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Modeling bacterial colonization and infection routes in health care settings: Analytic and numerical approaches

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AUTHOR-HIGHLIGHTS

- Construct and analyze a model for the spread of MRSA in health care settings.
- Includes colonization, infection, isolation and contamination among health care workers.
- Includes patient–patient and patient–HCW–patient transmission routes.
- Analytical computation of the basic reproduction number.
- Transmission pathways compared in hospitals and long-term care settings.

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ABSTRACT

Health-care associated infections are a major problem in our society, accounting for tens of thousands of patient deaths and millions of dollars in wasted health care expenditures each year. Many of these infections are caused by bacteria that are transmitted from patient to patient either through direct contact or via the hands or clothing of health care workers. Because of the complexity of bacterial transmission routes in health care settings, computational approaches are essential, though often analytically intractable. Here we describe the construction and detailed analysis of a model for bacterial transmission in health care settings. Our model includes both colonization and disease stages for patients and health care workers, as well as an isolation ward and both patient–patient and patient–HCW–patient transmission pathways. We explicitly derive the basic reproductive ratio for this complex model, a nine-term expression that contains all nine ways with which a new colonization can occur. Using key parameters found in the medical literature, we use our model to gain insight into the relative importance of various bacterial transmission pathways within health care facilities, and to identify which forms of interventions are likely to prove most effective in hospitals and long-term care settings. We show that analytical and numerical approaches can complement each other as we seek to untangle the complex web of interactions that occur within a health care facility.

1. Introduction

Health care-associated infections (HCAI) are a leading cause of morbidity and mortality in the United States. In 2002, approximately 1.7 million HCAIs were reported in U.S. hospitals, leading to nearly 99 000 deaths (Klevens et al., 2007). The additional cost of care attributable to health-care associated sepsis and pneumonia, two common clinical outcomes, are estimated at $5800–$32 900 per patient for sepsis and $12 700–$46 400 for pneumonia, and all HCAIs combined cause $17–$20 billion in added health care costs each year (Klevens et al., 2007; Eber et al., 2010; Zhan and Miller, 2003). Depending on the severity of their infections, patients who contract a HCAI while hospitalized will also increase their length of stay by about 10–20 days and their risk of mortality by 30–50% (Eber et al., 2010; Pirson et al., 2005; Kothari et al., 2009). Furthermore, recent hospitalization is the single largest risk factor for infection with antibiotic resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) in the community, making HCAIs a significant threat to the general public (Warshawsky et al., 2000; Chen et al., 2008). For these reasons, identifying the major transmission routes for infectious organisms in health-care settings and taking appropriate steps to minimize patient exposure are of crucial importance.

Because HCAI transmission is a complex process and observation of all individual transmission events is impossible, computational

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approaches have proven extremely useful in helping investigators evaluate the relative importance of different transmission routes, plan future studies, and determine the efficacy of possible interventions. Several recent models have specifically examined the spread of MRSA and other antibiotic-resistant organisms in hospital and community settings (Skov and Jensen, 2009; Webb et al., 2009; D'Agata et al., 2009; Cooper et al., 2004; Austin et al., 1999; Cooper and Lipsitch, 2004; Ancel Meyers et al., 2003; Bootsma et al., 2006; McBryde et al., 2007; Smith et al., 2004; D'Agata et al., 2007). However, realistic models often incorporate a bewildering array of parameters and prove difficult or impossible to approach analytically. In the context of hospital-acquired infections, this often means that certain important transmission pathways are ignored in the interest of model simplicity. For example, one hugely important reservoir of infection in hospitals is health care workers (HCWs); several studies have established that the hands of HCWs often act as vectors for the transmission of facility-acquired infections and that HCWs themselves are often colonized or contaminated with infectious organisms like MRSA (Aiello and Larson, 2002; Curtis and Cairncross, 2003; Pittet, 2001; March et al., 2010). Unfortunately, incorporating more complex transmission routes like HCW vectors into transmission models can easily cause the equations to become analytically intractable.

Here we model bacterial transmission in two very different health-care environments: hospitals and long-term care facilities (LTCFs). We chose these two institution types because they exist at two ends of a spectrum; at one end, patients mostly contact HCWs (hospitals) and at the other end, they mostly contact other patients (LTCFs). We wanted to confirm that our model would indeed capture these differences and reveal the most important transmission routes in each type of facility. Our most general model includes HCW vectors, multiple stages of infection, and an isolation ward for diseased patients. It contains four patient variables (susceptible, colonized, infected, and isolated), four HCW variables (clean, contaminated, colonized, both), and 25 parameters to capture the nuances of different types of bacterial infection and different health care settings and institutions. The model could, in principle, be used to compare transmission pathways across a variety of different health care facilities. Our goal is to carry out an analysis that applies as broadly as possible for all parameter values so that comparisons can be made across institutions.

The main step in this general analytic approach is our explicit calculation of the algebraic expression of the Basic Reproductive Ratio (R_0) (Heffernan et al., 2005) for this model, an expression that incorporates all of the model parameters and shows how they work together to contribute to the infectious process. We use Lyapunov functions (Simon and Jacquez, 1992; Simon et al., 1991) to perform this calculation, a general approach that should also work for other important classes of model. In combination with numerical simulations and carefully-chosen parameter values from the scientific literature, our results demonstrate that optimal intervention strategies do indeed differ between hospitals and long-term care settings. They also provide explanations for these differences in terms of individual parameter values and their impact on R_0. By attacking the problem in this way, we can gain insight into the structure of our model and better understand the role of each parameter within its overall architecture. This enables us to start untangling the complex web of interactions that occur within a health care facility, focusing our attention on the subset of interventions that is likely to do the most good.

2. The basic reproductive ratio

A key index in any analysis of disease spread is the basic reproductive ratio, R_0: the number of new infections attributable to an infected individual over the course of his or her infection in a population of susceptible individuals. The tipping point between disease take-off and die-out occurs at $R_0=1$. Alternatively, R_0 is the ratio:

$$\frac{\text{rate at which susceptible individuals become infected}}{\text{rate at which infected individuals lose their infection}}.$$

For simple epidemiological models involving homogeneous populations composed of susceptible, infected, and recovered individuals,

$$R_0 = \chi \cdot \beta \cdot L,$$

where χ is the average number of contacts per unit time, β is the probability of infection per contact, and L is the average length of the infectious period. In such simple models, when $R_0 > 1$, R_0 determines the rate of increase in the number of infected individuals and the endemic level of infection, Y^*, since $Y^* = 1-(1/R_0)$.

Most interesting epidemiological models, however, are of sufficient complexity that the exact expression for R_0 is neither obvious nor easily calculated. This is true for any realistic model of bacterial transmission in health-care settings, as well as a wide class of other interesting models.

3. A simple subsystem

To build intuition for the techniques and conclusions of our analyses, we begin with a simple model that displays features similar to those of the more elaborate one described later in the paper. Patients can either be MRSA-free (P_F) or colonized (P_C), while HCWs can either be MRSA-free (H_F) or contaminated (H_F^T), which means they harbor bacteria on their hands or clothing and have the potential to infect uncolonized patients. Table 1 contains a full description of these different states.

Each model day, the following events occur:

1. Patients enter the facility at a constant rate U. We assume that all incoming patients are uncolonized.
2. Free and colonized patients leave the facility at a rate μ. Because we wish to keep the total number of patients in the facility constant (i.e. we assume it is always operating at maximum capacity), we require that $U = \mu P_F + \mu P_C$.
3. Patients and HCWs interact at a rate χ, and each interaction event can potentially transmit infection or contamination. For instance, during a single contact a colonized patient contaminates the gloves, skin or clothing of a HCW with probability β_{CT}. In the other direction, a contaminated HCW infects a MRSA-free patient with probability β_{TP} per contact.
4. Colonized patients lose their colonization at a natural rate γ_P per day. Colonized patients are treated with antibiotics and the

Table 1
Description of the infection states of patients and health care workers. A *colonized* patient or HCW is colonized with MRSA but asymptomatic. A *contaminated* HCW is uncolonized with MRSA but harbors the bacteria on his or her hands or clothing. An *isolated* patient is quarantined in an isolation ward and does not interact with other patients.

Variable	Interpretation
P_F	Uncolonized patients
P_C	Colonized patients (but disease free)
P_D	Diseased but non-isolated patients
$P_{D'}$	Diseased and isolated patients
H_F	Uncolonized, uncontaminated HCWs
H_C	*Colonized* but uncontaminated HCWs
H_F^T	Uncolonized but *contaminated* HCWs
H_C^T	*Colonized* and *contaminated* HCWs
H_D	Diseased HCWs (leave facility immediately)