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Optimal control of methicillin-resistant *Staphylococcus aureus* transmission in hospital settings

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are caused by strains of *Staphylococcus aureus* bacteria with resistance to the standard antibiotics that are often used for the treatment of ordinary *Staphylococcus aureus* infections. In this study, a deterministic model is presented for the transmission dynamics of hospital- and community-acquired MRSA in a hospital setting. The disease-free equilibrium of the model is locally asymptotically stable whenever the associated reproduction number is less than unity. The disease persists in the community whenever the reproduction number is greater than unity. The sensitivity analysis results show that the model outputs are affected by the hand washing compliance rate, decolonization rate of health-care workers, environmental contamination rate, hospital admission rates, and the isolation rate of colonized patients. Optimal control theory is then applied to investigate the goal of minimizing the colonization and infection of patients and health-care workers with MRSA using two time control variables (effects of the decolonization of health-care workers and environmental contamination rates) obtained from the sensitivity analysis.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive bacterium with resistance to commonly used antibiotics for the treatment of ordinary *Staphylococcus aureus* infections. More than 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the drugs that are used most widely for the treatment of infections. Health-care associated MRSA (HA-MRSA) infections occur mainly among hospitals patients or residents of nursing homes, as well as in dialysis centers and other health care settings. According to the Centers for Disease Control (CDC), more than two million people acquire some form of clinically significant antibiotic-resistant infection each year, with at least 23,000 death as a consequence [1]. In particular, the CDC estimated that there were 80,461 invasive MRSA infections in 2011 with 11,285 related deaths. In addition, an unknown but much higher number of less severe infections occur in both the community and in health-care settings [1]. The economic impact of antibiotic resistance on the US economy is estimated to be as high as $20 billion in excess direct health-care costs, where the additional costs to society due to lost productivity are as high as $35 billion per year (2008 dollars) [1].

MRSA causes substantial morbidity and mortality, and it is endemic in hospitals and nursing homes. HA-MRSA infections are typically associated with individuals who have undergone invasive procedures or received indwelling medical devices,

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such as intravenous tubing or artificial joints, and/or antimicrobial therapy. By contrast, community-associated MRSA (CA-MRSA) infections arise in otherwise healthy individuals without obvious risk factors. CA-MRSA infections were first described in 1982 by Savoralatz et al. among intravenous drug abusers [2,3] and later reported during the early 1990s in patients without prior health-care contact in Western Australia and New Zealand, as well as in American children during the late 1990s [4–6]. The CA-MRSA strains are genetically distinct from traditional HA-MRSA [7,8], and they are more virulent and spread more rapidly than the traditional hospital-associated MRSA strains [4]. Five CA-MRSA lineages have been found worldwide: ST1-IV (USA400), ST8-IV (USA300), ST30-IV (Pacific/Oceania), ST59-IV and V (USA1000, Taiwan), and ST80-IV (European) [9]. CA-MRSA outbreaks in hospitals have been reported since 2003 in North America, Germany, Israel, Switzerland, Greece, and the UK, often in units such as pediatrics and obstetrics where the prevalence of HA-MRSA is low [10].

Numerous mathematical modeling studies of HA- and CA-MRSA have been performed to quantify the potential impact of the epidemic burden (see [8,11–16]). For instance, Chamchod, and Ruan [11] used mathematical models to investigate the transmission dynamics of MRSA and to determine factors that influence the prevalence of MRSA infections when antibiotics are given to patients to treat or prevent infections caused by either MRSA itself or other bacterial pathogens. Cooper [12] considered a mathematical model of both hospital and community reservoirs of MRSA colonization to explain substantial increases in HA- and CA-MRSA despite rigorous control policies. They showed how the timing of the intervention, the level of resource provision, and chance might combine to determine whether control measures succeed or fail. D′Agata et al. [13] developed a deterministic model to characterize the transmission dynamics of HA- and CA-MRSA in hospital settings, as well as for quantifying the emergence of co-colonization by both strains. Their results showed that the state of co-colonization becomes endemic over time and that there is typically no competitive exclusion of either strain. D′Agata et al. [14] developed a deterministic model to characterize the factors that contribute to the replacement of HA-MRSA with CA-MRSA, as well as quantifying the effectiveness of interventions for limiting the spread of CA-MRSA in health-care settings. Their results suggested that CA-MRSA will become the dominant MRSA strain in hospitals and health care facilities. Pressley [16] first formulated a model of HA- and CA-MRSA under the assumption that patients cannot be co-colonized by the two strains, where their results showed that competitive exclusion occurs between HA- and CA-MRSA strains. They also extended this model to include co-colonization of patients with the two strains, where the extended model barely exhibited competitive exclusion. Skov [8] presented a mathematical model to consider the influence of MRSA transmission in the community on the prevalence of MRSA in hospitals.

Some studies have indicated that the progression of MRSA can be explained mainly by contaminated health-care workers coming in direct contact with patients [12,17]. Chamchod and Ruan [11] studied the transmission dynamics of health-care workers in nursing homes and found that minimizing contact with the residents and following appropriate hand-washing procedures reduced the transmission of bacteria. Milazzo [17] showed that certain measures, such as improving hand hygiene compliance, barrier precaution policies, and effective staff management, can be taken to control the bacteria. Milazzo further suggested that relocating contaminated patients to separate wards may prevent MRSA from spreading quickly throughout a hospital [17]. Chow [18] showed that isolation has the potential to effectively control the progression of the disease.

In this study, the deterministic model developed by [19] is presented, which is a new deterministic model for the spread of CA-MRSA and HA-MRSA in hospital settings that includes health-care worker interactions with patients and contamination of the environment, where these features were absent from the models proposed by [11–13,16–18]. This model also allows for the isolation of infected patients, which is another feature that was absent from the models of [11–13,16,17]. Furthermore, this study considers time-dependent optimal control strategies associated with the decolonization of health-care workers and environmental contamination rates. Previously, optimal control theory has been applied to study control strategies involving MRSA [11], HIV/AIDS [20], tuberculosis [21,22], SARS [23], avian influenza [24–26], and malaria [27,28]. Thus, time-dependent control mechanisms are introduced into the model to represent the decolonization of health-care workers and environment contamination rates. The following questions are addressed in this study. What parameter has the greatest impact on MRSA transmission in a hospital setting. What is the optimal control strategy required to reduce disease transmission? What is the implication of increased control cost combinations?

The remainder of this paper is organized as follows. Section 2 describes the hospital- and community-acquired MRSA transmission model, which is followed by basic qualitative analysis. The uncertainty and sensitivity analyses of the model are presented in Section 3. The optimal control analysis and the objective functional are described in Section 4. Numerical results and the discussion are given in Section 5.

2. Model formulation

In the following, the deterministic model developed by [19] is presented and the model is formulated. The total patient population in the hospital, denoted by $N_H(t)$, is split into mutually-exclusive sub-populations of individuals who are uncolonized (U_P), colonized with a CA-MRSA strain (C_{CH}), colonized with a HA-MRSA strain (C_H), infected with CA-MRSA (I_{CH}), infected with HA-MRSA (I_H), and isolated patients (Q), such that

$$N_H(t) = U_P(t) + C_{CH}(t) + I_{CH}(t) + C_H(t) + I_H(t) + Q(t).$$