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Major article

Modeling the regional spread and control of vancomycin-resistant enterococci

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Background: Because patients can remain colonized with vancomycin-resistant enterococci (VRE) for long periods of time, VRE may spread from one health care facility to another.
Methods: Using the Regional Healthcare Ecosystem Analyst, an agent-based model of patient flow among all Orange County, California, hospitals and communities, we quantified the degree and speed at which changes in VRE colonization prevalence in a hospital may affect prevalence in other Orange County hospitals.
Results: A sustained 10% increase in VRE colonization prevalence in any 1 hospital caused a 2.8% (none to 62%) average relative increase in VRE prevalence in all other hospitals. Effects took from 1.5 to >10 years to fully manifest. Larger hospitals tended to have greater affect on other hospitals.
Conclusions: When monitoring and controlling VRE, decision makers may want to account for regional effects. Knowing a hospital's connections with other health care facilities via patient sharing can help determine which hospitals to include in a surveillance or control program.

Vancomycin-resistant enterococci (VRE) are a worldwide problem, having spread to at least 18 countries across 6 continents,[1] and enterococci are the second most common organism recovered from catheter-associated infections and skin and soft tissue infections in the United States.[2] Annual VRE burden estimates in US hospitals range from a conservative 20,931 infections (95% confidence interval [CI], 12,596-29,266), to a more liberal 85,586 (95% CI, 55,986-115,186) in 2004.[3] The number of US hospitalizations with VRE discharges more than doubled between the years 2000 and 2006, with an incidence of 9.48 hospitalizations with VRE infection per 100,000 population and 6.51 per 100,000 hospitalizations in 2006.[4]

Because patients can remain colonized with VRE for long time periods,[5,6] VRE might spread among health care facilities. At least 1 regional outbreak has been described.[7] Our previous social network analysis demonstrated that hospitals in the same county exchange extensive numbers of patients with each other through direct transfers and patients visiting multiple hospitals over time.[8] Although the growing problem of VRE has prompted individual hospitals to develop control measures and monitoring, hospitals may not have considered how VRE prevalence in other hospitals may affect these efforts. How much can 1 hospital's action (or nonaction) to reduce VRE prevalence affect another regional facility?

Understanding dynamic relationships among hospitals in a region could have important policy and decision making implications.[9,10] Without considering such relationships, decision makers may misattribute changes in a hospital's VRE burden to actions within that hospital, potentially leading to the allocation or removal of resources for control measures that may or may not appear to be effective. Lack of regional perspective may also cause officials to overlook the influence of other hospitals when planning VRE surveillance, prevention, or control programs; thus, it would be instructive to understand the degree to which same-region

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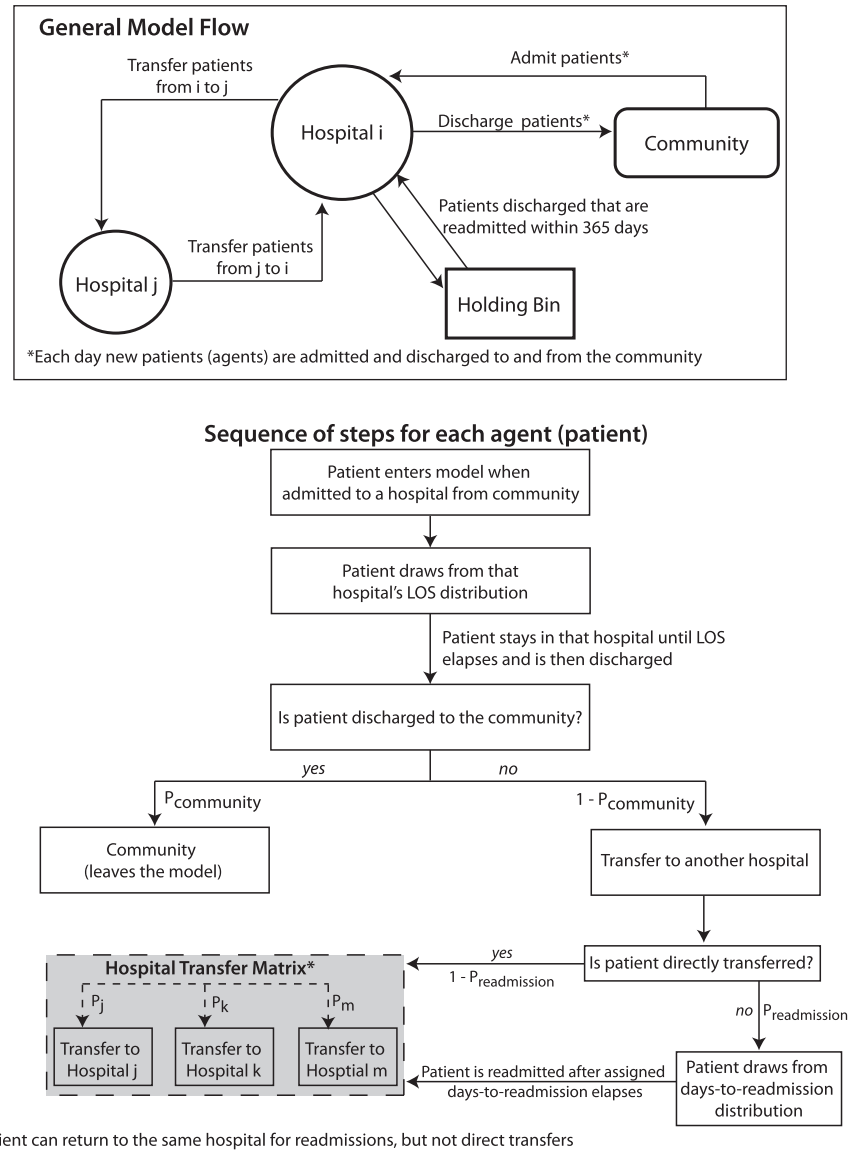

Fig 1. Schematic flow of patients in, out, and within the hospital network and the sequence of steps for each agent (patient) in Regional Healthcare Ecosystem Analyst, an agent-based model of patient flow. *LOS*, Length of stay.

hospitals may affect one another. We developed an agent-based model (ABM) of all adult acute care hospitals in Orange County, California, that simulated changes in VRE colonization prevalence in each hospital and determined how much and how quickly it affected other hospitals.

METHODS

We obtained 2006-2007 patient level admission and transfer data for all 29 adult acute care hospitals (3 children's hospitals were excluded) in Orange County[11] (serving a total population of 3.1 million). Of the 29 hospitals, 5 are long-term acute care facilities (LTACs), which primarily treat patients who have prolonged high-level medical needs. The data included length-of-stay (LOS), location where patient was admitted from or discharged to, and an encrypted patient identification code that allowed us to track patient movement between hospitals. Our model was constructed using probabilities generated from this real-world data by calculating hospital-specific proportions of 2006 patients discharged to the community, transferred from each hospital, or readmitted within 365 days.

Deterministic equation-based model (EBM)

We first developed a deterministic EBM that used mathematical equations to represent patient flow among the Orange County hospitals and community to guide the development of and help cross-validate the ABM (details available from the authors upon request).

Stochastic ABM

Because the EBM cannot account for the effects of parameter distributions or stochasticity (ie, fluctuations or errors in parameter values), this motivated development of the Regional Healthcare Ecosystem Analyst, a stochastic simulation ABM. The Regional Healthcare Ecosystem Analyst is a simulation model of all 29 acute care hospitals serving adults in Orange County and virtual patients

(each represented by a computational agent) moving amongst these hospitals and to and from the community, based on actual data.

Figure 1 is a diagram of our model's structure. Each hospital has a certain number of beds (based on hospital-specific data). Simulations proceed in 1-day time steps; each day patients enter each hospital, filling the beds. Upon hospital admission, each patient draws from that hospital's specific LOS distribution (see Table 1), which determines how many days a patient stays in that hospital. Once this LOS elapses, the patient leaves the hospital and has a probability of being discharged to the community (leaving the model) vs being transferred to another hospital. Each patient who is transferred to another hospital has a probability of direct transfer (immediately after discharge) vs a readmission (within 365 days with an intervening stay in the community), determined from actual facility data.[12] Each patient who is eventually readmitted draws from a days-to-readmission distribution (lognormal) that determines the time until readmission. Once this assigned days-to-readmission elapses, the patient has a probability of returning to the same hospital vs going to another hospital. These probabilities are obtained from Orange County data.

Each progressive day, new patients enter each hospital (representing admissions) and are assigned LOSs, whereas patients whose LOSs have elapsed leave the hospital (representing discharges and transfers).

Each patient either is identified as colonized or not colonized with VRE. The daily prevalence of VRE colonization in a hospital is equal to the number of VRE-colonized patients divided by the total number of patients in that hospital that day. We assumed that once patients acquired VRE, they did not lose colonization (ie, persistent colonization), because the duration of colonization can be rather lengthy, lasting over a year,[5,6,13] which is longer than the length of time most patients remain in the system in our simulation.

Table 1
Hospital characteristics and hospital dependent length-of-stay (LOS) distributions

	Hospital characteristics		Hospital-specific LOS (d)		Hospital-specific LOS for patients colonized with VRE (d)	
Hospital	2006 Admissions (n)	Mean LOS (d)	Mean (lnLOS)	Standard deviation (lnLOS)	Mean (lnLOS)	Standard deviation (lnLOS)
1*	388	34.0	3.3	0.7	3.4	0.64
2*	947	39.3	3.3	0.9	3.4	0.82
3*	3,082	9.0	1.7	0.8	2.4	1.2
4	7,111	5.7	1.6	0.7	2.2	0.6
5	15,058	5.8	1.5	0.7	2.3	0.7
6	4,540	5.7	1.4	0.7	2.2	0.8
7	21,488	4.6	1.4	0.6	2.0	0.7
8	9,202	3.9	1.2	0.5	1.9	0.6
9	2,481	4.5	1.3	0.6	1.9	0.6
10	6,932	4.0	1.3	0.6	2.0	0.5
11	2,366	8.0	1.6	0.7	2.0	0.5
12	14,347	6.8	1.5	0.8	2.3	0.8
13	13,755	5.3	1.5	0.6	2.3	0.7
14	14,281	4.8	1.4	0.6	2.2	0.6
15	16,095	4.8	1.4	0.7	2.2	0.8
16	4,028	4.3	1.3	0.6	2.0	0.6
17*	966	12.5	2.4	0.5	2.5	0.8
18	6,535	5.7	1.5	0.7	2.1	0.6
19	11,375	5.0	1.4	0.7	2.3	0.7
20	4,339	5.4	1.5	0.6	2.4	0.9
21	12,020	4.2	1.3	0.6	1.8	0.7
22	8,951	5.3	1.5	0.7	2.1	0.7
23	11,505	4.6	1.3	0.6	2.0	0.6
24	2,773	6.5	1.6	0.7	1.6	0.7
25	15,967	4.7	1.3	0.6	1.9	0.7
26	26,292	4.9	1.4	0.6	2.1	0.7
27	4,810	5.1	1.4	0.7	1.7	0.6
28	4,881	5.0	1.4	0.7	2.0	0.7
29*	1,819	4.8	1.1	0.5	2.7	0.4

lnLOS, natural log of the LOS (mean and standard deviation calculated after natural log conversion); *VRE*, vancomycin-resistant enterococci.
*Long-term acute care facility.

Experiments and sensitivity analyses

The primary purpose of the EBM was to help validate the Regional Healthcare Ecosystem Analyst program (ie, convergence of results when both were calibrated with similar parameters and divergence when stochasticity/parameter distributions were incorporated into the ABM). This consisted of calculating the differences between the changes in VRE colonization prevalence for each model. Simulations showed a median difference of 7.94×10^{-6} (range, 2.7×10^{-8} to 0.0029) between the models when utilizing the same input parameters; therefore, all reported results came from the Regional Healthcare Ecosystem Analyst. Our experiments comprised 5 categories: (1) moderate increase in VRE prevalence in 1 hospital; that is, increasing prevalence from 5%-15% (analogous to a moderate single center VRE outbreak); (2) large increase in VRE prevalence change in 1 hospital; that is, increasing prevalence from 5%-50% (analogous to a large single center VRE outbreak); (3) regional change in VRE prevalence; that is, moderate (5%-15%) and large (5%-50%) increase in the 5 hospitals in and around the City of Orange (analogous to a multicenter VRE outbreak); (4) free-rider experiments (ie, if all Orange County hospitals except 1 complied with VRE control measures [decreasing prevalence from 15%-1%], would that single rogue hospital benefit from the other hospitals' efforts?); and (5) countywide VRE control (ie, can countywide control be achieved by decreasing its prevalence in a subgroup of hospitals—such as the largest hospitals—by average daily census)?

Sensitivity analyses accompanied each set of experiments: LOS analysis varied LOS from 1 day to actual hospital-specific distributions; LOS for VRE-colonized patients colonized analysis looked at the effects of applying longer LOSs to VRE-colonized patients (Table 1) (we assumed the LOS would be approximately 1.55-fold longer for VRE-colonized patients compared with the overall LOS, based on a previous study[14]); increased rate of interfacility transfer or readmission for VRE-colonized patients analysis explored the effects of making VRE-colonized patients 30% more likely to be either directly transferred between hospitals or readmitted within 1 year; and time to hospital readmission analysis explored effects of immediate hospital readmissions vs readmission delays.

For each experiment we determined the relative change in VRE prevalence (ie, new equilibrium prevalence compared with pre-perturbation levels) and the time to steady state, defined as the amount of time it takes for VRE colonization prevalence in a hospital to achieve its new equilibrium. Results from the Regional Healthcare Ecosystem Analyst represent averages of all simulation realizations (50,000) for each experiment.

RESULTS

Moderate increase in VRE prevalence in 1 hospital

Figure 2 utilizes bubble maps to display results from a set of 29 experiments. Each column within the bubble maps represents 1 experiment perturbing VRE colonization prevalence from 5%-15% in the hospital listed at the top and the resulting effects in the other hospitals in the county listed on the *y*-axis. Each row thus represents the resulting relative change in VRE colonization prevalence in the hospital on the *y*-axis when each hospital in the county experiences a VRE outbreak 1 at a time. Few hospitals could escape the effects of changing the VRE epidemiology in 1 hospital because the presence of bubbles in nearly every row of each column reflects each hospital's potential widespread influence throughout Orange County. When

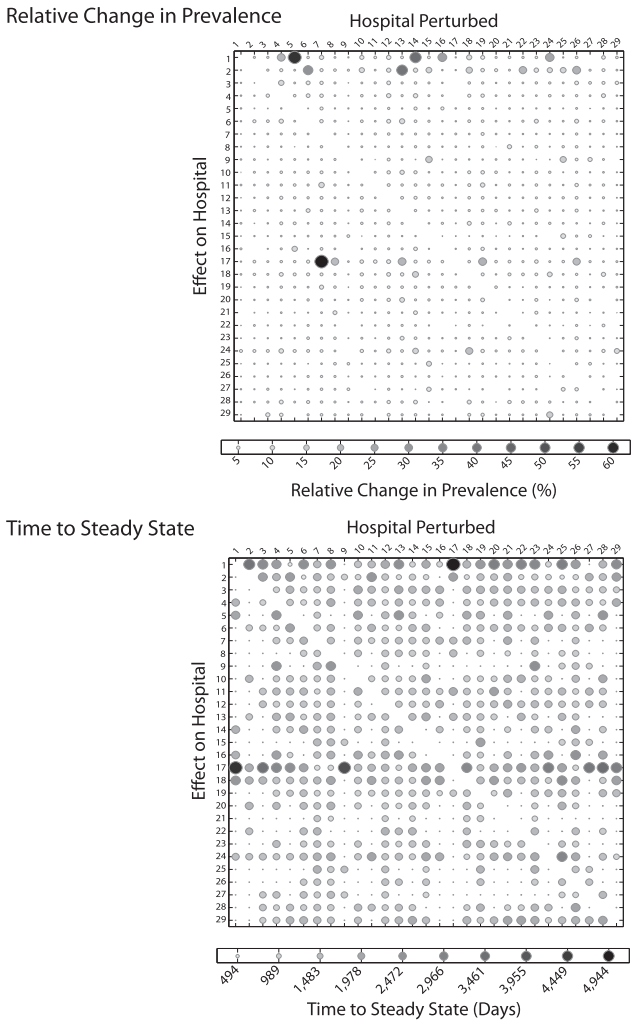

Fig 2. Bubble maps showing the change in vancomycin-resistant enterococci (VRE) prevalence and time to equilibrium of a moderate (5%-15%) VRE prevalence increase in single hospitals on each of the other hospitals in the county when patient length of stay was based on hospital-specific length-of-stay distributions and VRE status, had an increased rate of interfacility transfer for VRE patients, and when time to readmission varied. For each, the larger and darker the bubble, the greater the VRE prevalence change or the longer it took to reach equilibrium.

patient LOS was based on hospital-specific LOS distributions and VRE status, VRE-colonized patients had an increased rate of interfacility transfer, and time to readmission varied (Fig 2), a moderate VRE prevalence change in any 1 hospital resulted in an average relative increase of 2.8% (range, 0%-61.9%) in other Orange County hospitals. Putting this in terms of annual admissions, a 2.8% VRE increase translates to 11 VRE-colonized patients per 388 yearly admissions or 898 VRE-colonized patients in a hospital with 32,082 yearly admissions. On the other hand, a 61.9% increase translates to 240 VRE patients per 388 yearly admissions or 19,859 additional VRE patients for 32,082 annual admissions.

In general, the larger the hospital with an increased VRE prevalence, the greater the effect it had on the other hospitals. The greatest overall relative change in VRE colonization prevalence occurred in 2 LTACs when the hospitals with which they shared the most patients experienced outbreaks; 1 experienced a rise in VRE prevalence of 57.5% and the other 61.9% in response to outbreaks in their most closely affiliated hospital.

Changes in hospital VRE prevalence were not substantially affected by changes in patient LOS, changes in interfacility transfer, and time to readmission; overall, the average relative prevalence change ranged from 2.2%-2.8%. Changing only the likelihood of interfacility transfers or readmissions among VRE patients caused a slight decrease, with the maximum relative change shifting from 82.3%-74.6%. Only adding a delay for hospital readmissions slightly decreased the average relative prevalence change (range, 2.1%-2.8%).

Most hospitals did not reach their new equilibrium until after 1.5 years (Fig 2). Although equilibrium prevalence was not sensitive to patient LOS and time to readmission, time to equilibrium was affected. When readmissions were immediate, it ranged from 41.2-94.4 days when LOS increased from 1 day to a hospital-specific distribution based on VRE status. Delaying the time to readmission increased this substantially (range, 1.3-2.5 years). There was no difference between time to equilibrium for LTACs vs other hospitals.

Large increase in VRE prevalence change in 1 hospital

Increasing the VRE colonization prevalence to 50% expectedly augmented the affect on the network. The average relative prevalence change (range, 10.4%-11.1%) was more pronounced compared with moderate outbreaks (range, 2.2%-2.8%). The maximum relative prevalence increase (287.6%) occurred in a LTAC in response to a large outbreak in its most closely affiliated hospital. Time to steady state was also substantially longer (range of average time, 23-345 years). There were no notable differences in the times to equilibrium between hospitals and LTACs.

Regional change in VRE prevalence

Experiments boosting VRE colonization prevalence in the hospitals around the City of Orange had an even more notable effect on the rest of the Orange County hospitals. A 15% prevalence increase in this geographic cluster resulted in an average relative 9.83% (range, 2.4%-77.4%) VRE colonization prevalence increase in all other hospitals. A 50% change resulted in a 44.6% average relative increase (range, 10.8%-351.3%).

Free-rider experiments

These experiments demonstrated that a hospital could gain some benefits when all other hospitals decreased their VRE colonization prevalence. The free-riding hospital could experience a relative decrease ranging from 6.6%-89.1% (average, 24.7%) in prevalence when all other hospitals dropped their prevalence from 15%-1%. LTACs realized the largest decreases (range, 20.7%-89.1%). The maximum relative decrease among all other non-LTAC hospitals was 36.6%. Time to steady state ranged from 18.3 days-2.6 years (average, 1.8 years).

Countywide VRE control

Table 2 shows how each hospital was affected when different numbers of Orange County hospitals achieve total VRE control (0% prevalence); that is, how many hospitals need to be part of a countywide control program to achieve noticeable effects throughout the county.

DISCUSSION

Our study demonstrates how extensive patient sharing among different hospitals in a single region substantially influences VRE burden in those hospitals. We found that even hospitals at opposite ends of a large county can affect each other because patient sharing

Table 2
Relative change in prevalence (%) in hospitals not implementing vancomycin-resistant enterococci (VRE) control measures in simulating the achievement of countywide VRE control

	No. of hospitals implementing VRE control measures					
	2	7	12	17	22	27
Hospital	Relative change in prevalence (%)					
1	−4.20	−39.5	−64.0	−78.9	−80.3	*
2	−12.8	−48.4	−65.5	*	*	*
3	−5.2	−10.9	−14.3	−20.7	*	*
4	−3.8	−11.3	−18.7	*	*	*
5	−3.1	*	*	*	*	*
6	−6.0	−17.4	−24.5	−31.4	*	*
7	*	*	*	*	*	*
8	−2.8	−6.7	−14.8	*	*	*
9	−1.9	−21.2	−22.1	−22.6	−26.5	−26.5
10	−2.8	−11.3	−18.0	*	*	*
11	−9.6	−15.1	−22.9	−26.5	−29.3	*
12	−3.7	*	*	*	*	*
13	−3.1	*	*	*	*	*
14	−1.6	−6.5	*	*	*	*
15	−1.5	*	*	*	*	*
16	−2.1	−10.6	−17.2	−19.2	−19.7	*
17	−49.3	−67.1	−82.7	−94.9	−96.2	*
18	−2.8	−10.7	−24.4	*	*	*
19	−5.0	−9.9	*	*	*	*
20	−4.4	−12.8	−18.3	−21.2	*	*
21	−0.9	−3.1	*	*	*	*
22	−1.2	−2.8	*	*	*	*
23	−2.9	−9.0	*	*	*	*
24	−2.2	−10.5	−22.0	−36.0	−39.5	*
25	−1.5	*	*	*	*	*
26	*	*	*	*	*	*
27	−4.0	−13.2	−13.9	−15.1	*	*
28	−1.7	−6.2	−14.9	−21.2	*	*
29	−2.1	−6.1	−10.7	−15.4	−19.6	−24.8

*Hospitals that have implemented control measures.

is not always tied to geographic proximity. Even the smallest and least connected hospitals still affected VRE burden in other regional hospitals. Moreover, a hospital can knowingly or unknowingly free-ride on other hospitals' VRE control efforts, with increasing benefits gained as more and more hospitals achieve control. We suggest that fully appreciating the fluctuations in a given hospital's VRE prevalence may require studies and surveillance across regional facilities rather than just looking at cause and effect within the hospital itself. This is particularly true when regional hospitals have extensive patient sharing. Knowing a hospital's connections with other hospitals via both direct and indirect patient sharing can be important. We previously reported that patient sharing is often greatly underappreciated. When compared with the number of direct patient transfers between hospitals, patients who have an intervening stay at home or elsewhere before being readmitted to another facility constitute >50% of the total Orange County patient sharing.[8]

The other key take-home point is the extended time horizon over which epidemiology studies and surveillance should occur. As our study indicates, the effects of a moderate rise in endemic VRE prevalence in 1 hospital can take months and often years to fully manifest across a region, so current effects seen may reflect changes and control (or lack of control) policies instituted in neighboring facilities a long time ago. Thus, declaring a control strategy a success or failure may be premature if the effects from other hospitals' strategies are not understood from prior months or years.

Greater communication among regional hospitals could facilitate improved design of VRE studies and surveillance. Because financial and operational alliances among hospitals can drive patient sharing,[15] further understanding these alliances and other coordinated efforts between facilities who share patients can improve our understanding of VRE spread. Similarly, lowering barriers to cooperation and collaboration among hospitals (eg, developing regional control programs, coordinating VRE control campaigns, and performing regional research studies) could favorably influence regional VRE prevalence as has been shown in at least 1 study.[16] Finally, we demonstrate the potential utility of models in assisting the planning and interpretation of epidemiologic studies, quality improvement strategies, and public health surveillance. Models can forecast which hospitals may be affected to what degree and how long these effects may take to transpire, saving considerable time, effort, and expense.

Limitations

Computer models are simplifications of real life and cannot capture all complexities and heterogeneities that exist.[17] Our baseline VRE prevalence for LTACs may be underestimates; higher prevalence in LTACs would only enhance the spread of VRE throughout the hospitals in the county. Although a large diversity of hospitals and hospital types were included, it is unclear how generalizable our findings may be to other counties. Because the focus of this study was to elucidate how patient movement alone could influence the observed VRE prevalence, our model did not include the transmission of or selection pressure on VRE, 2 potential areas for future evaluations.

CONCLUSIONS

VRE surveillance and control measures could be more effective and more elucidative if they include all or a large subset of hospitals across a region. Knowing a hospital's connections with other health care facilities via patient sharing can help determine which hospitals to include in a surveillance or control program. Because the effects of VRE colonization prevalence change in 1 hospital can take months to years to fully manifest, patience and long-term follow-up may be essential when tracking VRE control.

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