (MRSN) to model the virulence factors, φ (Table 1, column C). These longitudinal data consist of 6 years of MRSA, CRE, and VRE infections in one representative hospital provided by the Walter Reed Army Institute of Research (WRAIR) MRSN. The virulence factors are derived from the MRSN’s original data, based upon the highest increase in the rate of a specific infection, in 2 consecutive years, over a 6-year period (MRSN, 2017). The virulence factors (φ, an input into the models) measure the rate of progression from colonization to infection. Direct costs of infections were determined from Zimlichman et al. (2013). Associated litigation costs (i.e., indirect costs) were also estimated and incorporated. Indirect costs incorporate decreased productivity, reduction of wages, premature death, and burden upon family members who become caretakers (Marchetti & Rossiter, 2013). Costs of infection include indirect and direct costs.

Costs for commercial off-the-shelf items used in the interventions were determined from these vendors: Johnson & Johnson, Medline Industries Inc., Purell (HW intervention), Biological Controls, and Qualitair (RH and NP interventions). This investigation was conducted from a healthcare-system perspective. Costs are in 2017 US dollars.

The number of contacts per HCW with possibly unwashed hands is eight, based on the literature supporting the high efficacy of the HW alteration (Boyce, 2013). The costs for reducing these contacts with unwashed hands to zero with
<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Scenario #1, Trade-Off Analysis of RH and HW</th>
<th>Scenario #2, Trade-off Analysis of HW and NP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost of Infections Path</td>
<td>Virulence ($f$)</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>$400,000 MRSA 0.08 Large Hospital $600,000</td>
<td>$395.2 K (66%)</td>
<td>$152.0 K (25%)</td>
</tr>
<tr>
<td>$250,000 CRE 0.22 Large Hospital $600,000</td>
<td>$433.9 K (72%)</td>
<td>$166.1 K (28%)</td>
</tr>
<tr>
<td>$150,000 VRE 0.4 Medium Hospital $250,000</td>
<td>$426.4 K (71%)</td>
<td>$173.6 K (29%)</td>
</tr>
<tr>
<td>$400,000 MRSA 0.08 Medium Hospital $250,000</td>
<td>$33.1 K (18%)</td>
<td>$67.8 K (38%)</td>
</tr>
<tr>
<td>$250,000 CRE 0.22 Medium Hospital $180,000</td>
<td>$96.8 K (54%)</td>
<td>$79.8 K (43%)</td>
</tr>
<tr>
<td>$150,000 CRE 0.22 Medium Hospital $250,000</td>
<td>$33.1 K (13%)</td>
<td>$67.8 K (27%)</td>
</tr>
<tr>
<td>$250,000 CRE 0.66 Medium Hospital $180,000</td>
<td>$96.4 K (54%)</td>
<td>$83.6 K (46%)</td>
</tr>
<tr>
<td>$150,000 CRE 0.66 Medium Hospital $250,000</td>
<td>$119.5 K (48%)</td>
<td>$86.3 K (35%)</td>
</tr>
<tr>
<td>$400,000 MRSA 0.08 Small Hospital $60,000</td>
<td>$0.0 K (0%)</td>
<td>$15.1 K (25%)</td>
</tr>
<tr>
<td>$250,000 VRE 0.066 Small Hospital $60,000</td>
<td>$0.0 K (0%)</td>
<td>$18.7 K (31%)</td>
</tr>
<tr>
<td>$150,000 VRE 0.4 Small Hospital $60,000</td>
<td>$0.0 K (0%)</td>
<td>$20.4 K (34%)</td>
</tr>
</tbody>
</table>

Note. Interventions were applied to bed censuses that varied according to facility size: large hospitals = 134 beds; medium hospitals = 56 beds; small hospitals = 13 beds. Columns A–C = parameters for the multidrug-resistant pathogen. Column B = costs of infection. Column C = virulence factor ($f$), determined from 6 years of original longitudinal data. Column D = facility size. Column E = respective budgets for trade-off analysis. Columns F and G represent the optimized percent of budget allocations for Scenario #1 (RH and HW). Column H represents the number of respective infections in Scenario #1 that result without the implementation of the intervention. Column I represents the number of infections in Scenario #1 that occur after the implementation of the intervention. Column J represents the efficiency of the intervention. Column J is measured by the reduced number of infections per $1,000 spent. The most efficient intervention has the lowest value in Column J. Columns K and L represent the optimized percent of budget allocations for Scenario #2 (HW and NP). Column M represents the number of infections in Scenario #2 that occur without this intervention. Column N annotates the number of infections in Scenario #2 after the use of the respective intervention. Column O also represents the efficiency of the intervention of Scenario #2 (HW and NP), which is quantified as the reduced number of infections per $1,000 spent. Optimum distribution of funds that result in minimization of infections and intervention costs can occur without use of 100% of the budget. Pathogens: MRSA = methicillin-resistant Staphylococcus aureus; HW = handwashing stations; CRE = carbapenem-resistant Enterobacteriaceae; VRE = vancomycin-resistant Enterococci. Infection numbers that resulted in decimal values and are rounded up to the nearest value. These two values are different when the decimal is accounted for.
the HW alteration were $143,300 (large facility), $64,512 (medium), and $15,438 (small).

We assumed that without an RH alteration, 1% of those uninfected will be infected by each colonized patient. The cost of reducing this infection rate to zero for the RH alteration was $725,254 (large facility), $304,216 (medium), and $89,387 (small). We assumed that without an NP alteration, 1% of uninfected patients will be infected by each colonized patient via aerosolization. The cost of reducing this to zero for the NP alteration is $4,178,408 (large facility), $1,462,200 (medium), and $208,920 (small). Multiple studies demonstrate the effectiveness of negatively pressured, HEPA-filtered rooms (Boswell & Fox, 2006).

The investigation determines p values using a one-way Analysis of Variance (ANOVA); p values less than .05 were considered to be statistically significant. This alteration was conducted for medical facilities that previously did not have hand sanitizers placed outside patient treatment rooms. More details on the costs incorporated into the alteration costs are available in the Supplemental Section.

**Simulation method.** We used MATLAB to analyze the ordinary differential equations (ODEs) of the model using the Runge–Kutta technique. Chamchod and Ruan’s (2012) baseline differential equations represent the transmission of pathogenic bacteria (MRSA, CRE, VRE; see Figure 2, Supplemental Methods section). Additionally, Chamchod and Ruan cite and utilize over 12 scientific papers to determine the parameters used in the baseline transmission model (ODEs). The input variables (see Figure 2A and 2B; Supplemental Methods section) in these differential equations are used to quantify factors that affect transmission of infection.

This technique resembles a modified version of the S-I-R-S (susceptible, infectious, recovered, susceptible) model. This modeling technique calculates theoretical rates of infection based on the characteristics of the population at risk. We utilized the MATLAB fmincon solver to determine the optimal budget allocation for each alteration in an intervention, to minimize overall cost.

**Results**

The scenario diagram (see Figure 1) summarizes the key optimized resource allocation results.

**Optimization Results Across Models**

Table 1 lists the parameters for the multidrug-resistant pathogen (Table 1, columns A–C), facility size (Table 1, column D), and respective budget trade-off analysis (Table 1, columns F-J and K-O). Costs of infection (Table 1, column B; Marchetti & Rossiter, 2013, Zimlichman et al., 2013) were determined based on literature and frequency of infection over a 6-year time period (MRSN, 2017).

Our model determined the optimal allocation of funding for three preventative measures. We used the model to apportion funds between the following two trade-off, design scenarios: (see Table 1) Scenario #1: rooms with relative humidity control and improved HW; Scenario #2: installation and operation of negative pressure rooms and improved HW.

Optimized solutions of Scenario #1 (RH and HW) and Scenario #2 (HW and NP) are presented in columns F–G, I–J, and K–L, N–O, respectively (Table 1). Columns I and M in Table 1 calculate the preintervention, annual number of infections. Based on the results in Table 1 and Figure 1, we can state the following general remarks: Relative humidity control combined with improved HW provides the greatest reduction of infections. Cost-effectiveness and efficiency of interventions are reflected by a low value for the reduced infections per $1,000 expended (Table 1, columns J and O).

The values in columns F and G do not always sum to the values in column E. This is because the intervention can sometimes achieve the optimum result (i.e., the greatest reduction in number of infections) without using all of the available budget. For the same reason, the values in columns K and L may not sum to the values in column E. The two extreme examples, one in each scenario, show that optimization of infection control is achieved by spending only one quarter (25%) of the available funds. This is because the cost of increasing the intervention effort beyond the optimal level was not offset by the associated cost savings of reduced infections.
Figure 1. Scenarios run in optimization models. This figure depicts the decision tree processes involved in the investigation. RH = relative humidity alteration; HW = handwashing alteration; NP = negative pressure alteration; yellow = large hospital scenarios; blue = medium hospital scenarios; olive green = small hospital scenarios; # = with respect to MRSA pathogen; ^ = with respect to CRE pathogen; * = with respect to VRE pathogen; MRSA = methicillin-resistant Staphylococcus aureus; CRE = carbapenem-resistant Enterobacteriaceae; VRE = vancomycin-resistant Enterococci.
Infections

With the implementation of relative humidity control and handwashing: In a large hospital, there was a reduction of 12 infections in the case of MRSA, 28 infections in the case of CRE, and 42 infections in the case of VRE. In a medium hospital, there was a reduction of 3 infections in the case of MRSA, 10 infections in the case of CRE, and 14 infections in the case of VRE.

A. Ordinary Differential Equations from the Baseline Transmission Model (Chamchod & Ruan, 2012).

U = Uncolonized Patient,
C = Colonized Patient,
I = Infected Patient,
H = Uncontaminated Health Care Worker,
Hc = Contaminated Health Care Worker

\[
\begin{align*}
\frac{dU}{dt} &= (1 - \lambda_c - \lambda_i)U - \frac{\alpha}{N_h} b_p U H_c - \gamma_r U + \omega C \\
\frac{dC}{dt} &= \lambda_c U - \frac{\alpha}{N_h} b_h U H_c - \rho t I - (\varphi + \gamma_c + \omega) C \\
\frac{dI}{dt} &= \lambda_i U + \varphi C - (\gamma_i + \rho t) I \\
\frac{dH}{dt} &= -\frac{\alpha}{N_h} b_h C H - \frac{\alpha}{N_h} b_h I H + \mu H_c \\
\frac{dH_c}{dt} &= +\frac{\alpha}{N_h} b_h C H + \frac{\alpha}{N_h} b_h I H - \mu H_c
\end{align*}
\]

C. Objective (Goal) Function

Minimize \( f(x_1, x_2) = c_1 I + c_2 x_1 + c_2 x_2 \)

\[ f(x_{HW}, x_{RH}) = c_1 I + c_{HW} x_{HW} + c_{RH} x_{RH} \]

Where,

- \( c_1 = \) cost of infection
- \( I = \) number of infections
- \( c_1 = \) cost of intervention \( 1 \) (e.g. \( HW \))
- \( c_2 = \) cost of alteration \( 2 \) (e.g. \( RH \))
- \( x_1 = \) decision variable / budget allocation in % for alteration \( 1 \) (e.g. \( HW \))
- \( x_2 = \) decision variable / budget allocation in % for alteration \( 2 \) (e.g. \( RH \))

D. Constraints for Objective (Goal) Function

\[
\begin{align*}
g_1(x_1, x_2) &= c_1 x_1 + c_2 x_2 \leq \text{Budget} : u_1 \\
g_2(x_1, x_2) &= x_1 + x_2 \leq 1 : u_2 \\
g_3(x_1, x_2) &= x_1 \geq 0 : u_3 \\
g_4(x_1, x_2) &= x_2 \geq 0 : u_4 \\
g_5(x_1, x_2) &= x_1 \leq 1 : u_5 \\
g_6(x_1, x_2) &= x_2 \leq 1 : u_6
\end{align*}
\]

Where \( u_i \) is the dual variable associated with the constraint \( g_i(x_1, x_2) \), \( i = 1, 2, 3, 4, 5, 6 \)

Figure 2. Mathematical equations for optimization models. (A, top left) Baseline transmission model, ordinary differential equations (Chamchod & Ruan, 2012). (B, top right) Parameter definitions (Chamchod & Ruan, 2012). (C, bottom left) Objective (goal) function for optimization of decision variables. (D, bottom right) Constraints for objective (goal) function and associated dual variables.

Infections

With the implementation of relative humidity control and handwashing: In a large hospital, there was a reduction of 12 infections in the case of MRSA, 28 infections in the case of CRE, and 42 infections in the case of VRE. In a medium hospital, there was a reduction of 3 infections in the case of MRSA, 10 infections in the case of CRE, and 14 infections in the case of VRE.
of CRE, and 16 infections in the case of VRE. In a small hospital, there was a reduction of two infections in the case of CRE and three infections in the case of VRE (and no reduction in the case of MRSA).

With the implementation of negative pressure and handwashing: In a large hospital, there was a reduction of 10 infections in the case of MRSA, 22 infections in the case of CRE, and 31 infections in the case of VRE. In a medium hospital, there was a reduction of 3 infections in the case of MRSA, 9 infections in the case of CRE, and 15 infections in the case of VRE. In a small hospital, there was a reduction of two infections in the case of CRE and three infections in the case of VRE (and no reduction in the case of MRSA).

**Cost Savings From the Interventions**

The high cost of these expensive strategies (negative pressure rooms and relative humidity control) is justified by the cost savings, as detailed below:

Among the 12 trials in Scenario #1 and in the absence of either of these two alterations (RH and HW), the model projected an average of 17 infections (rounded up to the next whole number). *Whereas in the presence of these alterations (postintervention)*, the model projected an average of only five infections. Thus, the difference of 12 infections represents the number of infections prevented. The distribution of funds between the two alterations was optimized to maximize the number of infections prevented. The model further projected that spending $1,000 would prevent an average of 0.0688 infections (Table 2, column E). On average, spending $18,406 would prevent one infection (total cost expended across each scenario, divided by total infections prevented).

**Associations**

Certain trends were evident across the three species of pathogenic bacteria. The models generally demonstrated an inverse relationship between the budget and HW resource allocation, that is, as the budget decreases, the resource allocation to HW increases. The budget and NP resources are directly proportional to one another, that is, as the budget decreases, NP resource allocation also decreases.

Another association is that within the $180,000–$250,000 budget range, increased RH resource allocation will optimally protect against increasingly virulent species of bacteria.

**Bed Count (i.e., Facility Size)**

As the bed count increases, NP resourcing also increases. Therefore, NP resource allocation is directly proportional to the bed count.

This investigation determined the prioritization order of pairs of alterations, to minimize infection and cost. Specific examples of unanticipated results are discussed below.

**Specific Examples**

**MRSA and large and medium hospitals.** When evaluating alterations for MRSA infections in large and medium hospitals, as the available budget decreases, RH resource allocation decreases. Specifically, when a budget of $600 K is used, RH has priority (see Table 1, column F).

**CRE and large hospitals.** As the budget decreases from $600,000, RH resourcing decreases. At
### Table 2. Analysis and Significance of Trade-Offs Between Three Interventions.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Scenario #1, Relative Humidity Control and Handwashing Stations</th>
<th>Scenario #2, Handwashing Stations and Negative Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Humid B</td>
<td>Hand Wash C</td>
</tr>
<tr>
<td>Trial #</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 2</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>3 to 4</td>
<td>72%</td>
<td>28%</td>
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<tr>
<td>5 to 6</td>
<td>71%</td>
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<tr>
<td>7 to 8</td>
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<tr>
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<td>13%</td>
<td>27%</td>
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<tr>
<td>11 to 12</td>
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<td>13 to 14</td>
<td>39%</td>
<td>32%</td>
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<tr>
<td>15 to 16</td>
<td>54%</td>
<td>46%</td>
</tr>
<tr>
<td>17 to 18</td>
<td>48%</td>
<td>35%</td>
</tr>
<tr>
<td>19 to 20</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>21 to 22</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td>23 to 24</td>
<td>0%</td>
<td>34%</td>
</tr>
<tr>
<td>Means, standard deviations</td>
<td>36.2%</td>
<td>32.8%</td>
</tr>
<tr>
<td>(± 28.5%)</td>
<td>(± 6.9%)</td>
<td>(± 4.0 infections)</td>
</tr>
<tr>
<td>Difference in means, p values</td>
<td>3.4%</td>
<td>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note. Table depicts the statistical analysis for Trials 1–24: means and standard deviations (Columns B, C, D, E, F, G, H, and I), difference in means (columns C and G), and associated p values (columns D, E, H, and I). p Values were calculated using a one-way ANOVA statistical test. The p value, p = .000135, demonstrates statistical significance between the budget percentage allocations (Scenario #1, columns B and C) and the numbers of infections postintervention (Scenario #1, column D). The p value, p = .000291, demonstrates statistical significance between the budget percentage allocations (Scenario #1, columns B and C) and the number of reduced infections per $1,000 expended (Scenario #1, column E). The p value, p = .001219, demonstrates statistical significance between the budget percentage allocations (Scenario #2, columns F and G) and the number of infections postintervention (Scenario #2, column H). The p value, p = .004359, demonstrates statistical significance between measures (across the values) for the budget percentage allocations (Scenario #2, columns F and G) and the number of reduced infections per $1,000 expended (Scenario #2, column I). p Values less than .05 were determined to have a statistically significant difference.

<sup>a</sup>Represents different values when accounting for decimals. <sup>b</sup>Statistically significant based on a one-way ANOVA test.
$600,000, RH is at 72% (in Scenario #1) and NP is at 69% (in Scenario #2); thus, the delta between NP and RH, between the scenarios, is 3% (see Table 1, columns F and L). In these instances, delta designates an absolute difference; more specifically, it is the absolute percentage difference in allocated funds between any two alterations.

**Statistical analysis.** In Table 2, we provide a brief statistical analysis of all of our design scenarios to identify global trends in our results. Columns B, C, D, and E show a summary of the model results for Scenario #1. Averaging over all trials, our model proposed investing 36.2% in relative humidity control and 32.8% in improved HW, which produced a mean difference of 3.4%. The average number of infections postintervention, across the 24 trials of Scenario #1, was 5 infections (rounded up from 4.3), with a $p = .000135$. Using a one-way ANOVA across the budget allocation percentages (Table 1, columns F and G) and the reduced infections per $1,000 (Table 1, column J) results in $p = .000291$.

Similarly, Table 2, columns F, G, H, and I show a summary of model results for Scenario #2. The model proposed investing an average of 16.4% of the allocated budget in negative pressure rooms and 34.7% in improved HW, which produced a mean difference of 18.3%. The average reduction of infections across the trials of Scenario #2 was seven infections (rounded up from 6.2), with $p = .00122$. Using a one-way ANOVA statistical analysis across the budget allocation percentages (Table 1, columns K and L) and the reduced infections per $1,000 (Table 1, column O) results in $p = .00436$.

**Discussion**

Our research questions focus on optimizing cost and effectiveness of these interventions in various scenarios (see Figures 2; Supplemental Results) and on comparing the combined effectiveness of a pair of alterations to another feasible pair. The overall reduction of infections is greater in Scenario #1 (RH and HW) than in Scenario #2 (HW and NP).

The overall reduction of infections is greater in Scenario #1 (RH and HW) than in Scenario #2 (HW and NP).

The results demonstrate an inverse relationship between the budget and handwashing alterations, with the exception of the small hospital MRSA scenario (see Table 1). As the budget increased, handwashing resourcing decreased. The benefit of HW is significant, but maximum benefit can be obtained with a relatively small investment. This effect is supported by a study undertaken in ICU environments (Jayaraman et al., 2014), which demonstrates that when handwashing compliance is at an extremely high level, the benefits plateau.

The benefit of HW is significant, but maximum benefit can be obtained with a relatively small investment.

For any of the three bacterial species, and within the $180,000 to $250,000 budget range, there is an inverse relationship between the budget and resource allocation for the relative humidity alteration (see Table 1). The NP alteration is directly proportional to the budget. These findings are likely due to the expense of these alterations as well as their impact on mitigating transmission of pathogenic bacteria from a colonized to an uncolonized patient. The RH and HW scenarios best contain multidrug-resistant bacteria. The HW and NP alterations generally had the largest allocation of resources for the larger sized healthcare facilities (see Figure 1).

These results can be generalized to facilities (or sections thereof) of various sizes by simply modifying the bed count in the model. The associated up-front costs can also be adjusted in the models as needed. Methods described in this article can be used to allocate resources in the face of epidemics or facility outbreaks. Finally, these methods can be used to inform decision-making when unexpected funding becomes available.
Limitations

The infectious disease data derive from a single, representative, medium-sized hospital. Incorporation of data from multiple healthcare facilities would likely improve the ability to apply these determinations to a diversity of facilities. This investigation only evaluated three multidrug-resistant pathogenic bacteria and does not include other causes of HAIs that may not necessarily be due to an MDRO, such as *C. difficile*. An additional limitation is that the impact of the bacterial infection by age-group is not evaluated.

Conclusion

In this study, we developed a novel mathematical approach that integrates hospital design and infection control within a budget framework. We used original longitudinal data, representing 6 years of observation in a single facility. The budget allocations are representative of funding that a facility, based on its size, would likely receive for annual repairs and renovations. In this research, we have determined how cost-effective resource allocation enhances the built environment to provide effective infection control to reduce the transmission of three bacterial pathogens from one human host to another.

We have conducted this analysis for 24 scenarios. Each scenario represents a unique combination of facility size, facility budget, pathogen virulence, and alteration pairing. Each of these pairs is derived from combinations of HW, negative pressure rooms, and control of relative humidity between 40% and 60%.

Determinations from these models can inform infection control strategies as architects, owners, engineers, and medical providers plan, design, and renew healthcare facilities. With this information, designers and planners can exercise novel insights as to the interactions between the built environment, expenditure of resources, and HAIs. In doing so, they are better prepared to address the containment of multidrug-resistant pathogens that are endemic in healthcare facilities today.

Implications for Practice

- This knowledge better prepares healthcare facilities for the containment of multidrug-resistant pathogens.
- These mathematical optimization tools can better inform design decisions made by healthcare executives and project delivery teams, helping bolster patient safety and enhance environments of care.
- These findings contribute to knowledge that can shape best practices among hospital design, including better use of RH control and negatively pressured patient rooms, as well as greater compliance of existing HW practices.

Authors’ Note

The article has been reviewed by the Walter Reed Army Institute of Research. There are no objections to its presentation. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.

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Supplemental Material
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References


