Control of Vancomycin-Resistant Enterococci: One Size Fits All?

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Infection caused by vancomycin-resistant enterococci (VRE) is associated with high morbidity and mortality rates; it poses a serious threat, in particular, to immunosuppressed patients. It generates high costs and challenges infection-control programs. Here, we look at the insights that mathematical models offer into the epidemiology of VRE colonization and infection, the potential benefits of various infection-control interventions, and the possibility of designing a tailored approach to controlling VRE. Models show that epidemics of VRE infection in diverse institutions may differ in the relative contributions of cross-transmission and the influx of new cases, as well as in the various mechanisms of local transmission. They also highlight the phenomenon of decreasing returns associated with many interventions and, hence, the need to identify the most important routes of transmission, to break the weakest links in the chain of transmission, and to contain the influx of cases of VRE infection. These observations also provide insights into the management of infection with other antibiotic-resistant nosocomial pathogens.

Since vancomycin-resistant enterococci (VRE) were first described in 1987 [1], clinicians have seen monoclonal outbreaks in specialized hospital wards (such as intensive care and transplant units) evolve to polyclonal endemicity throughout the entire North American medical system. VRE infection is associated with high morbidity and mortality rates and high costs and is particularly problematic for immunosuppressed patients [2]. New antibiotics, such as linezolid, daptomycin, and quinupristin/dalfopristin, are active against VRE, but they are expensive, and resistant strains have already developed. Transfer of resistance genes from VRE to Staphylococcus aureus was confirmed in vitro years ago [3], and clinical cases of infection with a vancomycin-resistant S. aureus strain carrying a vanA gene that originated in VRE have been described recently [4]. VRE infection poses a serious threat to patients and drains important resources from the medical system; therefore, VRE control should remain first on the agenda of infection control programs.

The risk presented to the patient by the emergence of VRE in US hospitals resulted in the first elaboration of pathogen-specific control guidelines [5, 6]. These guidelines did not succeed in curbing the nosocomial epidemic. On one hand, there is concern regarding the strength of the evidence supporting these guidelines, which may partly account for the disappointing adherence to recommendations [7]. On the other hand, the complexity of VRE transmission obscures the impact of infection-control policies on epidemic outcome. VRE infection is the tip of an iceberg: 10–20 times more patients are colonized than are infected. In addition, there are at least 4 variables that contribute to the spread of VRE in hospitals: poor infection-control practices, admission of patients who are already colonized, antibiotic use, and prolonged stays by patients [8].

Classical studies of the epidemiology of infection due to resistant microorganisms have important limitations, such as the difficulties in randomizing wards (which constitute the unit of analysis), in selecting appropriate controls, and in adjudicating among the effects of multiple infection-control interventions. Mathematical models have been used in attempts to remedy these limitations. How modeling could be used to improve our understanding of the spread of antibiotic resistance in general has been reviewed previously [9]. Here, we look at the insights that models offer into the epidemiology of VRE...
colonization and infection (hereafter, VRE epidemiology), the potential benefits of various infection control interventions, and the possibility of designing a tailored approach to VRE control. Although we restrict our focus to VRE, these observations also provide insights into other antibiotic-resistant nosocomial pathogens.

**MATHEMATICAL MODELS AND VRE EPIDEMIOLOGY**

Pathogen transmission via the contaminated hands of health care workers (HCWs) is the most important transmission route for VRE. Conceptually, VRE transmission resembles a vector-borne disease, such as malaria, with an HCW playing the mosquito’s role. The classical Ross-MacDonald model for malaria was adapted as an initial model to describe VRE epidemiology within hospitals [10]. In this model, patients and HCWs are separated in 2 compartments, noncolonized and colonized, and the flow of patients and HCWs from one compartment to another is described with differential equations (figure 1). Critical assumptions are as follows: (1) colonization, once established, lasts until patient discharge or death, (2) HCWs do not act as sources, and (3) there is no direct transmission from patient to patient. These assumptions hold true for critically ill (and thus bed-bound) patients in intensive care units.

A central concept in mathematical modeling is $R_o$, the basic reproductive number, representing the number of secondary cases generated from one colonized patient in a VRE-naive population. Epidemics occur if $R_o > 1$. The reproductive number depends on the number of contacts ($\alpha$), the transmission probability per contact ($\beta$), and the duration of infectiousness ($D$).

$$R_o = \alpha \times \beta \times D \quad (1)$$

Because VRE are transmitted via HCWs, transmission results from 2 processes: contamination of the hands of HCWs followed by patient colonization.

$$R_o = R_{HCW}^{\text{contamination}} \times R_{\text{patient colonization}} \quad (2)$$

A more explicit formulation contains the number of contacts ($\alpha$), the number of HCWs ($N_{HCW}$), the number of patients ($N_p$), the per contact probability of VRE transmission from patient to HCW ($\beta_1$) and from HCW to patient ($\beta_2$), and the duration of infectiousness for the HCW ($D_{HCW}$) and the patient ($D_p$).

$$R_o = (\alpha \times N_{HCW} \times \beta_1 \times D_p) \times (\alpha \times N_p \times \beta_2 \times D_{HCW})$$

$$R_o = \alpha^2 \times N_{HCW} \times N_p \times \beta_1 \times \beta_2 \times D_{HCW} \times D_p \quad (3)$$

Figure 1. Flowchart summarizing the indirect transmission of vancomycin-resistant enterococci (VRE) from patient to health-care worker to patient in a unit and possible infection-control measures. Colonized admission, admission of a colonized patient; colonized discharge, discharge of a colonized patient. Reprinted with permission, from [10], copyright 1999, National Academy of Science, USA.

The model describes relationships among $R_o$, the average prevalence of VRE infection at the unit, and the prevalence of VRE infection on admission (figure 2). Even with low $R_o$ values, VRE endemicity may still persist, because endemicity depends on prevalence at admission and on the length of stay distribution. The crucial and often unrecognized role of persistently colonized patients in the epidemiology of antibiotic resistance was also demonstrated in 2 other mathematical models [11, 12]. Although theoretically appealing, $R_o$ is difficult to determine, because it is almost impossible to accurately measure the probabilities of colonization and contamination ($\beta_1$ and $\beta_2$). However, when the remaining variables are determined, the model can be fitted to epidemiological observations. In doing so, Austin et al. [10] estimated the $R_o$ of VRE transmission to be $\sim 3$.

These models are deterministic, in that solving the differential equations predicts a single possible outcome. Deterministic models are accurate when dealing with large populations with homogenous mixing. VRE transmission, however, typically occurs in small hospital units, and fluctuations in prevalence that are due to chance are natural. For these situations, stochastic models are preferred. For example, if an average of 20% of patients admitted in an intensive care unit are colonized with VRE at admission and there are 2 patients admitted per day, the daily prevalence at admission can be 0, 50%, or 100%, depending on how many of the newly admitted patients have VRE colonization. A computer program generates random simulations of admissions with an average prevalence of VRE col-
### INFECTION-CONTROL INTERVENTIONS

The challenge for infection control is to modulate transmission parameters in order to reduce $R_o$ to $< 1$ without compromising the quality of patient care [14]. According to the model of vectorborne diseases, the numbers of patients colonized depends on the number of patients with VRE colonization who are admitted and discharged and the frequency of cross-transmission. Mathematically, the transmission dynamics of VRE is described by the following formula:

$$\frac{dY_p}{dt} = \lambda \Phi - \gamma Y_p + a \beta X_p Y_n$$

where $Y_p$ represents the number of colonized patients, $X_p$ represents the number of noncolonized patients, $Y_n$ represents the number of contaminated HCWs, $\lambda$ represents the admission rate (in patients per day), $\Phi$ represents the proportion of patients already colonized on admission, $\gamma$ represents the discharge rate of colonized patients (in patients per day), $a$ represents the number of contacts per HCW per day, and $\beta$ represents the probability of transmission from HCW to patient. From this formula, it follows that the prevalence of VRE infection can be reduced by decreasing the rate of admission of patients with VRE colonization, increasing the rate of discharge of colonized patients, and preventing cross-transmission. The occurrence of cross-transmission can be diminished by reducing the number of contacts, the transmission probability, and the number of contaminated HCWs.

### Hand hygiene.

Hand hygiene is the most advocated infection-control measure. Levels of compliance with hand disinfection procedures are always "too low." The minimal levels required for "sufficient" compliance have never been determined, though only levels close to 100% might be acceptable to patients and regulatory agencies. Rates of compliance with hand hygiene vary widely, with the average being ~40%, and achieving a persistent increase is an elusive goal [15]. Interventions to improve it are mostly multimodal, including monitoring, frequent feedback, and education, and are accompanied by engineering measures, especially the provision of easy access to alcohol hand-rub dispensers. In deterministic models, hand hygiene is associated with the phenomenon of decreasing returns. With a complete absence of hand hygiene, initial increases in compliance lead to a marked drop in the prevalence of VRE colonization, but further increases have a smaller impact (figure 3). According to model predictions, in intensive care units with an $R_o$ of ~3, hand hygiene compliance rates of 65% are needed to reduce the effective $R_o$ to <1, and in dialysis units with lower $R_o$ values, compliance rates should be at least 40% [10, 11]. It is useful to determine baseline levels of compliance before strategies to promote hand hygiene are implemented. Institutions with high compliance at baseline may be...
Cohorting. In order to transmit VRE, HCWs need to have contact with VRE-colonized and non-VRE–colonized patients, in that order. This double contact is represented by the squared quantity $\chi^2$ in formula 3, and it underscores the critical role of contact rates. Cohorting of patients can be used to prevent this chain of events (figure 1). In many intensive care units, nurses already have some level of cohorting, because they provide care to a limited number of patients. In such settings, the level of cohorting could be defined as the likelihood that, after a patient contact, the next patient contact will be with the same patient. With an optimal functioning nurse-to-patient ratio of 1:1, the cohorting level is 100% and cross-transmission via nurses’ hands is impossible. In less optimal situations, patients can be separated into cohorts: VRE-colonized patients, non-VRE–colonized patients, and patients whose status of colonization is unknown. HCWs are assigned to each cohort and to physicians’ rounds on the basis of their VRE isolation status, and they examine the non-VRE–colonized patients first and the VRE-colonized patients last. In intensive care units with low nurse-to-patient ratios, staff cohorting may be easier than geographical separation. Cohorting on hospital wards can include geographical separation (i.e., use of isolation wards), but this requires good coordination with hospital administrators and sufficient availability of beds and staff [16]. The lack of popularity of cohorting in the United States is partly the result of the chronic shortage of nurses and hospital beds. Although some decrease in the bed-occupancy rate is inevitable, cohorting does not always require that double-occupancy rooms be transformed into single-occupancy rooms, because patients with VRE-colonization can share a room.

Similarly to hand hygiene, cohorting has a nonlinear effect on the prevalence of VRE. An initial increase in the cohorting ratio is associated with a larger impact on the prevalence than are additional increases in the ratio. Cohort levels usually depend on staffing levels. Staff deficits have an amplifying effect, because lower HCW-to-patient ratios are associated with increased workload, higher contact rate, lower cohorting level, and lower rate of compliance with hand hygiene [17].

In addition to general measures, such as improvement of adherence to hand hygiene and optimization of cohorting levels, our armamentarium also contains specific interventions that aim to reduce the likelihood of identified carriers becoming sources of transmission for other patients: namely, barrier precautions and contact isolation. Such a strategy starts with an identification of sources. Because infection rates are much lower than colonization rates, reliance on the results of clinical cultures leaves an important number of potential sources unidentified. Therefore, active surveillance for VRE colonization is an essential part of infection control. Optimal schemes to obtain surveillance cultures should balance costs and benefits, which differ between clinical settings. On the basis of a stochastic mathematical model, Perencevich et al. [18] concluded that active surveillance on admission, with strict isolation of colonized patients, results in a 40% decrease in colonization rate, compared with the colonization rate that results when there is no surveillance or reliance on positive culture results. Sensitivity analyses showed that active surveillance is more effective in hospital settings with a high prevalence of VRE colonization at admission and a high transmission. An economic model of the costs and benefits of active surveillance presented by the same investigators suggested that active surveillance costs approximately $4100 per life-year saved, which most health policy makers consider cost-effective [19]. Implementation of a prediction rule to identify patients at high risk of having VRE colonization at admission is also helpful for targeting surveillance strategies and for improving the cost/benefit ratio of active surveillance [20].

**ANTIBIOTIC STEWARDSHIP**

Reducing the selective pressure of antibiotic use through antibiotic stewardship is another pillar of VRE control. The use of vancomycin does not change vancomycin-susceptible enterococci into VRE. This occurs if the bacteria acquire a transposon containing the vanA or vanB genes, which is a rare event. However, use of antibiotics provides VRE a selective growth advantage. Some patients are colonized with low numbers of VRE that go undetected by conventional culture methods. Antibiotic therapy allows VRE to multiply, and colonization becomes apparent. Moreover, a higher bacterial load increases the likelihood that contact between an HCW and a patient will
Table 1. Targeted measures to control risk factors for vancomycin-resistant enterococci transmission and infection.

<table>
<thead>
<tr>
<th>Risk factor, by type of transmission</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Local cross-transmission</td>
<td></td>
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<tr>
<td>Poor hand hygiene</td>
<td>Increase the rate of hand hygiene compliance to at least 50–60%</td>
</tr>
<tr>
<td>High rate of antibiotic consumption</td>
<td>Antibiotic stewardship</td>
</tr>
<tr>
<td>Nursing shortage</td>
<td>Increase cohorting and the rate of hand hygiene compliance</td>
</tr>
<tr>
<td>Increased length of stay</td>
<td>Initiate active surveillance and cohorting and decrease length of stay</td>
</tr>
<tr>
<td>Environmental contamination</td>
<td>Disinfect surfaces</td>
</tr>
<tr>
<td>High prevalence of VRE among patients admitted</td>
<td>Initiate active surveillance, cohorting, and multi-institutional collaborative efforts for VRE control</td>
</tr>
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lead to the contamination of the hands of HCW ($\beta$, in formula 3) and the likelihood that contamination of other patients through the hands of HCWs will lead to overt colonization ($\beta$, in formula 3). Antibiotics such as clindamycin and cephalosporins provide VRE with selective growth advantages, whereas piperacillin may reduce intestinal VRE loads [21].

With the advent of linezolid, quinupristin/dalfopristin, and daptomycin, there are now antibiotics active against VRE. Elimination of carriage by these agents has a tremendous impact on VRE epidemiology in hospital settings, but there is a concern that using them for carriage suppression will accelerate the development of resistance [10, 11]. Indeed, emergence of resistance to these new antibiotics has already been described [22, 23].

**LIMITATIONS OF CURRENT MODELS**

The available models do not include other epidemiologic aspects of VRE transmission, such as direct patient-to-patient transfer and acquisition through environmental contamination. Although there are few data on person-to-person transmission, this route is relevant in the community and in long-term care facilities, where patients are more mobile. Under such circumstances, models of vectorborne disease provide less accurate results. Nevertheless, the reproductive number $R_0$ can be calculated with formula 1 and depends on the frequency of contacts between patients, the rates of transmission from patient to patient, and the duration of infectiousness.

Because VRE are very hardy microorganisms that survive on surfaces for days, the environment also affects transmission rates [24]. Transmission from environment can occur via HCWs’ hands and directly from environment to patient [25, 26]. As long as a patient’s immediate environment has a colonization and/or contamination status similar to that of the patient, the patient’s environment could be considered an extension of the patient, and the principles of the models of vectorborne disease should still apply.

**THE RIGHT TOOL FOR THE EPIDEMIC**

Optimal use of resources for infection control requires detailed information on the dynamics of VRE epidemiology. Knowledge only of the prevalence of VRE in the hospital unit might lead to false interpretations, even when that knowledge is based on surveillance cultures. For example, hospital units A, B, and C in figure 2 have the same endemic prevalence of 60%. In unit A, VRE colonization is mainly the result of local cross-transmission, and in unit C, most patients are admitted with VRE and cross-transmission is minimal. Infection-control practitioners should strive to determine the underlying mechanisms of endemicity, because the optimal approach for control differs. Hospital unit A requires aggressive infection control to limit cross-transmission, whereas unit C would benefit from a collaborative effort to limit the sources of VRE. Institutions face a “prisoner’s dilemma” situation. VRE control is expensive and is successful only if other facilities in the network also control VRE. Otherwise, the uncontrolled epidemic from one setting spills into the referral network [12]. The solution lies in collaborative action, and repeated interactions between institutions usually foster cooperation. Through active surveillance, institutions may gather information about the partners in the network, identify potential sources of VRE, and require institutions with high levels of transmission to adopt VRE control measures. In the long term, sharing information reduces VRE-related costs for all. This collaboration can be local or may involve external parties as arbiters. The Siouxland VRE Control Task Force (in areas of Iowa, Nebraska, and South Dakota) is an example of a successful, regional VRE control program that incorporated both local representatives and the Centers for Disease Control and Prevention [27].

If cross-transmission occurs frequently, as in hospital unit A (figure 2), further exploration of the causes of transmission is necessary. The most commonly encountered causes are a lack of compliance with infection-control measures, a high rate of antibiotic use, understaffing, an increased length of stay, and
an increased level of environmental contamination (table 1). If compliance with hand hygiene is low, efforts should be made to increase it. Studies quantifying the interactions of individual infection parameters are needed to provide evidence-based and quantitative recommendations. For now, it should be advised to increase levels of compliance with hand hygiene to at least 50%–60% and to implement cohorting where possible. Judicious use of antibiotics should be reinforced, and active surveillance should be instituted for patients with longer stays. Although understaffing has complex causes, its deleterious effects on nosocomial infection can be mitigated by higher rates of compliance with hand hygiene and the implementation of cohorting. Disinfection of surfaces is useful if there is heavy environmental contamination, and molecular fingerprinting can trace the source of an infection if there are reasons to think there is a common source or an epidemiologically important environmental reservoir.

CONCLUSION

Mathematical models are a time-honored tool of population biologists and offer many insights into VRE epidemiology and control. They formalize our current understanding of the epidemiology, integrate existing data, and anticipate outcomes for different scenarios of infection control. Models illustrate how VRE epidemiology in diverse institutions differs in the relative contributions of cross-transmission and influx of colonized patients, and in the various mechanisms of local transmission. They also highlight the phenomenon of decreasing returns that is associated with many interventions. It is important to quantify the most important routes of transmission, to break the weakest links in the chain of transmission, and to develop multi-institutional, collaborative efforts to contain the influx of VRE. Although model predictions are not unexpected, the optimal strategy for control of VRE is not always apparent. Our forecasting abilities are currently limited, as is our knowledge of the risk of transmission and the cost-effectiveness of interventions in different settings. With better data, our understanding of the underlying epidemiological dynamics and the accuracy of model predictions will improve, and control of VRE will become more effective.

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References


