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Advancing Antimicrobial Resistance Surveillance

An Empirical Approach to Deriving a Composite Drug Resistance Index for Urinary Tract Infections

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Background

The threat of antibiotic resistance has severe implications on the treatment of infectious diseases. It has been estimated that 2 million people in the United States acquire serious bacterial infections that are resistant to antibiotic treatments and 23,000 people die each year as a direct result of these infections[1]. Communicating the importance of antibiotic resistance to constituencies outside of infectious diseases and microbiology is increasingly important in order to galvanize action. Such audiences may not readily identify with information designed for specialized fields; long lists of specific organisms and antibiotic classes may mean little to lay decision makers. Some have called for work toward "A Dow Jones Industrial Average" – like measure which relates to a meaningful change in the impact of antibiotic resistance on health in society.

Following Laxminarayan and Klugman[2] who have published a method of calculating a "drug resistance index" for a specific organism, we sought to further develop this index in two ways:

1) We aimed to calculate a drug resistance index (DRI) for a common, clinically relevant syndrome, cystitis (caused by various bacterial species) for which antibiotics are generally prescribed empirically
2) We aimed to inform this model not only by population based antibiotic utilization data, but by exact estimates of indication-specific utilization for cystitis

Methods

Antibiotic utilization data between 2007 and 2010 were obtained from the BC PharmaNet database of outpatient prescriptions for oral antibiotics. Relevant drug classes in the analysis included penicillins with extended spectrum, first- and third-generation cephalosporins, sulfonamides and trimethoprim, fluoroquinolones, and nitrofuran derivatives. Prescriptions were linked to diagnostic codes for cystitis (ICD-9 codes 595.x) from the BC Medical Service Plan (MSP) billing database.

Antibiotic resistance (non-susceptibility) data were obtained from BC Biomedical Laboratories for *Escherichia coli*, *Enterococcus spp.*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* and restricted to isolates obtained from urine samples between the years 2007 and 2010.

For the microbiological approach, DRIs were calculated according to the formula:

$$DRI = \sum_{k} \sum_{i} \rho_{ikj}^{t} q_{ikj}^{t} w_{ij}$$

ρ_{ikj}^{t} is the proportion of urinary isolates for organism *i* non-susceptible to drug class *k* at time *t* for sub-group *j* (e.g., overall, sex, age group, sex-age)

q_{ikj}^{t} is the proportional utilization rate for drug class *k* used to treat cystitis caused by organism *i* at time *t* for sub-group *j*. Note, for the microbiological approach, not all drug classes are used for each organism *i*.

w_{ij} is a weighting factor based on the proportion of urinary isolates tested for each organism *i*. for sub-group *j*

For the empirical approach, proportional utilization rates were held constant across uropathogens for drug class k at time t; resistance rates for uropathogens inherently resistant to a given drug class were assumed to be 100%.

Both approaches included a static (implementation of a baseline proportional utilization rate for each year) as well as an adaptive (implementation of the year-specific proportional utilization rate) version of the equation.

Percentile confidence intervals (CIs) were calculated using non-parametric bootstrap methods with m=1,000 simulations performed on an approximately 10% sample drawn at random from the full dataset. Analyses were performed separately for adults ≥15 years old and children <15 years old due to differences in antibiotic measurements between these groups (i.e. defined daily doses (DDD) per 1000 person-days for adults and total prescriptions per 1000 person-days for children). Trends over time were assessed using the non-parametric Spearman Rank test. All analyses were performed using SAS 9.3 statistical software (SAS Inc., Cary, NC).

Results**

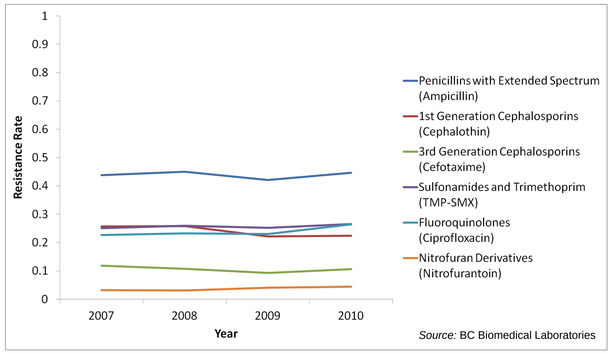

Figure 1. Proportion of *E.coli* isolates non-susceptible to relevant drug classes among adults ≥15 years old. *E.coli* comprised 78% of urinary isolates in the sample.

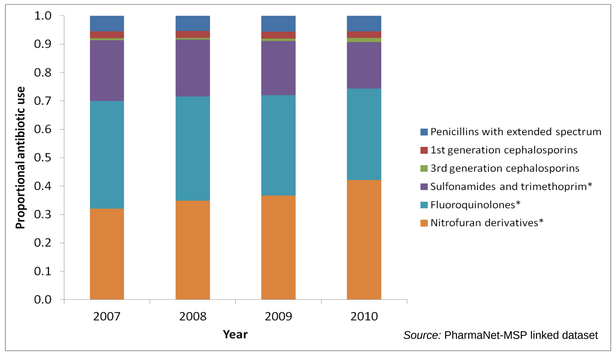

Figure 2. Proportional use of antibiotics for cystitis among adults ≥15 years old.

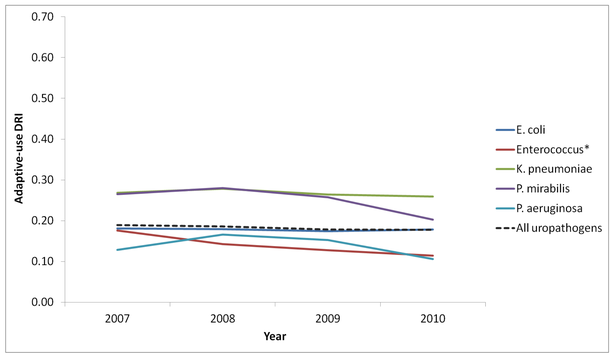

Figure 3. Adaptive-use DRI for each pathogen among adults ≥15 years of age calculated using the microbiological approach. The composite, weighted DRI across all uropathogens is shown in the bold, dashed line.

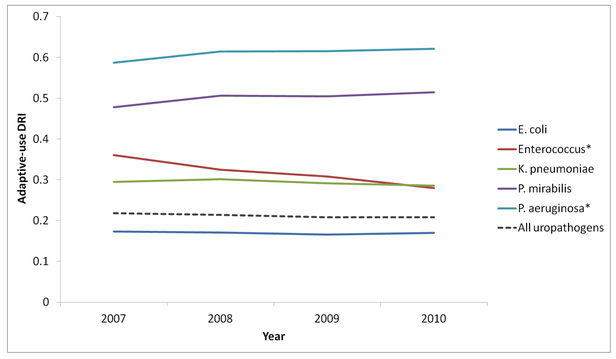

Figure 4. Adaptive-use DRI for each pathogen among adults ≥15 years of age calculated using the empirical approach. The composite, weighted DRI across all uropathogens is shown in the bold, dashed line.

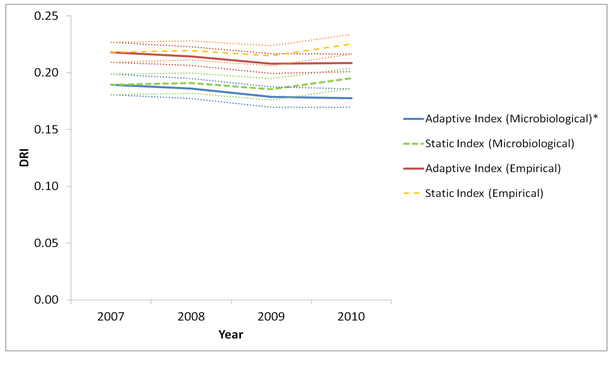

Figure 5. Adaptive-use and static-use composite drug resistance indices (DRIs) for adults ≥15 years of age calculated using the microbiological and empirical approaches.

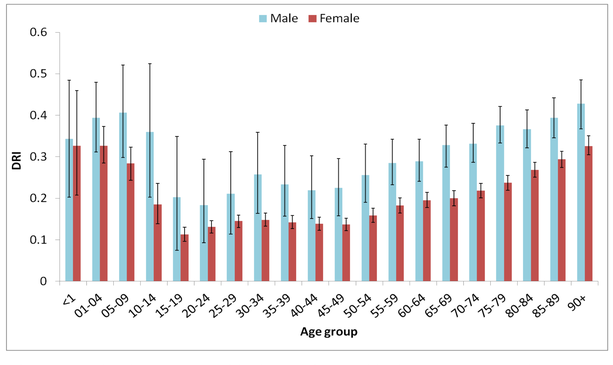

Figure 6. Adaptive-use, empirical DRIs for cystitis, by age group and sex, over all years (2007-2010) with 95% confidence intervals.

* Trends over time are statistically significant according to the non-parametric Spearman Rank test (p<0.01).

** Please note the values presented here differ slightly from those submitted in the abstract due to modifications in analyses

Key Findings

- Using the microbiological approach, DRIs calculated among adults ≥ 15 years of age decreased from 18.9% (95% CI = 18.0% to 19.9%) in 2007 to 17.8% (95% CI = 17.0 % to 18.6%) in 2010 (rho=-1.00; p<0.001)
- Using the empirical approach, DRIs calculated among adults ≥ 15 years of age decreased from 21.8% (95% CI = 20.9% to 22.7%) in 2007 to 20.9% (95% CI = 20.8% to 21.6%) in 2010, although the trend over time was non-significant (rho=-0.80; p=0.200)
- On average, DRIs calculated using the empirical approach were 3% higher than DRIs calculated using the microbiological approach
- In both microbiological and empirical approaches, the absolute difference between the static- and adaptive use DRIs increased over time

Discussion

The DRI gives the average effectiveness that a prescribed treatment for cystitis employs a drug to which the organism is not susceptible. Our study furthers Laxminarayan and Klugman's work by using indication-specific drug utilization data, analyzing the variation in DRI by age and sex, and looking at a DRI for a clinical syndrome, cystitis, rather than a single organism. In this study, the DRI is relatively stable over the short time span and is highly influenced by the large proportion of *E. coli* isolates non-susceptible to fluoroquinolones and the corresponding frequent use of this drug class for the treatment of cystitis.The adaptive-use model shows that physicians modifying their prescription practices (e.g. switching to nitrofurantoin) are mitigating what would otherwise be a progressively worsening trend.

Several limitations for this study can be noted. Only 4 years of line-listed data were available with which to calculate an index. More interesting trends may be observed over a longer time frame. The utilization data includes outpatient prescriptions of oral antibiotics only and thus applies largely to community therapy. Urine cultures used to inform the index are less likely to be performed for younger women who may be less likely to be infected with resistant organisms. In addition, laboratories do not routinely perform susceptibility testing for *S. saprophyticus*, a common uropathogen believed to be susceptible to most antibiotics used to treat cystitis. As a result, the DRI presented here may be an overestimate due to the exclusion of this organism.

Conclusion

A single indicator can be derived to describe the overall pattern of resistance for a relevant clinical syndrome. It is hopeful that further development of DRIs will ultimately allow for a "A Dow Jones Industrial Average" – like measure to describe the impact of antibiotic resistance in human health and better inform policies and program implementation.

References

1. U.S. Department of Health and Human Services,Centers for Disease Control and Prevention. (2003). *Antibiotic Resistance Threats in the United States, 2013.* Retrieved from http://www.cdc.gov/drugresistance/threat-report-2013/
2. Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. *BMJ Open* 2011; 1(2):e000135.

Acknowledgements

The authors wish to thank collaborators who provided data required to conduct this study: BC Ministry of Health and BC Biomedical Laboratories. We also wish to acknowledge the Pharmaceutical Services Division at the BC Ministry of Health for providing funding to support the ongoing evaluation of the *Do Bugs Need Drugs?* Program.