The Impact of Persistent Gastrointestinal Colonization on the Transmission Dynamics of Vancomycin-Resistant Enterococci

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Vancomycin resistance among enterococci is increasing rapidly throughout the world [1]. The transmission dynamics of vancomycin-resistant enterococci (VRE) and factors contributing to their dissemination are complex [2]. Numerous variables and interactions need to be considered, including the duration of gastrointestinal VRE colonization, the number of patients and health care workers (HCWs), the frequency of patient contacts, and compliance with infection control practices. These dynamic interactions and their impact on the rate of VRE acquisition are difficult to investigate in classic clinical studies.

We developed a mathematical model to describe these nonlinear and dynamic interactions between patients and HCWs and to simulate patterns of VRE dissemination. A system of equations was formulated using parameter estimates obtained by direct observation of patient-HCW interactions and biological assumptions of VRE transmission. Using this baseline model, simulations were performed to quantify the contribution of various components of the model to the transmission dynamics of VRE and to predict their effects on the endemic prevalence of VRE. The setting of an outpatient long-term hemodialysis unit was used as the model for these interactions because it facilitated direct observation of a defined patient population. Furthermore, VRE is spreading rapidly in hemodialysis units [3–8]. The Centers for Disease Control and Prevention reported that the rate of dialysis centers with ≥1 patient harboring VRE increased from 11.5% to 34.1% in 1999 [3]. This exponential increase in the prevalence of VRE among patients receiving hemodialysis underscored the need to understand the transmission dynamics in this population.

Methods

Mathematical model. The model depicts the transmission dynamics of VRE in an outpatient hemodialysis unit and describes the endemic prevalence of VRE colonization reached over time among patients receiving chronic hemodialysis.

There are a total of \( N_r \) patients and \( N_h \) HCWs in the hemodialysis unit at baseline. Each patient enters the unit for 4 h, 3 times/week for hemodialysis treatment. At baseline, a proportion of patients will be colonized (\( Y_r \)) and uncolonized (\( X_r \)) with VRE, and a proportion of HCWs will have contaminated (\( Y_h \)) and uncontaminated (\( X_h \)) hands. Uncolonized patients become colonized with VRE through the hands of HCWs, which become contaminated with VRE after contact with a colonized patient. During each hemodialysis session, there are \( \alpha_p \) contacts between HCWs and patients. During each contact, uncolonized patients and uncontaminated HCWs have a certain probability of becoming colonized (\( \beta_p \)) or contaminated (\( \beta_h \)) with VRE. The duration of hand contamination (\( 1/\mu \)) and HCW compliance with hand hygiene (\( \eta \)), including hand washing or changing gloves between each patient contact, are considered in the model. Once colonized, patients revert to an uncolonized state after a certain period of time (\( 1/\gamma_p \)). New patients enter the dialysis unit to initiate dialysis (\( \Lambda \)), of which a proportion (\( \phi \)) may be colonized with VRE. Patients leave the dialysis unit permanently at death or temporarily when admitted to the hospital. The life expectancy among patients receiving chronic hemodialysis is equal to the total length of stay in the dialysis unit for uncolonized patients (\( 1/\gamma_h \)). A subset of uncolonized and colonized patients (\( X_h \) and \( Y_h \), respectively) will leave the dialysis unit temporarily when admitted to a hospital. During the length of hospital admission...
(1/\gamma_c), colonized patients (Y_p) do not contribute to the dissemination of VRE in the dialysis unit. A proportion (\omega) of uncolonized patients (X_p) may have acquired VRE during their hospitalization, before returning to the hemodialysis unit. A schematic diagram of the model is given in figure 1.

The model consists of 6 differential equations that describe VRE transmission among uncolonized and colonized patients (X_p and Y_p, respectively), uncontaminated and contaminated HCWs (X_h and Y_h, respectively), and uncolonized and colonized patients who leave the unit during an admission to the hospital and are later readmitted to the unit (X_a and Y_a, respectively; see the Appendix). To simplify the model, 2 assumptions were made. First, the model assumes that the environment does not contribute to the transmission dynamics of VRE. Although VRE has been recovered from inanimate surfaces, contamination is transient, with low colony counts [9]. Thus, it was assumed that the role of the environment in the dissemination of VRE is secondary to cross-transmission through the hands of HCWs. Second, since patients departing from the hemodialysis unit as a result of renal transplantation represent a small percentage of the population receiving hemodialysis, this factor was not entered into the model.

**Parameter estimates at baseline.** Parameter estimates were obtained from a 120-bed outpatient hemodialysis unit affiliated with Vanderbilt University Medical Center (VUMC; Nashville, TN). The number and length of hospitalizations at VUMC and the number of new admissions for the initiation of hemodialysis were obtained from a previous study describing the rate of VRE colonization after hospital admission was obtained from outpatient dialysis units [5, 6]. The fraction of newly colonized patients with VRE after hospital admission was obtained from a prospective surveillance study describing the rate of VRE acquisition among patients receiving chronic hemodialysis who were admitted to VUMC [7].

**Model simulations.** To describe the impact of varying specific parameters on the endemic level of VRE colonization over time in the hemodialysis unit, several model simulations were performed. These simulations were as follows: (1) varying the duration of VRE colonization (1/\gamma_c) from 12 to 52 weeks; (2) increasing the rate of VRE acquisition (\omega) in the hospital from 0% to 40%; (3) increasing compliance (\eta) with hand hygiene from 0% to 100%; (4) decreasing the ratio of patients to HCWs (\rho) from 8:1 to 1:1; (5) increasing the number of patients who are colonized with VRE when they go to the hospital for a temporary stay; and (6) decreasing the ratio of patients to HCWs (\rho) from 8:1 to 1:1.

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**Figure 1.** A compartment model of the transmission dynamics of vancomycin-resistant enterococci (VRE) in a chronic hemodialysis unit. The following variables were used: X_p (Y_p), the no. of uncolonized (colonized) patients in the clinic; Y_h, the no. of contaminated health care workers (HCWs) in the clinic; N_h, the total no. of HCWs in the clinic; X_a (Y_a), the no. of uncolonized (colonized) patients absent from the clinic for a hospital admission; a_p, the no. of contacts between HCWs and patients each session; b_p, the probability of a patient becoming colonized per session; b_h, the probability of an HCW becoming contaminated per session; \eta, HCW compliance with hand hygiene; 1/\gamma_c, the period of time before a colonized patient reverts to uncolonized state; \lambda, the rate at which new patients enter the clinic; \phi, the proportion of new patients already colonized; 1/\gamma_u, the length of hospital stay for a temporarily absent patient; and \omega, the fraction of uncolonized patients who become colonized during a temporary stay in the hospital.
initiating hemodialysis ($\phi$); and (6) varying the proportion of patients receiving chronic hemodialysis who were colonized at baseline in the unit ($Y_0$) from 0% to 30%.

**Basic reproductive number.** To quantify the impact of these simulations on the endemic prevalence of VRE over time, the basic reproductive number was defined: $R_0 = \frac{\alpha_p^0 f \beta_p \rho (1 - \eta)}{\mu (\eta + \gamma_p)}$. $R_0$ describes the expected number of patients who become colonized with VRE (secondary cases) as a result of 1 colonized patient (primary case). The value of $R_0$ depends only on the parameters in the model and is independent of the initial numbers of the patient and HCW populations (see Appendix). In the case that the acquisition parameter $\omega = 0$ (i.e., no colonized patients return from the hospital to the unit after temporary absence), the endemcity or extinction of the epidemic is predicted by $R_0$. If $R_0 > 1$, then VRE colonization becomes endemic in the dialysis unit as patients acquire VRE. If $R_0 < 1$, then secondary cases are insufficient to sustain the epidemic, and over time VRE colonization is eliminated from the dialysis unit. By computing the value of $R_0$ for each simulation, the effect on VRE dissemination can be quantified and compared in the case that $\omega = 0$. In the case that the acquisition parameter $\omega > 0$ (i.e., some patients return from the hospital to the unit as colonized after temporary absence), the epidemic always becomes endemic, whether $R_0 > 1$ or $R_0 < 1$. In this case, the percentage of colonized patients at endemicity can be predicted by the model in terms of the parameters and independently of the initial population values (see Appendix).

### Results

**Baseline model.** Initial values used in the baseline model are presented in Table 1, and parameter values are presented in Table 2. An observed compliance rate of 40% ($\eta = 0.4$), a patient:HCW ratio of 4:1 ($\rho = 4$), a 10% baseline prevalence of VRE among patients receiving chronic hemodialysis ($X_1[0] = 0.9N_p$ and $Y_0 = 0.1N_p$), and 0% colonization among new patients who are initiating hemodialysis ($\phi = 0$) were entered into the baseline model. Given a constant influx of patients into the hemodialysis unit who have acquired VRE de novo in the hospital at a rate of 20% and an efflux of colonized patients who die or who revert to an uncolonized state, the model predicts an endemic level over time of ~12% colonization among patients receiving chronic hemodialysis (figure 2). This endemic level will be reached over time, regardless of the number of patients who are colonized with VRE at the start of the epidemic. Furthermore, increasing the number of patients initiating hemodialysis who are colonized with VRE does not affect the prevalence of VRE (data not shown).

**Other model simulations.** Given an endemic prevalence of 12% predicted by the baseline model, the simulations demonstrated the following effects:

1. Increasing the duration of VRE gastrointestinal colonization ($1/\gamma_p$) from 12 to 52 weeks increased the endemic prevalence of VRE from 12% to 70% (figure 3A).

2. Eliminating VRE acquisition in the hospital ($\omega = 0$) was the only simulation that extinguished VRE from the dialysis unit. However, even if every patient acquired VRE in the hospital ($\omega = 1$), the peak prevalence would only reach 26% (figure 3B).

3. The effect on the endemic prevalence of decreasing the patient:HCW ratio was marginal for ratios < 4:1 but was significant for ratios > 4:1. Increasing the ratio to 8:1 ($\rho = 8$) resulted in a peak prevalence of 42%. When the ratio was decreased to 1:1 ($\rho = 1$), the prevalence decreased to 3% (figure 3C).

4. The effect on the endemic prevalence of increasing hand-hygiene compliance was marginal when compliance was > 50% but was significant when compliance was < 50%. Decreasing compliance to 0% ($\eta = 0$) resulted in a peak prevalence of 35%. When compliance increased to 100% ($\eta = 1$), the prevalence decreased to 3% (figure 3D).

5. If VRE acquisition in the hospital is eliminated ($\omega = 0$), then the patient:HCW ratio ($\rho$) can be increased from 1:1 to 4:1 with no effect on the prevalence. For example, if $\omega = 0$, then VRE elimination occurs for ratios of < 4:1 ($\eta < 4$). If acquisition is not eliminated, then increasing the ratio to < 4:1 is marginal but decreasing the ratio to > 4:1 is significant (figure 4A).

### Table 1. Initial values for the baseline mathematical model describing the transmission dynamics of vancomycin-resistant enterococci in an outpatient hemodialysis unit.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symbol</th>
<th>Initial Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncolonized patients</td>
<td>$X_p$</td>
<td>108</td>
</tr>
<tr>
<td>Uncontaminated HCWs</td>
<td>$X_0$</td>
<td>29</td>
</tr>
<tr>
<td>Colonized patients</td>
<td>$Y_p$</td>
<td>12</td>
</tr>
<tr>
<td>Contaminated HCWs</td>
<td>$Y_0$</td>
<td>1</td>
</tr>
<tr>
<td>Absent uncolonized patients</td>
<td>$X_s$</td>
<td>0</td>
</tr>
<tr>
<td>Absent colonized patients</td>
<td>$Y_s$</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE:** HCW, health care worker.

### Table 2. Parameter estimates/values for vancomycin-resistant enterococci (VRE) transmission in an outpatient hemodialysis unit.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of HCWs to patients</td>
<td>$\rho$</td>
<td>4</td>
</tr>
<tr>
<td>Contact rate</td>
<td>$\alpha_p$</td>
<td>12</td>
</tr>
<tr>
<td>Compliance with hand hygiene (%)</td>
<td>$\eta$</td>
<td>0.4 (40)</td>
</tr>
<tr>
<td>Probability of hand contamination per contact (%)</td>
<td>$\beta_p$</td>
<td>0.4 (40)</td>
</tr>
<tr>
<td>Probability of colonization per contact (%)</td>
<td>$\gamma_p$</td>
<td>0.06 (6)</td>
</tr>
<tr>
<td>Duration of hand contamination, weeks</td>
<td>$1/\mu$</td>
<td>0.01</td>
</tr>
<tr>
<td>Colonized patients initiating hemodialysis</td>
<td>$\phi$</td>
<td>0</td>
</tr>
<tr>
<td>Length of stay of patients in dialysis unit, weeks</td>
<td>$1/\gamma_p$</td>
<td>300</td>
</tr>
<tr>
<td>Duration of colonization, weeks</td>
<td>$1/\gamma_c$</td>
<td>12</td>
</tr>
<tr>
<td>New patients initiating hemodialysis per week</td>
<td>$\Lambda$</td>
<td>0.5</td>
</tr>
<tr>
<td>Length of a hospital admission, weeks</td>
<td>$\gamma_a$</td>
<td>1</td>
</tr>
<tr>
<td>Rate of VRE acquisition during hospitalization (%)</td>
<td>$\omega$</td>
<td>0.2 (20)</td>
</tr>
<tr>
<td>Rate uncolonized patients enter hospital</td>
<td>$\sigma$</td>
<td>0.01</td>
</tr>
<tr>
<td>Rate colonized patients enter hospital</td>
<td>$\tau$</td>
<td>0.01</td>
</tr>
<tr>
<td>No. of patients</td>
<td>$N_p$</td>
<td>120</td>
</tr>
<tr>
<td>No. of HCWs</td>
<td>$N_c$</td>
<td>30</td>
</tr>
</tbody>
</table>

**NOTE:** HCW, health care worker.
The effect of increasing hand-hygiene compliance ($h$) was similar to that of decreasing the patient:HCW ratio ($r$). If VRE acquisition in the hospital is eliminated ($v = 0$), then compliance with hand hygiene ($h$) can be decreased with no effect on the prevalence. For example, if $v = 0$, then VRE is eliminated when compliance is $> 40\%$ ($\eta > 0.4$). If acquisition is not eliminated, then increasing compliance to $> 50\%$ is marginal but decreasing compliance to $< 50\%$ is significant (figure 4B).

**Basic reproductive number ($R_0$).** The only simulations that resulted in extinguishing the epidemic were obtained by eliminating VRE acquisition in the hospital ($\omega = 0$) and requiring that the basic reproductive number $R_0 < 1$. If $\omega > 0$, then VRE will always remain endemic, regardless of the value of $R_0$. Compared with other simulations, when there is $0\%$ hospital acquisition, increasing the duration of colonization ($1/\gamma_c$) had the most impact on the number of secondary cases (figure 5). If colonization persists from 24 to 52 weeks, then $R_0$ increases from 2 to 4 (figure 5A). In contrast, the maximum value of $R_0$ is 1.5 if compliance ($\eta$) is decreased to 0 or if the patient:HCW ratio ($\rho$) is increased to 6:1 (figure 5B and 5C). The graphs in figure 6 show the dependence of $R_0$ on both colonization and hand-hygiene compliance (figure 6A), patient:HCW ratio and hand-hygiene compliance (figure 6B), and colonization duration and patient hand-hygiene compliance (figure 6C).

**Discussion**

Mathematical modeling was used to understand the transmission dynamics of VRE in a long-term hemodialysis unit and to estimate the effect of various factors and interventions on patient-to-patient transmission. Specifically, the relative contributions of the duration of VRE gastrointestinal colonization among patients, hospital acquisition of VRE, compliance with hand hygiene, and patient:HCW ratio were compared. The model predicted that the endemic prevalence of VRE within the unit would reach 12\%, irrespective of the number of patients initially colonized. This steady state would be achieved by a constant influx of newly colonized patients, who acquired VRE during a hospital admission, and a constant efflux of colonized patients dying or reverting back to an uncolonized state. The model also predicted that prolonged VRE gastrointestinal colonization among patients resulted in a substantial increase in the endemic prevalence of VRE and confirmed the benefits of infection-control measures in limiting VRE cross-transmission among patients.

The basic reproductive number $R_0$, defined as the number of secondary cases generated by a single colonized patient, was used to quantify the impact of these factors and interventions on the endemic prevalence of VRE. Among all model simulations, prolonging the duration of patient colonization generated the highest number of secondary cases. For example, increasing hand-hygiene compliance ($\eta$) was similar to that of decreasing the patient:HCW ratio ($\rho$). If VRE acquisition in the hospital is eliminated ($\omega = 0$), then compliance with hand hygiene ($\eta$) can be decreased with no effect on the prevalence. For example, if $\omega = 0$, then VRE is eliminated when compliance is $> 40\%$ ($\eta > 0.4$). If acquisition is not eliminated, then increasing compliance to $> 50\%$ is marginal but decreasing compliance to $< 50\%$ is significant (figure 4B).

**Figure 2.** Simulation of the transmission dynamics of vancomycin-resistant enterococci, assuming the initial values (at time 0) of $X_p(0) = 120$ (no. of uncolonized patients), $Y_p(0) = 0$ (colonized patients), $X_h(0) = 30$ (uncontaminated health care workers [HCWs]), $Y_h(0) = 0$ (contaminated HCWs), $X_a(0) = 0$ (absent uncolonized patients), and $Y_a(0) = 0$ (absent colonized patients) and the parameters in table 2. The graph shows the percentage of patients colonized as a function of time, in weeks, beginning at time 0 in an infection-free clinic. The epidemic is introduced by patients returning from the hospital.

**Figure 3.** Percentage of patients infected with vancomycin-resistant enterococci (VRE) in the endemic population, assuming the initial values in table 1 and the parameters in table 2. The colonization duration ($1/\gamma_c$) is varied from 1 to 50 weeks (A), the acquisition parameter ($\omega$) is varied from 0 to 1 (B), the patient:health care worker (HCW) ratio ($\rho$) is varied from 0 to 8 (C), and the hand-hygiene parameter ($\eta$) is varied from 0 to 1 (D).
explored [20, 21]. VRE, including the role of nutrition and immunity, need to be however, other factors influencing the ecological milieu of [19]. Since antimicrobial therapy is frequently unavoidable, practises and ultimately decrease unnecessary antibiotic exposure utilization programs can improve antimicrobial prescribing prac-
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are judged to be unnecessary [18]. Multidisciplinary antibiotic 
times more often than other patients, of which 20% of doses 
receiving hemodialysis, for example, receive vancomycin 11 
which may be for inappropriate indications [16–18]. Patients 
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multiple comorbid illnesses and frequent hospitalizations promote 
is particularly relevant to patients who harbor VRE, since mul-
paramount to controlling the dissemination of VRE. This issue 
VRE stool densities [14, 15], judicious use of these agents is 
Since antibiotic exposure promotes colonization with higher 
VRE stool densities [14, 15], judicious use of these agents is 
whether patients permanently eradicate VRE from their gastro-
the gastrointestinal tract, lower densities of VRE in the stool are associ-
ated with a lower risk of environmental and skin contamination, 
both prerequisites for patient-to-patient transmission [14, 15]. 
Since antibiotic exposure promotes colonization with higher 
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times more often than other patients, of which 20% of doses 
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utilization programs can improve antimicrobial prescribing prac-
tices and ultimately decrease unnecessary antibiotic exposure 
[19]. Since antimicrobial therapy is frequently unavoidable, however, other factors influencing the ecological milieu of 
VRE, including the role of nutrition and immunity, need to be 
explored [20, 21].

The model also predicted that the only intervention that 
would permanently eradicate VRE from the unit would be pre-
venting patient acquisition of VRE during a hospital admission, 
thereby abolishing the constant influx of newly colonized patients 
entering the unit. The complete elimination of VRE acquisition in 
the hospital setting may not be a realistic goal. However, 
identification of newly colonized patients at the time of read-
mission to the hemodialysis unit could be achieved by performing 
screening rectal surveillance cultures on patients recently 
released from the hospital. These patients would be placed on 
contact precaution and would no longer contribute to the 
spread of VRE within the hemodialysis unit [22]. The feasibility 
of this intervention, however, will require further study. In other 
health care settings, such as the intensive care unit, screening 
rectal cultures at admission extinguished VRE endemicity, with 
an estimated cost savings of $4,100/life/year [13, 23]. The pres-
ent model also predicted that VRE screening would require less 
compliance with hand hygiene to achieve similar prevalence 
rates of VRE endemicity over time. For example, 60% compli-

![Figure 4](https://example.com/figure4.png)

Figure 4. Model predictions of the endemic prevalence of vanco-
mycin-resistant enterococci, assuming the initial values in table 1 
and the parameters in table 2. The patient:health care worker (HCW) 
ratio \( \rho \) is varied from 0 to 8, and the acquisition parameter \( \omega = 0.0, 
0.2, \) and 0.4 \( (A) \). The hand-hygiene parameter \( \eta \) is varied from 0 to 
1, and the acquisition parameter \( \omega = 0.0, 0.2, \) and 0.4 \( (B) \).

![Figure 5](https://example.com/figure5.png)

Figure 5. The basic reproductive no. \( R_0 = \frac{\sigma^2 \beta \gamma_0 (1 - \eta)}{\mu (\gamma_0 + \gamma_1)} \) as a function of the duration of colonization \( 1/\gamma_1 \), in weeks 
(\( A \)), the hand-hygiene compliance parameter \( \eta \) (\( B \)), and the patient: health care worker (HCW) ratio \( \rho \) (\( C \)). The parameters are \( \alpha_0 = 12.0 \) 
(no. of contacts between HCWs and patients each session), \( \beta_0 = 0.4 \) 
(probability of a patient becoming colonized per session), \( \beta_1 = 0.06 \) 
(probability of an HCW becoming contaminated per session), \( 1/\mu = 1/100.0 \) 
(duration of hand contamination of an HCW), and \( 1/\gamma_1 = 
300.0 \) (length of stay in the dialysis clinic). The other parameters in 
\( R_0 \), are \( 1/\gamma_0 = 12.0 \) (length of time before a colonized patient reverts to uncolonized state), \( \eta = 0.4 \) (HCW compliance with hand hygiene), 
and \( \rho = 4 \) (ratio of patients to HCW), except when they are indepen-
dent variables in the plots. The epidemic extinguishes if \( \omega = 0 \) (fraction 
of uncolonized patients who become colonized during a temporary 
stay in the hospital) and \( R_0 < 1 \).
Figure 6. The extinction and endemic regions determined by the parameters in the basic reproductive no. \( R_0 = \frac{\alpha_p^2 \beta_p \rho (1 - \eta)}{[\mu \gamma_p + \gamma_c]} \) in the case that the acquisition parameter \( \omega = 0 \). The parameters are \( \alpha_p = 12 \) (no. of contacts between health care workers [HCWs] and patients each session), \( \beta_p = 0.4 \) (probability of a patient becoming colonized per session), \( \beta_c = 0.06 \) (probability of an HCW becoming contaminated per session), \( 1/\mu = 1/100 \) (duration of hand contamination of an HCW), \( 1/\gamma_c = 300 \) (length of stay in the dialysis clinic), and patient:HCW ratio \( \rho = 4 \) (1/\gamma_c and \( \eta \) are variables) (A), colonization duration \( 1/\gamma_c = 12 \) (\( p \) and \( \eta \) are variables) (B), and hand-hygiene compliance \( \eta = 0.4 \) (1/\gamma_c and \( \rho \) are variables) (C). The epidemic extinguishes in the regions in which \( R_0 < 1 \) and becomes endemic in the regions in which \( R_0 > 1 \).

Compliance with hand hygiene, instead of 100%, would be required to reach an endemic prevalence of 3% if the rate of VRE acquisition in the hospital decreased from 20% to 0%. Since compliance with hand hygiene is often poor and never is 100% [24, 25], the additional benefit of these concurrent interventions is important to consider.

Although the factors and interactions influencing VRE transmission may be similar in different health care settings, the magnitude of their contribution to cross-transmission may vary in different patient populations. For example, although the present model demonstrated a benefit from infection-control interventions, the impact of hand hygiene and number of HCWs on decreasing cross-transmission of VRE among patients was less than that predicted by a mathematical model set in the intensive care unit [13]. These differences may reflect more-frequent contact between patients and HCWs in the intensive care unit, compared with the hemodialysis unit. The effect of duration of gastrointestinal colonization in the intensive care unit model was not assessed, since patients were discharged from the unit after \(~\sim 10\) days. In other health care settings, including long-term care facilities, where patients are housed indefinitely with substantially fewer interactions with HCWs than in an intensive care unit setting, the duration of colonization may influence the endemic prevalence more than compliance with infection-control interventions, as predicted from this mathematical model set in the hemodialysis unit.

Limiting the dissemination of VRE within health care institutions has focused on infection-control practices. The present model and several other studies have demonstrated that interventions such as improving hand hygiene between patient contacts or decreasing the patient:HCW ratio decrease the rate of VRE cross-transmission among patients [13, 26–28]. Although the problems and corrective methods have been identified, compliance with these measures remains the major limiting factor in achieving lower rates of VRE colonization. The present theoretical model emphasizes additional directions in which to focus preventive efforts, including decreasing the length of gastrointestinal colonization and limiting hospital acquisition of VRE. Epidemiological investigations are needed to validate this conceptual framework and, in particular, to quantify the extent of VRE cross-transmission in outpatient hemodialysis units.

Appendix

Mathematical Model of a Vancomycin-Resistant Enterococci (VRE) Epidemic in a Hemodialysis Unit

The mathematical model of the VRE epidemic in a hemodialysis clinic is given by a system of differential equations for the following populations: uncolonized patients (\( X_s \)), colonized patients (\( Y_s \)), uncontaminated health care workers (HCWs; \( X_h \)), contaminated HCWs (\( Y_h \)), absent uncontaminated patients (\( X_a \)), and absent colonized patients (\( Y_a \)). Each population is a function of time \(( t \) in weeks and has prescribed initial values at time 0. The rates of change of these populations are governed by the following equations:

\[
\begin{align*}
\frac{dX_s}{dt} &= \Lambda - \alpha_p \beta_p (1 - \eta) \frac{Y_h}{N_h} X_s - \gamma_s X_s + \gamma_c Y_s - \sigma X_s \\
&
+ (1 - \omega) \gamma_c X_s ,
\end{align*}
\]

\[
\begin{align*}
\frac{dY_s}{dt} &= \alpha_p \beta_p (1 - \eta) \frac{Y_h}{N_h} X_s - \gamma_s Y_s - \gamma_p Y_s - \tau Y_s + \omega \gamma_c X_s + \gamma_c Y_s ,
\end{align*}
\]

\[
\begin{align*}
\frac{dX_h}{dt} &= -\alpha_p \rho \beta_p \frac{Y_h}{X_p + Y_p} X_s + \mu Y_h ,
\end{align*}
\]

\[
\begin{align*}
\frac{dY_h}{dt} &= \alpha_p \rho \beta_p \frac{Y_p}{X_p + Y_p} X_s - \mu Y_h ,
\end{align*}
\]

\[
\begin{align*}
\frac{dX_a}{dt} &= \sigma X_s - \gamma_c X_a ,
\end{align*}
\]

\[
\begin{align*}
\frac{dY_a}{dt} &= \gamma_c X_a ,
\end{align*}
\]
and

\[ \frac{dY_p}{dt} = \tau Y_p - \gamma_a Y_a. \]

The explanation of these equations is as follows (see figure 1): the change in uncolonized patients per week \((dX_p/dt)\) equals the gain \((\Lambda)\) of new admissions per week (all new admissions are assumed to be uncolonized), minus the loss \(\alpha_p\beta_p(1 - \eta)(Y_a/N_\text{h})X_p\) due to colonization, minus the loss \(\gamma_aX_a\) due to uncolonized patients leaving permanently, plus the gain \(\gamma Y_p\) due to colonized patients returning to uncolonized status, minus the loss \(\sigma X_p\) due to uncolonized patients leaving temporarily, plus the gain \((1 - \omega)\gamma X_a\) due to uncolonized patients returning from temporary absence. Here, \(\alpha_p\) is the total number of contacts of a patient with an HCW per week (the number of visits per week times the number of contacts per visit); \(\beta_p\) is the probability per contact that an uncolonized patient becomes colonized; \(\eta\) is the fraction of HCW compliance with hand hygiene (\(\eta = 0\) means no compliance and \(\eta = 1\) means perfect compliance); \(N_\text{h}\) is the total number of HCWs (\(N_\text{h}\) is assumed to be constant); \(Y_a/N_\text{h}\) is the fraction of contaminated HCWs; \(1/\gamma_a\) is the length of stay, in weeks, of an uncolonized or colonized patient; \(\sigma\) is the rate at which uncolonized patients leave temporarily; \(\omega\) is the fraction of uncolonized patients who leave temporarily and are later readmitted as colonized; \(\tau\) is the rate at which colonized patients enter the hospital; and \(1/\gamma\) is the duration of absence, in weeks, of patients who leave temporarily and are later readmitted.

The change in colonized patients per week \((dX_a/dt)\) equals the gain per case \(\alpha_p\beta_p(1 - \eta)(Y_a/N_\text{h})X_p\) due to colonized patients becoming colonized, minus the loss \(\gamma_aY_a\) due to uncolonized patients leaving permanently, minus the loss \(\gamma Y_a\) due to colonized patients returning to uncolonized status, minus the loss \(\tau Y_a\) due to colonized patients leaving temporarily, plus the gain \(\omega \gamma X_a\) due to formerly uncolonized patients returning from temporary absence as colonized, plus the gain \(\gamma Y_a\) due to colonized patients returning from temporary absence (assuming that colonized patients who were temporarily absent remain colonized). Here, \(1/\gamma\) is the duration, in weeks, of colonization of a colonized patient (i.e., \(\gamma\) is the reciprocal of the duration).

The change in the number of uncolonized HCWs per week \((dX_p/dt)\) equals the loss \(\alpha_p\beta_p[Y_p/(X_p + Y_p)]X_p\) due to contamination plus the gain \(\mu Y_p\) due to recovery from contamination. Here, \(\beta_p\) is the probability per patient contact that an uncolonized HCW becomes contaminated, \(\rho\) is the ratio of patients to HCWs (\(\rho\) is assumed to be constant), and \(1/\mu\) is the duration of contamination of an HCW. The change in contaminated HCWs per week \((dY_p/dt)\) equals \(-dX_p/dt\).

Finally, the change \(dY_p/dt\) in uncolonized patients who are temporarily absent equals the gain \(\alpha_X\) of uncolonized patients entering the hospital minus their rate of return to the clinic \(\gamma X_a\), and the change \(dY_a/dt\) in colonized patients who are temporarily absent equals the gain \(\tau Y_a\) from the colonized patient class minus their return \(\gamma Y_a\) to the clinic.

For a given set of parameters and initial conditions, the solutions of this system of equations are uniquely determined. In the examples presented in the present study, the solutions stabilized over time to equilibrium values, for which explicit formulas may be determined. The behavior of the solutions can be distinguished into the following 2 cases, depending on the fraction \((\omega)\) of returning colonized patients:

1. If \(\omega = 0\), then the asymptotic limit of \(Y_p(t)\) as \(t \to \infty\) depends on whether the basic reproductive number, \(R_0 = [\alpha_p^2 \beta_p \rho (1 - \eta)]/[\mu (\gamma_a + \gamma)],\) is \(> 1\) or \(< 1\). If \(R_0 < 1\), then the epidemic extinguishes: limit \(\to Y_p(t) = 0\), and limit \(\to Y_a(t) = N_\text{h}/\gamma_a\). If \(R_0 > 1\), then the epidemic becomes endemic: limit \(\to Y_p(t) = [\Lambda (R_0 - 1) \mu]/[\gamma_a (R_0 \mu + \alpha_p \beta_p \rho)] > 0\) and limit \(\to Y_a(t) = [\Lambda (\mu + \alpha_p \beta_p \rho)]/[\gamma_a (R_0 \mu + \alpha_p \beta_p \rho)].\)

2. If \(\omega > 0\), then the epidemic always becomes endemic:

\[
\text{limit } Y_p(t) = \frac{\Lambda (R_0 - 1) \gamma \mu + (\alpha_p \beta_p \rho - \mu) \gamma \sigma + \sqrt{[(R_0 - 1) \gamma \mu + (\alpha_p \beta_p \rho - \mu) \gamma \sigma]^2 - 4 \Gamma (\gamma \mu)}}{2 \gamma \mu + (\alpha_p \beta_p \rho - \mu) \gamma \sigma}
\]

and \(\text{limit } Y_a(t) = (N_{\text{h}}/\gamma_a) - \text{limit } Y_p(t)\), where \(\gamma = \gamma_a + \gamma\).

If \(\omega > 0\), then there is always a source of newly colonized patients returning from temporary absence, and the epidemic cannot be eliminated.

The formula above for the endemic state limit \(Y_p(t)\) in case 2 is always positive, whether \(R_0 > 1\) or \(R_0 < 1\), and is always greater than the value in the formula for the endemic state limit \(Y_p(t)\) in case 1. The asymptotic limits in both case 1 and case 2 depend on the parameters but not on the initial values at time \(t = 0\). However, the rate of convergence to the asymptotic limits (i.e., how fast the asymptotic limits are approached) depends on both the parameters and the initial values. The parameters in the formulas for the epidemic basic reproductive number \(R_0\) and the asymptotic limits of \(X_p, Y_p, X_a, Y_a\) and \(\gamma\) provide a means to predict the severity of the epidemic and to gauge the importance of such factors as hand-hygiene compliance, patient:HCW ratio, and screening of patients who leave temporarily.

References

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