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Evaluating Relationships Between Antimicrobial Use and Bacterial Resistance: Comparison of the Statistical Power Achieved for Different Regression Methods

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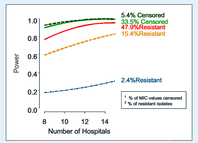
ABSTRACT

Background: Although antimicrobial use has been linked to resistance, many studies fail to identify an association. One limitation is the qualitative (ranked) nature of susceptibility data (sensitive, intermediate, and resistant). As demonstrated by a model describing the relationship between decreased susceptibility and increased use of levofloxacin (ICAAC 2003, K-1397), regression modeling of continuous MIC values is possible. The relative statistical power of these approaches is of interest.

Methods: Using simulated MIC data based on the above-described model for levofloxacin susceptibility and use, linear regression accommodating censored MIC values (censored regression) at the isolate level was compared to simple linear regression modeling of the % of isolates collected at an institutional level that were resistant, and to logistic regression modeling of isolates (i.e., with a dichotomous outcome by isolate, resistant or non-resistant). The power of each method to detect the model relationship was evaluated.

Results: Not unexpectedly, power for each method increased with increasing numbers of hospitals and number of isolates. Power was generally higher for censored regression than other approaches across all conditions, especially with high censoring or a low % of resistance. For example (see Figure below), although the power of logistic regression was maximized at % resistance = ~ 50%, the power for censored regression was higher, even with moderate censoring.



Conclusions: Analysis of MIC data is more sensitive than qualitative susceptibility data, and thus increases the likelihood of identifying risk factors for resistance development.

INTRODUCTION

Since the introduction of antimicrobial agents, analyses of epidemiological data have consistently demonstrated associations between increased antimicrobial use and increased bacterial resistance. However, not all studies evaluating the relationship between use and resistance have demonstrated a statistically significant association. In such cases, this could be due to a genuine lack of association, small sample size, limited duration of observation, poor quality of data and/or limitations of study design.

An important limitation of institutional-based analyses involving antimicrobial use and bacterial resistance is the qualitative (or ranked) nature of microbiological susceptibility data available for analysis. Microbiologic data is usually obtained from hospital antibiograms which show the proportion of isolates that were sensitive, intermediate or resistant to an agent of interest over a given study period. Until recently, the more quantitative form of antimicrobial susceptibility data (i.e., the minimum inhibitory concentration (MIC)) was not utilized. A limitation of analyzing qualitative susceptibility is that relationships between potential risk factors and bacterial resistance can only be detected when a relatively large proportion of a bacterial population crosses the MIC breakpoint for resistance.

Previously, we described the relationship between increased out-patient levofloxacin use and susceptibility of community-acquired *S. pneumoniae* isolates using censored regression. Using simulation and a simplified version of the relationships described by that model, these analyses were undertaken to compare the relative statistical power of different regression methods to detect relationships between antimicrobial use and bacterial resistance.

OBJECTIVE

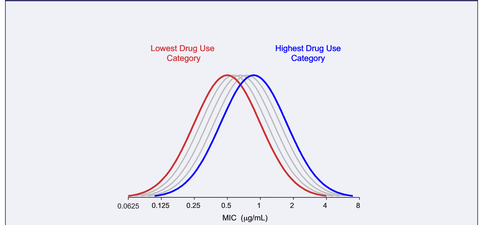
To describe and assess the available statistical power for detecting relationships between antimicrobial use and bacterial resistance using simulation and modeling methods chosen based on the nature of the collected data. In particular, to determine if analyses of individual isolate data using MIC values provide greater statistical power than analyses of clusters of isolates collected at the institutional level.

METHODS

The following steps describe the generation of the simulated MIC data:

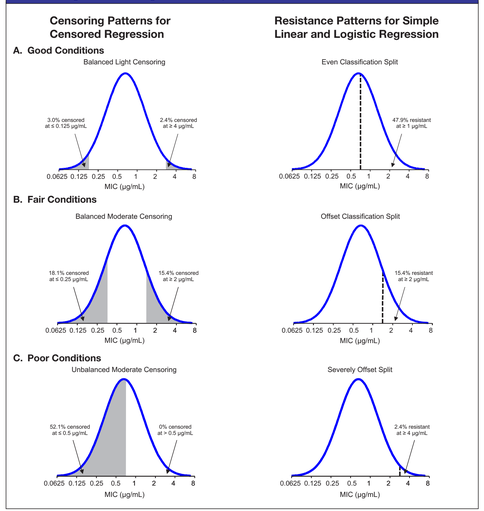
- The simulated dataset was based on the original observed dataset which was gathered from the following sources:
  - Antimicrobial susceptibility, patient- and institution-specific data for *S. pneumoniae* blood isolates were collected from patients in US hospitals participating in the SENTRY Antimicrobial Surveillance Program (1997-2002).
  - Annual regional quinolone usage data (1997-2002) were obtained from Intercontinental Medical Statistics (IMS) and were matched using designated "Metropolitan Statistical Areas" to the geographical region surrounding each SENTRY Program hospital.
- The primary outcome variable for the original dataset was the *in vitro* activity of levofloxacin against *S. pneumoniae,* which was measured by the reference broth microdilution minimum inhibitory concentration (MIC).
- The number of institutions in the simulated dataset ranged from 8 to 18, while the number of isolates collected per institution per year ranged from 4 to 10.
- Levofloxacin use in the simulated dataset was handled in the following manner:
  - Drug use was defined as an ordinal categorical variable with 5 levels, ranging from least to most use.
  - The 1997 drug use category for each hospital was assigned at random according to a uniform distribution among the 3 lowest use levels.
  - Treating drug use categories as integers, a random yearly increase in the category level was assigned for each institution according to a continuous uniform distribution over the interval from 0.5 to 1.
  - The yearly increase in drug use category was applied to each subsequent year for each hospital based on rounded integer values.
  - Log_2 MIC values were created with a model equation that assigned a mean value of -1 (i.e., MIC = 2^{-1} = 0.5 µg/L) to the lowest drug use category, and an increase to the mean log_2 MIC of 0.2 units with each increase in drug use category. Based on this model, coefficients of 0.2, 0.4, 0.6, and 0.8 were assigned for the drug use categories of 2, 3, 4, and 5, respectively. Therefore, the overall shift in log_2 MIC was 0.8 across the spectrum of levofloxacin use (Figure 1).

Figure 1. MIC distributions stratified by drug use category



- A normally distributed residual error with standard deviation of 1 was added to each simulated log_2 MIC value.
- Finally, the log_2 MIC values were rounded to the nearest integer so that the resulting MIC values would be powers of 2.
- As shown in Figure 2, censored MIC and resistance patterns under censoring and resistance classification conditions ranging from 'good' to 'poor' were imposed upon the simulated MIC data to approximate different scenarios.

Figure 2. Censored MIC and resistance patterns for censored, simple linear and logistic regression under good, fair and poor conditions



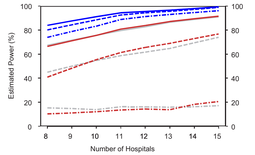
- Censored regression models were used to assess for relationships between bacterial susceptibility (using MIC values for individual isolates) and drug use; MIC data represented the outcome (dependent) variable.
- Using simple linear regression, the relationship between drug use and bacterial susceptibility was tested among clusters of isolates collected at the institutional level (outcome variable = % of isolates that were resistant); Using logistic regression, this relationship was tested among isolates classified as resistant or non-resistant.
- Statistical power was estimated for censored, simple linear and logistic regression methods by computing the percent of simulations for which the test of the relationship between drug use and bacterial susceptibility was significant at an α= 0.05.
- Graphs were produced to display the estimated power for different numbers of institutions (range 8 to 18) and different numbers of isolates per hospital (range 4 to 10).

RESULTS

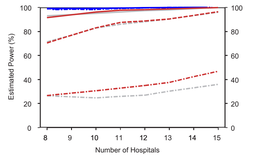
- As expected, the simulations demonstrated that statistical power increased as either the number of hospitals or the number of isolates collected per hospital increased (Figure 3).
- Statistical power was similar between the simple linear and logistic regression analyses of MIC values for isolates which were classified as resistant or non-resistant.
- Power for the censored regression analyses of censored MIC values was superior to both the simple linear and logistic regression methods, even when a larger proportion of MIC values was censored (see estimated power under poor conditions shown in Figure 3).

Figure 3. Estimated statistical power for censored, simple linear and logistic regression analyses

a. 4 isolates per hospital



b. 7 isolates per hospital



c. 10 isolates per hospital

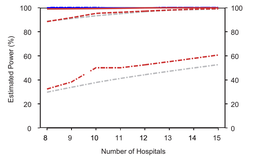


Figure Legend

CONCLUSIONS

- In comparison to statistical methods applied to isolates merely classified as resistant or non-resistant, statistical power was greater for censored regression using measured MIC values collected at the isolate level.
- Appropriately planned data collection, including the use of MIC values and censored regression, provide the potential to detect relationships between antimicrobial use and bacterial resistance using smaller samples than necessary for analyses of antibiogram data collected by institution.
- Furthermore, evaluation of factors predictive of increases in MIC values allows for the detection of shifts in the MIC distribution (even relatively small shifts) much earlier, thus allowing for interventions prior to emergence of alarming rates of bacterial resistance.
- Long-standing national and international surveillance programs such as the SENTRY Antimicrobial Surveillance Program, which collect extensive isolate-, patient- and institution-specific data, provide the opportunity to gain insights about the predictors of resistance using smaller but richer datasets.

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