Carbapenem-resistant Acinetobacter baumannii (CRAB) infections are increasing, and they are associated with an increased risk of mortality in hospitalized patients. Linear regression is commonly used to identify concurrent trends, but it cannot quantify the relationship between risk factors and resistance. We developed a model to quantify the impact of antibiotic consumption on the prevalence of CRAB over time. Data were collected from January 2007 to June 2013 from our institution. Quarterly antibiotic consumption was expressed as defined daily dose/1,000 inpatient days. Six-month prevalence of CRAB was expressed as a percentage of all nonrepeat A. baumannii isolates tested. Individual trends were identified using linear regression. Antibiotic consumption from 2007 to 2011 was input as a step function in a relationship with CRAB. Model fit was evaluated by visual inspection and the residual sum of squares. The final model was validated using the best-fit (95% confidence interval) parameter estimates and antibiotic consumption to predict CRAB prevalence from January 2012 to June 2013. Cefepime, ertapenem, and piperacillin-tazobactam consumption and CRAB prevalence increased significantly over time. CRAB prevalence was best correlated to ertapenem (use sensitive; $r^2 = 0.76$), and accounting for additional concurrent antibiotic use did not significantly improve model fit. Prospective validation with ertapenem consumption correlated well with CRAB observations, suggesting good predicting ability of the model. Our model provided the quantitative impact of antibiotic consumption on CRAB. We plan to further refine this model to account for multiple risk factors. Interventions should focus on controlling risk factors with the highest impact on resistance.

The prevalence of carbapenem-resistant Acinetobacter baumannii (CRAB) is escalating in all parts of the world (1, 2). Locally, carbapenem resistance is found in almost 50% of all blood isolates of Acinetobacter species within Singapore (2). CRAB is implicated in a wide range of nosocomial infections and is associated with many outbreaks within institutions (3). Many first-line antibiotics are ineffective for CRAB infections, resulting in increased risk of mortality and morbidity in hospitalized patients (4–6). With limited new therapeutic agents on the horizon, there is a greater emphasis on controlling risk factors associated with the rise in CRAB and reducing its transmission.

The development of CRAB appears to be associated with multiple risk factors. These factors can be antibiotics, such as imipenem, 3rd-generation cephalosporins (7), or any prior antibiotic treatment (8, 9), all of which have been associated with CRAB. Nondrug risk factors, such as surgery (9), duration of hospitalization (8), and previous admission to an intensive care unit (7, 8, 10), have also been associated with CRAB.

Risk factors associated with resistance are traditionally identified in case-control studies (11). Simple linear regression analyses are commonly used to explore individual trends of factors and of resistance over the same time frame, and significant associations between trends are then examined by correlational analysis (12–15). However, correlation between trends is limited in determining the quantitative relationship between risk factors and resistance, because the trends may be far from linear. Without a good understanding of the relative impact of risk factors on resistance over time, it is difficult to prioritize countermeasures and design long-term strategies. A more robust quantitative relationship would guide the use of finite resources for tackling resistance.

In addition to correlation analysis, model structures such as time series and transfer function analysis have been suggested as an alternative with a more realistic description of the relationship between risk factors and resistance over time (11, 16). The idea behind the combined autoregressive integrated moving average (ARIMA) time series/transfer function analysis is as follows: a model with random inputs is used to account for fluctuations of resistance over a time period. Then, an alternative model that includes a deterministic input (e.g., amount of antibiotic over time) is formulated. If this model generates predictions of resistance closer to the observed values, it is logical to infer that the antibiotic has an effect on resistance. While this idea provides better insight than simple correlation, it employs an ARIMA structure, which is inherently linear and therefore useful over a limited range of resistance values. To address this issue, in this study we developed a nonlinear dynamic model to capture the dynamic effect of various risk factors on resistance. We implemented this idea to quantify the relationship between risk factors and the development of CRAB. This would guide the use of limited resources by enabling the prioritization of intervention(s) with the greatest impact on CRAB development.
**RESULTS**

**CRAB prevalence.** Overall, there were 4,341 nonrepeat *A. baumannii* isolates tested from January 2007 to June 2013, and 3,414 were nonsusceptible to imipenem or meropenem (overall CRAB prevalence was 78.6%). More than 200 isolates were tested every 6 months. Using linear regression, a significant increase in CRAB was seen from 2007 to 2011 ($r^2 = 0.45; P = 0.001$).

**Antibiotic consumption.** The average antimicrobial use over the study period was 16.3 DDDs per 1,000 inpatient days. Piperacillin-tazobactam was the most highly utilized antibiotic, with a mean DDD of 36.7 per 1,000 inpatient days, followed by ertapenem, meropenem, imipenem, and cefepime. The linear fit confirmed a significant increase in cefepime ($r^2 = 0.85$), ertapenem ($r^2 = 0.58$), and piperacillin-tazobactam ($r^2 = 0.91$) consumption from 2007 to 2011 ($P < 0.001$ for all). However, consumption of meropenem did not increase significantly over time. Similarly, imipenem consumption had a nonsignificant decrease over the same period.

**Measure of infection control adherence.** The total numbers of hand rub and hand wash bottles utilized over the same time frame were approximately 160,000 and 260,000, respectively. The mean quarterly utilizations of hand rub and hand wash bottles were 57 and 94 bottles per 1,000 inpatient days. Linear fit confirmed that utilization of hand wash had a significant decrease over the 5-year period, ($r^2 = 0.27; P = 0.02$), while the utilization of hand rub had a nonsignificant increase.

**Mathematical modeling.** Among the 3 model structures explored, the best fit was obtained using a linear dynamic model structure with nonlinearity in the input (antibiotic consumption), as shown in equation A3 of Appendix 1. Ertapenem consumption (Fig. 1A) was found to be the best single predictor of the observed CRAB prevalence ($r^2 = 0.76$) (Fig. 1B), followed by piperacillin-tazobactam. The best-fit parameter estimates are shown in Table 1. We have also briefly examined quarterly CRAB prevalence. Overall, antibiotic consumption was found to predict the 6-month prevalence of CRAB better. Hence, further model exploration focused on 6-month CRAB prevalence.

Accounting for a time delay of 3 months with antibiotics did not improve the model fit ($r^2 < 0.5$ for all antibiotics). An attempt to account for concurrent piperacillin-tazobactam use on top of ertapenem consumption similarly did not significantly improve the fit of the model, despite using a wide range of weighting parameters. We also attempted to account for a negative factor concurrently with ertapenem. Accounting for either hand wash or hand rub utilization concurrently with ertapenem did not improve model fit with a nominal range of hand hygiene parameters (data not shown).

**Validation of the model.** Model validation was performed using the best-fit parameter estimates (including the 95% confidence interval limits) and ertapenem consumption from January 2012 to June 2013 (Fig. 1A). Using only the most impactful risk factor identified, the predicted 95% CI of CRAB prevalence from the nonlinear model was in general agreement with actual observed CRAB values (Fig. 2).

**DISCUSSION**

Tracking drug resistance among pathogens is a major research area in epidemiology. Simple correlation is commonly employed to explore concurrent trends over the same time frame between variables (such as antibiotic consumption or infection control ad-
herence) with resistance (12–14). However, it cannot quantify the relationships between risk factors. In our study, we found that the increase in carbapenem-resistant *A. baumannii* grossly coincided with the increase in cefepime, ertapenem, and piperacillin-tazobactam consumption. These variables appeared related to CRAB, as shown by the linear regression results. Typically, efforts would be put in place to reduce the consumption of all 3 antibiotics concurrently to tackle the rising development of CRAB. Without knowledge of the quantitative relationship between antibiotics and CRAB, it would not be possible to prioritize interventions toward the antibiotic with the greatest impact on resistance. The anticipated effect of different restriction strategies cannot be projected as well.

Alternative modeling approaches have been proposed as a way forward to address this pitfall (16). Since simple correlation of linearly approximated trends is limited to describing a monotonic increase or decrease over time, it cannot effectively account for oscillating trends over time. There are alternative models better suited to address the effect of cyclical antibiotic selective pressure (11). ARIMA models can account for fluctuations of variables over time and estimate correlations between them. However, they cannot be customized to account for inherently nonlinear behavior, such as the ceiling effect of an output variable (i.e., resistance values in the range of 0 to 1) (11). In prior work, we have used different modeling approaches to study the pharmacokinetics and pharmacodynamics of antibiotics as they relate to resistance development in an individual host (20–22). In this study, we employed similar mathematical frameworks to study the development of CRAB in a hospital at the system level (20). Conceptually, this can be thought of as treating our entire hospital as a single patient. We evaluated different model structures based on the premise that an increase in development of CRAB is associated with increasing antibiotics consumption, since it is one of the most important risk factors published in the literature (7–9). Our model design also incorporated a bacterial fitness cost that would lead to a natural decline of resistance in the absence of selective pressure. To ensure the clinical relevance of our model, its structure was such that the resistant proportion would be between 0 and 1 at all times. Finally, to substantiate the utility of the model, we used the best-fit parameter estimates and ertapenem consumption from January 2012 to June 2013 to predict CRAB prevalence.

The correlation of resistance to antibiotic consumption appeared to be best characterized by the model structure with linear resistance dynamics and a nonlinear risk factor effect. This model added to conventional analysis by differentiating among antibiotics whose consumption had a significant impact on CRAB (i.e., use sensitive) and those which were use insensitive. In contrast to cefepime, our model suggested that ertapenem and piperacillin-tazobactam were "use-sensitive" antibiotics since their cyclical consumption patterns were significantly correlated to the level of

![FIG 1](https://example.com/fig1.png) 
**FIG 1** Institution quarterly ertapenem consumption (A) and model fit to the data ($r^2 = 0.762$) (B).

![FIG 2](https://example.com/fig2.png) 
**FIG 2** Predictive performance of the model.

### TABLE 1 Final parameter estimates of the best-fit model

<table>
<thead>
<tr>
<th>Antibiotic(s)</th>
<th>$r^2$</th>
<th>$C_{rate}$</th>
<th>$C_{level}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem*</td>
<td>0.76</td>
<td>0.08 ± 0.06</td>
<td>3.70 ± 0.94</td>
</tr>
<tr>
<td>Piperacillin-tazobactam*</td>
<td>0.72</td>
<td>0.08 ± 0.11</td>
<td>9.07 ± 3.37</td>
</tr>
<tr>
<td>Cefepime</td>
<td>0.68</td>
<td>0.01 ± 0.14</td>
<td>0.001 ± 0.03</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.68</td>
<td>0.02 ± 0.04</td>
<td>1.02 ± 2.07</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.68</td>
<td>0.02 ± 0.03</td>
<td>0.20 ± 5.67</td>
</tr>
</tbody>
</table>

* Parameter estimates are shown as means ± standard deviations. *, use-sensitive antibiotic.
CRAB prevalence. This knowledge could guide antibiotic stewardship policies and direct the use of limited resources toward more impactful measures to control resistance.

In addition to the basic model, several additional features were briefly explored. Previous modeling studies had shown that when changes in antibiotic consumption were made, corresponding changes in infection rates occurred within several weeks to months (11). In our study, no improvement in model fit was achieved by considering a quarterly time delay. Since CRAB prevalence was collected in 6-month cycles, subtle changes could already have been captured within the same collection time frame. We also evaluated the effect of multiple antibiotics concurrently. Since both ertapenem and piperacillin-tazobactam were shown to be use sensitive, we explored whether accounting for the consumption of these 2 antibiotics simultaneously would improve model fit. However, when we accounted for ertapenem and piperacillin-tazobactam using a wide range of relative weights (as reflected by the parameter $\alpha$), we did not find any improvement of fit to the data. Our attempt to account for negative risk factors with the utilization of hand wash and hand rub bottles similarly did not improve the fit of the model. All mathematical models are simplifications of the interactions between selected input factors and an observed output (23). Our model may have oversimplified the actual interaction between risk factors. Hence, further exploratory studies are still needed to refine the model to better describe the relationship between multiple risk factors and CRAB prevalence.

Despite using only ertapenem consumption data, the prospective predictions of CRAB were in general agreement with observed values, demonstrating reasonable predicting ability of our model. Our simple mathematical model represents an improvement in the understanding of the development of CRAB. Using tangible epidemiological data, this model is a proof-of-concept attempt to model resistance beyond an individual host (20). Using these predictions, our model could be used to guide institutional policies to control CRAB in a more efficient manner.

In contrast to findings of previous studies in Pseudomonas aeruginosa (12, 24, 25), we found that ertapenem consumption was associated with a rise in CRAB prevalence. Ertapenem is presumed to have a lower potential to induce resistance in P. aeruginosa or A. baumannii, given the intrinsic resistance in both organisms. A previous study found that CRAB in Singapore was attributed to a wide variety of carbapenemases (26). A high level of selective drug pressure from ertapenem could have driven the dissemination and selection of carbapenem resistance observed. We did not study the resistance mechanisms of CRAB in our institution. Further studies are needed to examine the role of ertapenem in the development of CRAB.

There are several limitations to our prototype framework. Currently, we have a number of possible model structures to account for different positive and negative risk factors. We hope to further refine our model in order to develop a general structure which can broadly account for multiple risk factors concurrently. We also did not account for intrahospital variability (e.g., between general wards and intensive care units), since our model evaluated the data at an institutional level. As with standard compartmental analyses, we assumed instantaneous and homogenous distribution within the institution. We focused on the overall pattern of antibiotic consumption and resistance compiled from different patient care units. However, a more specific prediction could be undertaken using a similar approach for any individual patient care unit. We also did not account for the impact of hospital and intensive care unit length of stay, hospital readmissions, prevalence of long-term acute care, or skilled nursing facility transfers, since these data were unavailable to us in the aggregate. Finally, defined daily doses might not represent overall antibiotic consumption very well in pediatric patients and patients requiring dosing adjustment based on end organ functions. Alternative measures, such as days of therapy, have been proposed (2, 27) and can also be used as model inputs.

Our study demonstrated the utility of a simple mathematical model to determine the quantitative impact of antibiotic consumption on CRAB. The model provides a general framework for future refinement, which can potentially incorporate additional nondrug variables beyond just antibiotic consumption (e.g., antimicrobial stewardship interventions, infectious disease consultations, ratio of nurse staffing, or isolation room occupancy rates). It is anticipated to be used as a decision support tool to identify risk factors with the highest impact on resistance and to guide the prioritization of interventions.

APPENDIX

To quantify the impact of antibiotic consumption on resistance over time, we developed and evaluated three dynamic model structures. Overall, the rate of change of resistance was modeled as a composite function of selective pressure and natural regression.

In our first model, the rate of change of resistance $\frac{dR(t)}{dt}$ is assumed to be correlated nonlinearly to both antibiotic consumption ($A$) and the instantaneous resistance proportion $R(t)$, as shown in equation A1, where $C_{\text{rise}}$ and $C_{\text{fall}}$ (defined below) are parameters to be estimated.

The term $[1 – R(t)]$ constrains the rate of change of resistance to 0 when the maximum resistance proportion $R(t) = 1$ is reached.

$$\frac{dR(t)}{dt} = (C_{\text{rise}}A - C_{\text{fall}}) \times R(t) \times [1 - R(t)] \tag{A1}$$

The qualitative behavior of the solution $R(t)$ of equation A1 for different levels of $A$ is graphically described in Fig. A1. The solution $R(t)$ is approximately exponential for values of $R(t)$ near 0 or 1, in which cases the nonlinear equation A1 is approximately linear (for constant $A$) as $\frac{dR(t)}{dt} \approx (C_{\text{rise}}A - C_{\text{fall}}) \times R(t)$ or $\frac{dR(t)}{dt} \approx (C_{\text{rise}}A - C_{\text{fall}}) \times [1 - R(t)]$, respectively.

The second model assumes a nonlinear relationship between antibiotic consumption and rate of change of resistance. The rise in resistance is linked to antibiotic consumption, and the natural resistance regression is linked to instantaneous resistance proportion, as shown in equation A2.

$$\frac{dR(t)}{dt} = [C_{\text{rise}}A - C_{\text{fall}}R(t)] \times [1 - R(t)] \tag{A2}$$

FIG A1 Qualitative behavior of solution $R(t)$ of equation A1 for different levels of $A$. 

5242 aac.asm.org Antimicrobial Agents and Chemotherapy
The qualitative behavior of the solution $R(t)$ of equation A2 for different levels of $A$ is graphically described in Fig. A2. The solution $R(t)$ is approximately exponential for values of $R$ near 0 or 1, in which cases the nonlinear equation A2 is approximately linear (for constant $A$) as $d[R(t)/dt] \sim C_{\text{rise}}A - C_{\text{fall}}R(t)$ or $d[R(t)/dt] \sim (C_{\text{rise}}A - C_{\text{fall}}I) \times [1 - R(t)]$, respectively.

In a third model, a broad nonlinear relationship is presumed between the rate of change of resistance and antibiotic consumption. The physiological limits are controlled at a local level, as shown in equation A3. The function $f$ must satisfy the following criteria: $f(0) = 0$ and $f(∞) \rightarrow 1$, in order to limit the rate of change of resistance to 0 when antibiotic consumption is sufficiently large. $C_{\text{rise}}$ is a parameter to be estimated.

$$\frac{dR(t)}{dt} = C_{\text{rise}}[f(A) - R(t)] \quad (A3)$$

A unique feature of this model is that an equilibrium resistance level, other than the system limits (i.e., 0% or 100%), could be attained. Many model structure options are possible using this general nonlinear framework. An example of such a function is shown in equation A4, where $C_{\text{level}}$ is a parameter to be estimated.

$$f(A) = \frac{A}{A + C_{\text{level}}} \quad (A4)$$

The theoretical relationship is graphically described in Fig. A3. By modifying the basic structure of the nonlinear model (equation A3), we also attempted to account for additional variables concurrently (equation A5). To address an additional positive risk factor ($B$), the nonlinear function was modified as shown in equation A6. To address an additional negative risk factor ($N$), the nonlinear function was modified as shown in equation A7. In both cases, $\alpha$ is a (weighting) parameter to be estimated.

$$\frac{dR(t)}{dt} = C_{\text{rise}}[f(A, B) - R(t)] \quad (A5)$$

$$f(A, B) = \alpha\left(\frac{A}{A + C_{\text{level}}} + (1 - \alpha)\left(\frac{B}{B + C_{\text{level}}}\right)\right) \quad (A6)$$

$$f(A, N) = \left(\frac{A}{A + C_{\text{level}} + \alpha N}\right) \quad (A7)$$

Abbreviations: $A$, antibiotic consumption at time $t$; $R(t)$, proportion of resistant population at time $t$; $C_{\text{rise}}$, a parameter linking $A$ to the rise of resistance over time; $C_{\text{fall}}$, a parameter linking the rate of change of resistance to $A$ and bacterial fitness cost; $C_{\text{level}}$, a parameter linking $A$ to the proportion of resistant population at equilibrium.

ACKNOWLEDGMENTS

We thank Brenda Ang, Li-Min Ling from the Department of Infectious Diseases, Prabha Krishnan from the Department of Microbiology, Bee-Fong Poh from the Infection Control Unit, and Wan-Peng Lim and Christine Teng from the Department of Pharmacy for their assistance throughout this project.

This work received no specific funding from any companies or institutions.

REFERENCES


17. CLSI. 2010. Performance standards for antimicrobial susceptibility testing; 20th informational supplement. CLSI M100-S21. CLSI, Wayne, PA.


