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COMMUNICATING TRENDS IN RESISTANCE: THE CASE FOR A DRUG RESISTANCE INDEX

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COMMUNICATING TRENDS IN RESISTANCE:

THE CASE FOR A DRUG RESISTANCE INDEX

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Abstract

Objectives: Antibiotic resistance is a growing problem worldwide, but communicating this challenge to policymakers and nonexperts is complicated by the multiplicity of bacterial pathogens and the distinct classes of antibiotics used to treat them. It is difficult, even for experts aware of the pharmacodynamics of antibiotics, to infer the seriousness of resistance without information on how commonly the antibiotic is being used and whether alternative antibiotics are available. Difficulty in aggregating resistance to multiple drugs to assess trends poses a further challenge to quantifying and communicating changes in resistance over time and across locations.

Design: We developed a method for aggregating bacterial resistance to multiple antibiotics, creating an index comparable to the composite economic indices that measure consumer prices and stock market values. The resulting drug resistance index and various subindices show antibiotic resistance and consumption trends in the United States, Latin America and Europe.

Results: The drug resistance index (DRI) based on use patterns in 1999 for *Escherichia coli* rose from 0.12 to 0.23 between 1999 and 2006. However, the adaptive DRI, which includes treatment of baseline resistant strains with alternative agents, climbed only from 0.12 to 0.15 during that period. In contrast, both the static-use and the adaptive DRIs for *Acinetobacter* spp. rose from 0.28 to 0.46 between 1999 and 2006.

Conclusion: Divergence between the static-use and the adaptive-use DRIs for *E. coli* reflects the ability of physicians to adapt to increasing resistance. However, antibiotic use patterns did not change much in response to growing resistance to *Acinetobacter* spp. because physicians were unable to adapt; new drugs for *Acinetobacter* spp. are therefore needed. Composite indices that aggregate resistance to various drugs can be useful for assessing changes in drug resistance across time and space.

Article Summary

Article focus:

- We propose a drug resistance index that can be used to communicate gaps in antibiotic effectiveness to nonexperts.

Key messages:

- Several different methods of computing DRI's are proposed. Data on bacterial susceptibility and antibiotic use can be used to compute a DRI on the proportion of antibiotics used to treat specific infections while data on anatomical site and type of infection can be used to create a DRI on infections defined by a specific anatomical site.
- Data for the construction of DRI's are becoming increasingly available and the construction of DRI's will make trends in resistance intelligible to nonexperts and useful to experts.

Strengths and limitations:

- The robustness of the resistance index depends on the quality of surveillance systems that generate the underlying data on susceptibility and antibiotic use.
- It is most likely that an immediate application of DRIs may be at the scale of the hospital where data on both resistance and antibiotic use are likely to be available.
- Further steps can include tying the resistance index to estimates of actual disease burden.

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The institutions that supported this work had no role in study conception, data collection, analysis and interpretation, and writing of the manuscript. All authors had full access to the data. RL, HG and KK had the final responsibility for the decision to submit for publication.

Conflict of interest statement

We declare that we have no conflict of interest.

INTRODUCTION

That antibiotics are losing effectiveness around the world is by now clear not just to the medical profession but also to those following media stories on the rise of superbugs. However, efforts to effectively communicate the challenge of antibiotic resistance to the lay public and policymakers have been somewhat unsuccessful. Despite increased attention in the United States and Europe to the resistance problem, there has been little progress in allocating financial resources either to conserve the effectiveness of existing drugs or to incentivize the development of new antibiotics. As one journal editor put it, "it is time that antibiotic resistance became an issue of popular concern rather than the interest of a few experts" (McConnell 2004). Several reasons explain why this has not happened.

First, policymakers are largely unfamiliar with the scientific names of pathogens. To a policymaker, that susceptibility of *Streptococcus pneumoniae* to penicillin is 40% may carry little meaning.

Second, data on the resistance of a pathogen to one or more drugs may be viewed out of context if substitutes to treat the infection exist. In the United States, growing resistance of *E. coli* to trimethoprim-sulfamethoxazole has been accompanied by a reduction in the proportion of patients treated with that drug. How should we view the increase in resistance to drugs that are declining in use? Is resistance as critical when we have near-substitutes that clinicians can deploy, such as imipenem in the case of *E. coli*? If doctors use injectable cephalosporins a hundred times more often than they do penicillin to treat invasive infections caused by *Streptococcus*

pneumoniae, shouldn't resistance to those cephalosporins carry more weight than resistance to penicillin?

Third, resistance goes up in some years and down in others, as seen in resistance of *Staphylococcus aureus* to oxacillin (MRSA) in several European countries (ECDC 2009) and *Acinetobacter* spp. to ciprofloxacin. In aggregate, has resistance to the antibiotics used most commonly to treat infections caused by these two pathogens increased or decreased over time?

Fourth is a problem specific to bacterial pathogens: antibiotic resistance affects not a single disease, like HIV, TB or malaria, but rather a set of syndromes and infections caused by different bacteria. A policymaker may understand that drugs to treat HIV/AIDS are failing but be unable to grasp the complexity of bacterial resistance. Therefore, information on susceptibility to a single pathogen and a single antibiotic cannot inform priority setting and allocation of health resources.

Here we propose a drug resistance index that can be used to communicate gaps in antibiotic effectiveness to nonexperts. This index is based on economic metrics like the consumer price indices or stock market indices, which are used in nearly every country. The purpose of these indices is simple—to quantify the average cost of purchasing a basic basket of goods and services deemed essential to living (in the case of price indices) or the average price of a basket of shares being traded (in the case of stock market indices). In our case, the metric should communicate the average effectiveness of the set of antibiotics that are used to treat a given bacterial infection.

METHODS AND DATA

Drug Resistance Indices

There are five attributes desirable in a drug resistance index (DRI). First, the DRI should be comparable across time and location so that it can be used to measure changes in drug effectiveness in a single country over time as well as to compare effectiveness across countries. Second, the DRI should be calculable with minimal data but be able to incorporate more information to improve precision when additional data become available. Third, the DRI should be simple enough that policymakers, the lay public and noninfectious disease medical practitioners can comprehend gaps in drug effectiveness, affordability and accessibility. Fourth, resistance of a pathogen to a specific drug should be weighted by the extent to which that drug is used for treating the pathogen, in much the same way that an inflation index weights the price of different commodities by the average share of income devoted to them. A change in the price of salt should affect the consumer price index by a smaller amount than an equal percentage change in the price of gasoline, which is used in greater quantities by the average household.

Finally, the resistance index should be sensitive to changes in the types of drugs being used. The first description of high-level resistance to ampicillin (beta-lactamase production) in *H. influenzae* (Khan, Ross et al. 1974) was sufficient to change empiric meningitis treatment from penicillin or ampicillin to the extended-spectrum cephalosporins in the developed world. Despite widespread beta-lactamase-producing *H. influenzae* and penicillin-resistant pneumococci, this shift has only recently begun in developing countries, as the extended-spectrum

cephalosporins come off patent and become affordable. The adaptive index for treatment of meningitis remains low in the developed world and is much higher in developing countries where alternative therapy thus remains limited in its availability.

Data

Computing the DRI requires data on bacterial susceptibility and antibiotic use. The scale at which these data are needed depends on the scale at which the resistance index is being computed—as low as the level of an individual healthcare facility or as high as a country or region. Ideally, resistance data are representative at the level for which the index is being computed. The weighting data are estimates of the shares of the different types of antibiotics as a proportion of treatments provided for pathogens covered by the index. These weights are based on antibiotic use data obtained from hospital pharmacies and commercial sources, such as IMS Health. In places where detailed antibiotic use data are not available, structured expert elicitation and other such methods can be used to elicit information on the proportions of antibiotics used to treat specific infections (Cooke 1991). For resistance indices related to infections defined by a specific anatomical site (pneumonia, meningitis, sepsis, urinary tract infection, UTI, etc) additional data are needed to weight each pathogen based on the etiologic fraction i.e. the proportion of infections they cause.

Example index

The drug resistance index (DRI) measures changes through time in the proportion of disease-causing pathogens that are resistant to the antibiotics commonly used to treat them. For the purpose of exposition, we have constructed a DRI for two pathogens, *E. coli* and *Acinetobacter* spp., using national US data on the proportion of isolates tested that are resistant and antibiotic consumption. The annual percentage change in the DRI is a measure of the rate of depletion of antibiotic effectiveness.

Since antibiotic use may change over time in response to changing levels of antibiotic resistance, we compare trends in the index to the counterfactual case where antibiotic use remains fixed to a baseline year. A static-use DRI allows assessment of the extent to which drug use has adapted in response to resistance and the burden that this resistance would have caused if antibiotic use patterns had not changed:

(1) $R_{i,fixed-use} = \sum_k \rho_{ik}^t q_{ik}^0$

where ρ_{ik}^t is the proportion of resistance among organism i to drug k at time t and q_{ik}^0 is the frequency of drug k used to treat organism i in the base year of the analysis.

Changing antibiotic use patterns over time may mitigate the burden of antibiotic resistance. To incorporate changing trends in antibiotic use, we also construct an adaptive version of the DRI; it aggregates the frequency with which infections from

a particular pathogen are resistant to antibiotic treatment and may be estimated as follows:

(2) $R_i = \sum_k \rho_{ik}^t q_{ik}^t$

where ρ_{ik}^t is the proportion of resistance among organism i to drug k at time t and q_{ik}^t is the frequency of drug k used to treat organism i at time t.

Implementing the DRI using US data

Prevalence of resistance ρ_{ik}^t was calculated using The Surveillance Network Database—USA. Frequency of drug use q_{ik}^0 for the United States was obtained from IMS Health. The Xponent database captures more than 70% of all prescriptions filled in the United States and uses a patented projection methodology to represent 100% coverage of all prescription activity.

Figures 1a and 1b show that resistance of *Escherichia coli* and *Acinetobacter* spp. inpatient isolates in the United States increased between 1999 and 2006. Rates of increase were remarkable for *Acinetobacter* spp. resistant to imipenem and fluoroquinolones, as well as for *E. coli* resistant to ciprofloxacin and ampicillin. Figures 2a and 2b show proportions of antibiotics used to treat *Acinetobacter* spp. and *E. coli*. These use patterns reflect the resistance data. For *Acinetobacter* spp., the predominant use is in injectable drugs, and our data show that most strains are resistant to a majority of available antibiotics. The oral agents listed are fluoroquinolones, and the replacement of ciprofloxacin by levofloxacin over this

period may be related to changing hospital formularies, which used increasing amounts of levofloxacin despite its somewhat lesser activity than ciprofloxacin against resistant Gram-negative species.

For *E. coli*, reductions in the inexpensive oral agents ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin are mirrored by increasing resistance and use of more expensive oral cephalosporins and expensive injectables, such as aztreonam. Of particular note is the increasing use of the last-resort injectable imipenem.

Static-use and adaptive-use DRIs are in Figure 3. For *Acinetobacter* spp., the static-use DRI increased more than 50%, from 0.28 to 0.46, while for *E. coli*, the static-use DRI increased from 0.12 to 0.23. The results show that for *E. coli*, the static-use DRI exceeds the adaptive-use DRI for all years, which increases only from 0.12 to 0.15. This rate of increase is much lower than for the static-use DRI, indicating that clinicians were able to effectively adapt antibiotic use patterns in response to trends in antibiotic resistance.

On the other hand, there is little difference between the static- and adaptive-use indices for *Acinetobacter*. The similarity between the two indices suggests that there is little room for clinicians to adapt antibiotic use patterns to decreasing treatment effectiveness.

DRIs for first-line therapy

Clinicians and policymakers may be more concerned about resistance to first-line treatments. Resistance to these drugs implies the loss of cheaper, more widely used alternatives and could affect drug procurement budgets if government facilities are

an important source of treatment. Trends in resistance to first-line treatments may also be important for setting national treatment guidelines, essential drug lists or hospital formularies.

Resistance to second-line treatments could indicate that the need to invest in new antibiotics is more urgent. The line-of-treatment DRI is calculated as

$$\textbf{(3)}\ R_{i,n-line} = \frac{\sum_{k \in T_n} \rho_{ik}^t q_{ik}^t}{\sum_{k \in T_n} q_{ik}^t}$$

where T_n is the set of *n*-line treatments. From here on, for simplicity, we report only the adaptive form of the index. An important caveat is that when a single antibiotic corresponds to an entire line of therapy, the models are equivalent to summarizing trends in resistance to this antibiotic over time.

Over the period 1999–2006, drugs commonly used as first-line therapies for urinary tract infections (UTIs) included amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones. Results separating antibiotics into first-line and non-first-line categories follow for *E. coli* outpatient isolates. The adaptive-use index of resistance to first-line therapies was much higher than the resistance to other therapies—moreover, resistance to first-line therapies increased substantially over the analysis period. Resistance to non-first-line therapies decreased over time, suggesting that new treatment options among these non-first-line drugs increased overall treatment effectiveness.

Affordability indices

Antibiotic resistance may force clinicians to use more expensive antibiotics to treat infections. An affordability index summarizes resistance trends among cheaper or more expensive antibiotics. Such an index could mirror a first-line treatment index, but not always. A model of resistance of an organism to drugs in a certain cost range may be estimated as follows:

(4) $$R_{i,affordability} = \frac{\sum_k \rho_{ik}^t q_{ik}^t}{\sum_k q_{ik}^t} \mid price(k) \in C \subseteq C_{ALL}$$

where $price(k)$ is the cost of treatment by drug k and C_{ALL} is the set of costs of treatment for each drug k.

Other potential indices

Clinicians do not usually have information on the infecting organism at start of empiric therapy, but they do have information on the site of infection. It would also be possible to set up indices based on the anatomical site and type of infection. Antibiotic use patterns would be straightforward, but resistance would have to be weighted against the etiological fraction of the different causative organisms.

Another potential index could contrast the relative drug effectiveness of Gram-positive vs. Gram-negative organisms.–Similar indices could cover all pathogens in inpatient versus outpatient settings. Finally, although we have presented results for antibiotic resistance, similar indices can be computed for other infectious diseases,

like HIV/AIDS, tuberculosis and malaria, for which resistance is a problem and the choice of therapeutics also varies over time.

For all indices discussed so far, subindices can be computed for different categories and subcategories of pathogens, and then combined to produce the overall index with weights reflecting their shares in the total of the antibiotics used for treatment.

Discussion

Antibiotic resistance imposes a substantial public health burden. Quantifying overall changes in resistance over time and across locations is difficult because resistance of pathogens to individual drugs must somehow be aggregated to assess overall burden. Here, we take a first step towards the development of resistance indices, summarizing resistance at the level of the infectious agent.

The results indicate that although clinicians have been able to adapt to increasing resistance in *E. coli* by switching to antibiotics that remain active, as indicated by the divergence between the static-use and adaptive DRI, they have had fewer alternatives in the case of *Acinetobacter* spp., where resistance is increasing to nearly all agents.

Although we have not presented data by disease condition, *E. coli* represents the vast majority of UTIs. Therefore, the DRI for *E. coli* is a useful proxy as a DRI for UTIs. However, for other pathogens, infections in different sites of the body represent different challenges and may not be well represented by a single index. For instance, pneumococcal infection of the bloodstream or lungs may be a different challenge

than pneumococcal disease in cerebrospinal fluid, which few drugs penetrate. The index should be based on the most recent and updated clinical breakpoints (S, I and R). These take into account the clinical effectiveness of a drug for a given infection. Clinical resistance in this context is determined by a careful analysis of all available data by international committees such as the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) in the USA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Thereby, the success of a given drug is defined not only by the bacterium's susceptibility to the drug, but also by its pharmacology with regards to the time course of the drug concentration in the human body (pharmacokinetics) and the biological effect of the drug at these concentrations on the bacteria (pharmacodynamics), and whenever available, by information on clinical outcomes.

Ultimately, the robustness of the resistance index will depend on the quality of surveillance systems that generate the underlying data on susceptibility and antibiotic use. Laboratory capacity remains inadequate in many parts of the world, although surprisingly large amounts of quality data are generated but remain underutilized due to the lack of dedicated surveillance systems. Susceptibility data are more likely to be reported from largely tertiary care facilities, where problems of resistance tend to be greater than in smaller, regional hospitals and could also vary by time of specimen collection (Laupland, Ross et al. 2007). Thus, trends are likely to be more accurate than absolute levels. However, data-related challenges are not unique to resistance; they confront government agencies charged with computing the consumer price index as well. DRIs could motivate better reporting

of resistance data from smaller facilities and provide an impetus to surveillance in both developed and developing countries.

National and regional data on antibiotic sales are increasingly available through companies like IMS, although in some countries, hospital prescriptions are not included. A more feasible, immediate application of DRIs may be at the scale of the hospital, where data on both resistance and antibiotic use are likely to be available.

The resistance index takes a first, important step towards making trends in resistance intelligible to nonexperts and useful to experts. Policymakers, particularly in developing countries, are interested in the implications of any public health intervention for morbidity, mortality and current and future drug procurement budgets. We need to translate susceptibility into metrics that policymakers can understand and care about. A further step would be to tie the resistance index to estimates of actual disease burden. For instance, how important is resistance to *Acinetobacter,* which typically causes fewer infections or deaths than *E. coli*? Translating the DRI into disease burden requires a careful, unbiased assessment of clinical outcomes of resistant infections, but in absence of these data morbidity and mortality rates of untreated infections may well suffice. Correlation between resistance levels and severity of infection does not imply that the direction of causality runs from resistance to poor outcomes. These and other methodological challenges should be the subject of future efforts.

License

Contributors

RL initiated and coordinated the research and conducted the analysis. RL wrote the manuscript and HG and KK reviewed and commented on the manuscript. All authors saw and approved the final version.

References

Cooke R. Experts in Uncertainty: Opinion and Subjective Probability in Science. Oxford: Oxford University Press; 1991.

ECDC [Internet]. "Antimicrobial resistance surveillance in Europe 2009." Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: European Centre for Disease Prevention and Control ; 2010 [updated 2010 Nov 24; cited 2011 Jan 16]. Available from: http://www.ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf

Khan W, Ross S, Rodriguez W, Controni G, and Saz AK . Haemophilus influenzae type B resistant to ampicillin. A report of two cases. Jama. 1974; **229**(3): 298-301.

Laupland KB, Ross T, Pitout JD, Church DL, and Gregson DB. Investigation of sources of potential bias in laboratory surveillance for anti-microbial resistance. Clin Invest Med. 2007; **30**(4): E159-166.

McConnell, J. Giving identity to the faceless threat of antibiotic resistance. Lancet Infect Dis. 2004 Jun; **4**(6): 325.

Figure 1a: Resistance trends of *Acinetobacter* spp. to six antibiotics in US, 1999–2006

Figure 1b: Resistance trends of *Escherichia coli* to thirteen antibiotics in US, 1999–2006

Figure 2a: Proportions of most-common antibiotics used to treat infections caused by *Acinetobacter* spp. in US (1999–2006)

Figure 2b: Proportions of most-common antibiotics used to treat infections caused by *E. coli* in US, 1999–2006

Figure 3: Static- and adaptive use resistance indices for *Acinetobacter* spp. and *E. coli* for US, 1999–2006

Figure 4: Antibiotic effectiveness indices for first-line therapy for *Acinetobacter* spp. and *E. coli* in US, 1999–2006

Note: First-line therapies for urinary tract infections are based on guidelines used at the University of Maryland Medical Center.[1]

Figure 5: Adaptive affordability indices for *Acinetobacter* spp. and *E. coli* in US, 1999–2006

Note: Cheap and expensive indices are based on daily cost at or under $10 and exceeding $10, respectively, in the case of *Escherichia coli*. For *E. coli*, cheap drugs include ampicillin, gentamicin and sulfamethoxazole-trimethoprim, cefazolin and tobramycin; expensive drugs include ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, imipenem, nitrofurantoin, and piperacillin. Cheap and expensive indices are based on daily cost at or under $100 and exceeding $100, respectively, in the case of *Acinetobacter* species. For *Acinetobacter* spp., cheap drugs were cefepime, ceftazidime, ceftriaxone and ciprofloxacin; expensive drugs include imipenem. Daily drug cost data were obtained from Cornell University's Weill Medical College.[2]

[1]http://www.umm.edu/patiented/articles/how_antibiotics_used_treating_urinary_tract_infections_000036_8.htm.

[2] http://www-users.med.cornell.edu/~spon/picu/referenc/abxcost.htm.

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April 5, 2011

Dear Editor,

The paper titled, "Communicating Trends in Resistance: The Case for a Drug Resistance Index", describes a new method for for evaluating and communicating drug resistance. The paper does not follow a specific reporting guideline as suggested by the options on your website.

Please feel free to contact us with any suggestions or questions.

Sincerely,

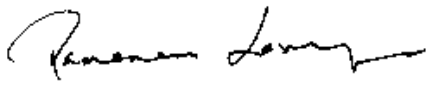

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Figure 1a: Resistance trends of *Acinetobacter* spp. to six antibiotics in US, 1999–2006

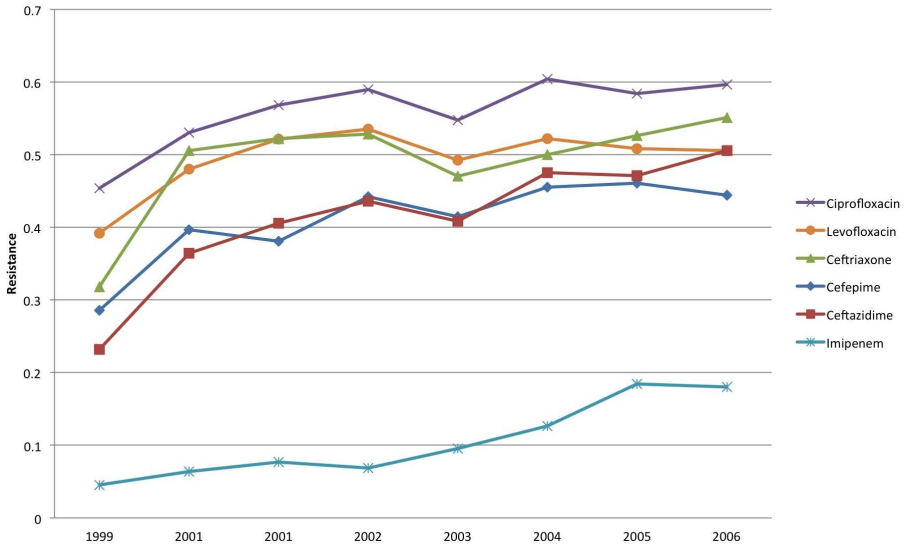

Figure 1a: Resistance trends of Acinetobacter spp. to six antibiotics in US, 1999–2006
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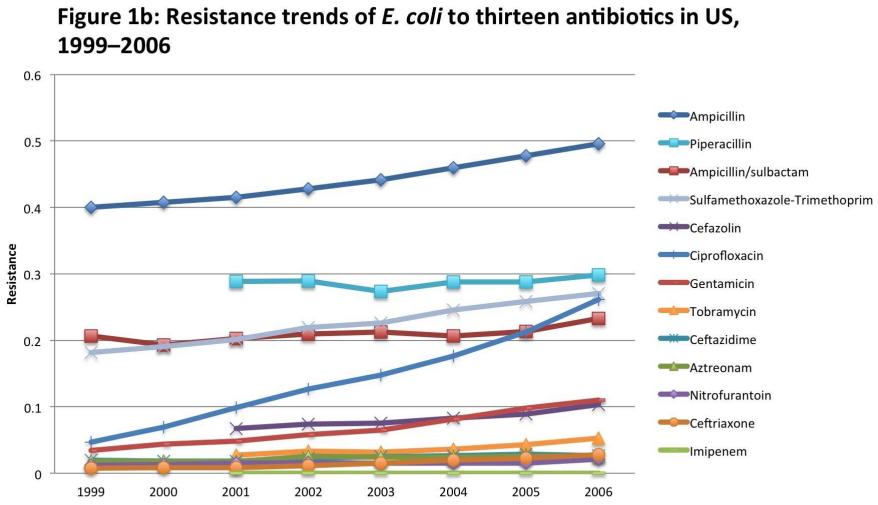

Figure 1b: Resistance trends of Escherichia coli to thirteen antibiotics in US, 1999–2006
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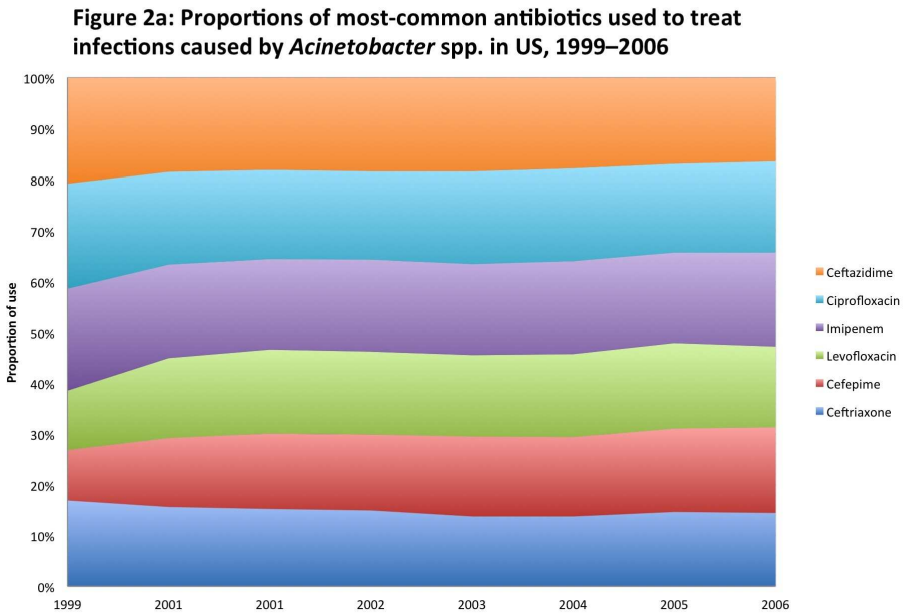

Figure 2a: Proportions of most-common antibiotics used to treat infections caused by Acinetobacter spp. in US (1999–2006)
705x529mm (72 x 72 DPI)

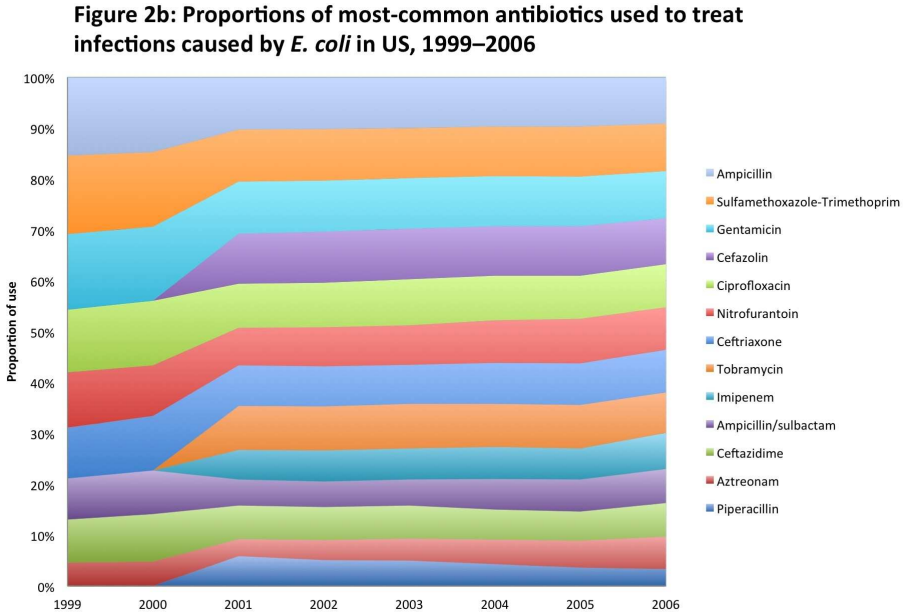

Figure 2b: Proportions of most-common antibiotics used to treat infections caused by E. coli in US, 1999–2006
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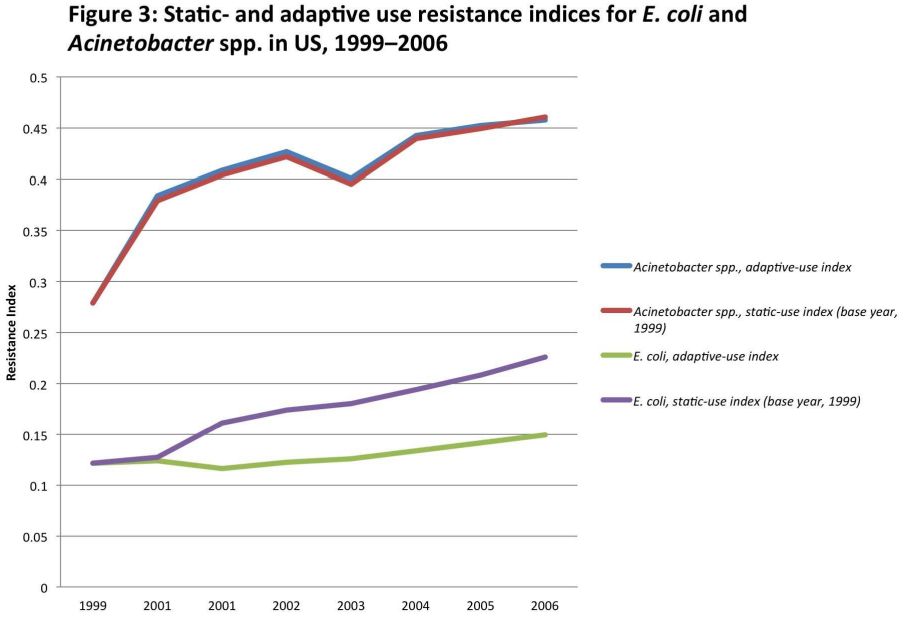
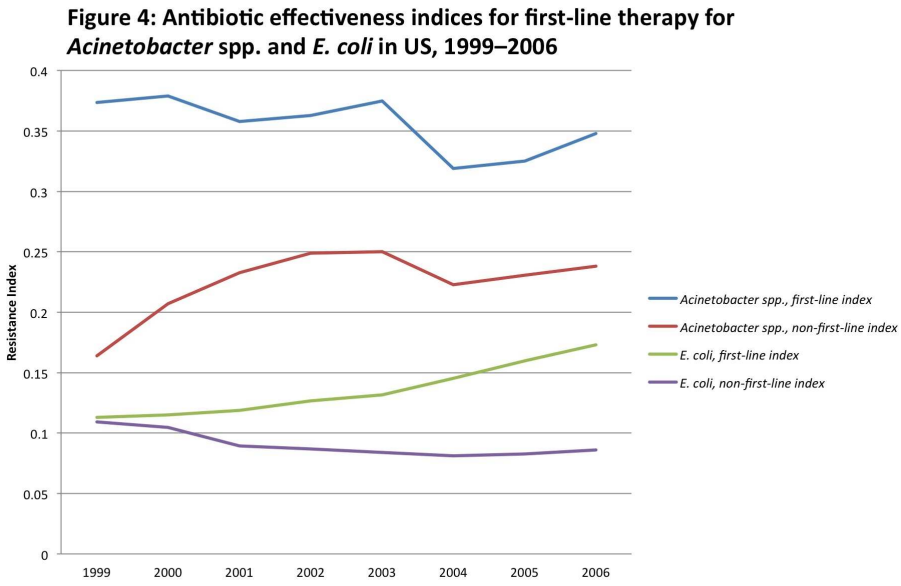


Figure 3: Static- and adaptive use resistance indices for Acinetobacter spp. and E. coli for US, 1999–2006
705x529mm (72 x 72 DPI)



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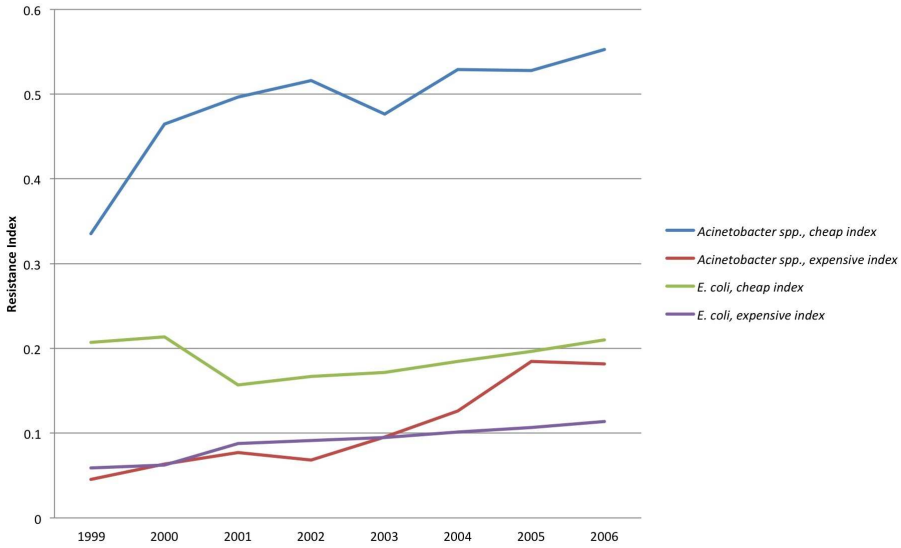

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COMMUNICATING TRENDS IN RESISTANCE USING A DRUG RESISTANCE INDEX

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COMMUNICATING TRENDS IN RESISTANCE USING A DRUG RESISTANCE INDEX

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: Antibiotic resistance is a growing problem worldwide, but communicating this challenge to policymakers and nonexperts is complicated by the multiplicity of bacterial pathogens and the distinct classes of antibiotics used to treat them. It is difficult, even for experts aware of the pharmacodynamics of antibiotics, to infer the seriousness of resistance without information on how commonly the antibiotic is being used and whether alternative antibiotics are available. Difficulty in aggregating resistance to multiple drugs to assess trends poses a further challenge to quantifying and communicating changes in resistance over time and across locations.

Methods: We developed a method for aggregating bacterial resistance to multiple antibiotics, creating an index comparable to the composite economic indices that measure consumer prices and stock market values. The resulting drug resistance index and various subindices show antibiotic resistance and consumption trends in the United States, but can be applied at any geographical level.

Findings: The drug resistance index (DRI) based on use patterns in 1999 for *Escherichia coli* rose from 0.25 (95% CI, 0.23 - 0.26) to 0.30 (95% CI, 0.29 - 0.32) between 1999 and 2006. However, the adaptive DRI, which includes treatment of baseline resistant strains with alternative agents, climbed from 0.25 to 0.27 (95% CI 0.25 – 0.28) during that period. In contrast, both the static-use and the adaptive DRIs for *Acinetobacter* spp. rose from 0.41 (95% CI 0.4 – 0.42) to 0.48 (95% CI 0.46 – 0.49) between 1999 and 2006.

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Interpretation: Divergence between the static-use and the adaptive-use DRIs for *E. coli* reflects the ability of physicians to adapt to increasing resistance. However, antibiotic use patterns did not change much in response to growing resistance to *Acinetobacter* spp. because physicians were unable to adapt; new drugs for *Acinetobacter* spp. are therefore needed. Composite indices that aggregate resistance to various drugs can be useful for assessing changes in drug resistance across time and space.

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Article Summary¶
Article focus:¶
We propose a drug resistance index that can be used to communicate gaps in antibiotic effectiveness to nonexperts.¶
Key messages:¶
Several different methods of computing DRI's are proposed. Data on bacterial susceptibility and antibiotic use can be used to compute a DRI on the proportion of antibiotics used to treat specific infections while data on anatomical site and type of infection can be used to create a DRI on infections defined by a specific anatomical site. ¶
Data for the construction of DRI's are becoming increasingly available and the construction of DRI's will make trends in resistance intelligible to nonexperts and useful to experts.¶
Strengths and limitations:¶
The robustness of the resistance index depends on the quality of surveillance systems that generate the underlying data on susceptibility and antibiotic use. ¶
It is most likely that an immediate application of DRIs may be at the scale of the hospital where data on both resistance and antibiotic use are likely to be available. ¶
Further steps can include tying the resistance index to estimates of actual disease burden.¶
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INTRODUCTION

That antibiotics are losing effectiveness around the world is by now clear not just to the medical profession but also to those following media stories on the rise of superbugs. However, efforts to effectively communicate the challenge of antibiotic resistance to the lay public and policymakers have been somewhat unsuccessful. Despite increased attention in the United States and Europe to the resistance problem, there has been little progress in allocating financial resources either to conserve the effectiveness of existing drugs or to incentivize the development of new antibiotics. As one journal editor put it, "it is time that antibiotic resistance became an issue of popular concern rather than the interest of a few experts" (McConnell 2004). Several reasons explain why this has not happened.

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First, policymakers are largely unfamiliar with the scientific names of pathogens. To a policymaker, that susceptibility of *Streptococcus pneumoniae* to penicillin is 40% may carry little meaning.

Second, data on the resistance of a pathogen to one or more drugs may be viewed out of context if substitutes to treat the infection exist. In the United States, growing resistance of *E. coli* to trimethoprim-sulfamethoxazole has been accompanied by a reduction in the proportion of patients treated with that drug. How should we view the increase in resistance to drugs that are declining in use? Is resistance as critical when we have near-substitutes that clinicians can deploy, such as imipenem in the case of *E. coli*? If doctors use injectable cephalosporins a hundred times more often than they do penicillin to treat invasive infections caused by *Streptococcus pneumoniae,* shouldn't resistance to those cephalosporins carry more weight than resistance to penicillin?

Third, resistance goes up in some years and down in others, as seen in resistance of *Staphylococcus aureus* to oxacillin (MRSA) in several European countries (ECDC 2009) and *Acinetobacter* spp. to ciprofloxacin. In aggregate, has resistance to the antibiotics used most commonly to treat infections caused by these two pathogens increased or decreased over time?

Fourth is a problem specific to bacterial pathogens: antibiotic resistance affects not a single disease, like HIV, TB or malaria, but rather a set of syndromes and infections caused by different bacteria. A policymaker may understand that drugs to treat HIV/AIDS are failing but be unable to grasp the complexity of bacterial resistance. Therefore, information on susceptibility to a single pathogen and a single antibiotic cannot inform priority setting and allocation of health resources.

Here we propose a drug resistance index that can be used to communicate gaps in antibiotic effectiveness to nonexperts. This index is based on economic metrics like the consumer price indices or stock market indices, which are used in nearly every country. The purpose of these indices is simple—to quantify the average cost of purchasing a basic basket of goods and services deemed essential to living (in the case of price indices) or the average price of a basket of shares being traded (in the case of stock market indices). In our case, the metric should communicate the average effectiveness of the set of antibiotics that are used to treat a given bacterial infection.

METHODS AND DATA

Drug Resistance Indices

There are five attributes desirable in a drug resistance index (DRI). First, the DRI should be comparable across time and location so that it can be used to measure changes in drug effectiveness in a single country over time as well as to compare effectiveness across countries. Second, the DRI should be calculable with minimal data but be able to incorporate more information to improve precision when additional data become available. Third, the DRI should be simple enough that policymakers, the lay public and noninfectious disease medical practitioners can comprehend gaps in drug effectiveness, affordability and accessibility. Fourth, resistance of a pathogen to a specific drug should be weighted by the extent to which that drug is used for treating the pathogen, in much the same way that an inflation index weights the price of different commodities by the average share of income devoted to them. A change in the price of salt should affect the consumer price index by a smaller amount than an equal percentage change in the price of gasoline, which is used in greater quantities by the average household.

Finally, the resistance index should be sensitive to changes in the types of drugs being used. The first description of high-level resistance to ampicillin (beta-lactamase production) in *H. influenzae* (Khan, Ross et al. 1974) was sufficient to change empiric meningitis treatment from penicillin or ampicillin to the extended-spectrum cephalosporins in the developed world. Despite widespread beta-lactamase-producing *H. influenzae* and penicillin-resistant pneumococci, this shift has only recently begun in developing countries, as the extended-spectrum cephalosporins come off patent and become affordable. The adaptive index for treatment of meningitis remains low in the developed world and is much higher in developing countries where alternative therapy thus remains limited in its availability.

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Data

Computing the DRI requires data on bacterial susceptibility and antibiotic use. The scale at which these data are needed depends on the scale at which the resistance index is being computed—as low as the level of an individual healthcare facility or as high as a country or region. Ideally, resistance data are representative at the level for which the index is being computed. The weighting data are estimates of the shares of the different types of antibiotics as a proportion of treatments indicated for pathogens covered by the index. These weights are based on antibiotic use data obtained from hospital pharmacies and commercial sources, such as IMS Health. In places where detailed antibiotic use data are not available, structured expert elicitation and other such methods can be used to elicit information on the proportions of antibiotics used to treat specific infections (Cooke 1991). For resistance indices related to infections defined by a specific anatomical site (pneumonia, meningitis, sepsis, urinary tract infection, UTI, etc) additional data are needed to weight each pathogen based on the etiologic fraction i.e. the proportion of infections they cause.

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Role of the Funding Source

The institutions that supported this work had no role in study conception, data collection, analysis and interpretation, and writing of the manuscript. All authors had full access to the data. All authors had the final responsibility for the decision to submit for publication.

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Example index

The drug resistance index (DRI) measures changes through time in the proportion of disease-causing pathogens that are resistant to the antibiotics commonly used to treat them. For the purpose of exposition, we have constructed a DRI for two pathogens, *E. coli* and *Acinetobacter* spp., using national US data on the proportion of isolates tested that are resistant and antibiotic consumption. The annual percentage change in the DRI is a measure of the rate of depletion of antibiotic effectiveness.

Since antibiotic use may change over time in response to changing levels of antibiotic resistance, we compare trends in the index to the counterfactual case where antibiotic use remains fixed to a baseline year. A static-use DRI allows assessment of the extent to which drug use has adapted in response to resistance and the burden that this resistance would have caused if antibiotic use patterns had not changed:

$$R_{i,\,fixed-use} = \sum_k \rho_{ik}^t q_{ik}^0 \quad (1)$$

where ρ_{ik}^t is the proportion of resistance among organism i to drug k at time t and q_{ik}^0 is the frequency of drug k used to treat organism i in the base year of the analysis.

Changing antibiotic use patterns over time may mitigate the burden of antibiotic resistance. To incorporate changing trends in antibiotic use, we also construct an adaptive version of the DRI; it aggregates the frequency with which infections from a particular pathogen are resistant to antibiotic treatment and may be estimated as follows:

$$R_i = \sum_k \rho_{ik}^t q_{ik}^t \quad (2)$$

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where ρ_{ik}^{t} is the proportion of resistance among organism $_i$ to drug k at time t and q_{ik}^{t} is the frequency of drug k used to treat organism $_i$ at time t.

Implementing the DRI using US data

Prevalence of resistance ρ_{ik}^{t} was calculated using The Surveillance Network Database - USA (TSN; Eurofins Medinet, Herndon, VA). TSN is a nationally and regionally representative database of bacterial species identification and antibiotic susceptibility results gathered from 300 US hospitals (Sahm et al. 1999). Frequency of drug use q_{ik}^{0} for the United States was obtained from IMS Health Xponent™ database. Xponent tracks more than 70% of all outpatient prescriptions in the United States using transaction records at retail pharmacies, and uses a patented projection methodology to represent 100% coverage of all prescription activity.

Confidence intervals for the indices were derived using a non-parametric bootstrap method with n = 10,000 observations drawn at random from each of the itemized datasets of antibiotic prescriptions and individual susceptibility tests and replicated m = 1,000 times. Statistical analysis was performed using STATA version 11 (Stata Corporation, College Station, Texas) and R version 2.13.1 (Free Software Foundation Inc, Boston, MA).

Figures 1a and 1b show that resistance of *Escherichia coli* and *Acinetobacter* spp. inpatient and outpatient isolates in the United States increased between 1999 and 2006. Rates of increase were remarkable for *Acinetobacter* spp. resistant to carbapenems and fluoroquinolones, as well as for *E. coli* resistant to fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX) and aminopenicillins. Figures 2a and 2b show prescribing

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proportions for antibiotics that were featured in the TSN database of susceptibility tests for *Acinetobacter* spp. and *E. coli* and are commonly used to treat gram-negative infections. For *E. coli* usage patterns have shifted towards increased fluoroquinolone and later generation cephalosporin use in lieu of less expensive alternatives such as aminopenicillins and TMP-SMX.

Static-use and adaptive-use DRIs are in Figure 3. For *Acinetobacter* spp., the static-use DRI increased by 17%, from 0.41 to 0.48 while for *E. coli*, the static-use DRI increased from 0.25 to 0.30. The results show that for *E. coli*, the static-use DRI exceeds the adaptive-use DRI for all years, which increases from ~~0.12 to 0.15~~ 0.25 to 0.27 from 1999 to 2006. This rate of increase is ~~much~~ lower than for the static-use DRI with a statistically significant difference for 2006, indicating that clinicians were able to effectively adapt antibiotic use patterns in response to trends in antibiotic resistance.

On the other hand, there is little difference between the static- and adaptive-use indices for *Acinetobacter*. The similarity between the two indices suggests that there is little room for clinicians to adapt antibiotic use patterns to decreasing treatment effectiveness.

DRIs for first-line therapy

Clinicians and policymakers may be more concerned about resistance to first-line treatments. Resistance to these drugs implies the loss of cheaper, more widely used alternatives and could affect drug procurement budgets if government facilities are an important source of treatment. Trends in resistance to first-line treatments may also be important for setting national treatment guidelines, essential drug lists or hospital formularies.

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For *E. coli*, reductions in the inexpensive oral agents ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin are mirrored by increasing resistance and use of more

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Resistance to second-line treatments could indicate that the need to invest in new antibiotics is more urgent. The line-of-treatment DRI is calculated as

$$R_{i,n-line} = \frac{\sum_{k \in T_n} \rho_{ik}^t q_{ik}^t}{\sum_{k \in T_n} q_{ik}^t} \quad (0)$$

where T_n is the set of n-line treatments. From here on, for simplicity, we report only the adaptive form of the index for *E.coli*. An important caveat is that when a single antibiotic corresponds to an entire line of therapy, the models are equivalent to summarizing trends in resistance to this antibiotic over time.

Over the period 1999–2006, drugs commonly used as first-line therapies for urinary tract infections (UTIs) included trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones (Taur and Smith, 2007). Results separating antibiotics into first-line and non-first-line categories follow for *E. coli* isolates. The adaptive-use index of resistance to first-line therapies was lower than the resistance to other therapies (figure 4). However, resistance to first-line therapies increased at a much higher rate, a likely consequence of their widespread use. Resistance to non-first-line therapies remained unchanged over time, suggesting that new treatment options among these non-first-line drugs preserved their overall effectiveness.

Affordability indices

Antibiotic resistance may force clinicians to use more expensive antibiotics to treat infections. An affordability index summarizes resistance trends among cheaper or more

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$$R_{i,n-line} = \frac{\sum_{k \in T_n} \rho_{ik}^t q_{ik}^t}{\sum_{k \in T_n} q_{ik}^t}$$ ¶

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expensive antibiotics. Such an index could mirror a first-line treatment index, but not always. A model of resistance of an organism to drugs in a certain cost range may be estimated as follows:

$$R_{i,affordability} = \frac{\sum_k \rho_{ik}^t q_{ik}^t}{\sum_k q_{ik}^t} \mid price(k) \in C \subseteq C_{ALL} \quad (0)$$

where $price(k)$ is the cost of treatment by drug k and C_{ALL} is the set of costs of treatment for each drug k.

The adaptive DRI for high cost drugs used to treat *E coli* was lower indicating overall lower levels of resistance to higher cost drugs (figure 5). However, there was an upward trend in the adaptive index for higher cost drugs indicating that as resistance increased, there was a limited set of higher cost-drugs that physicians could prescribe leading to an increasing DRI. Interestingly, the low-cost adaptive DRI for *E coli* has remained relatively flat, consistent with the overall unchanged trend in DRI for *E coli*.

Other potential indices

Clinicians do not usually have information on the infecting organism at start of empiric therapy, but they do have information on the site of infection. It would also be possible to set up indices based on the anatomical site and type of infection. Antibiotic use patterns would be straightforward, but resistance would have to be weighted against the etiological fraction of the different causative organisms.

Another potential index could contrast the relative drug effectiveness of Gram-positive vs. Gram-negative organisms.–Similar indices could cover all pathogens in inpatient versus

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$$R_{i,affordability} = \frac{\sum_k \rho_{ik}^t q_{ik}^t}{\sum_k q_{ik}^t} \mid price$$

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outpatient settings. Finally, although we have presented results for antibiotic resistance, similar indices can be computed for other infectious diseases, like HIV/AIDS, tuberculosis and malaria, for which resistance is a problem and the choice of therapeutics also varies over time.

For all indices discussed so far, subindices can be computed for different categories and subcategories of pathogens, and then combined to produce the overall index with weights reflecting their shares in the total of the antibiotics used for treatment.

Discussion

Antibiotic resistance imposes a substantial public health burden. Quantifying overall changes in resistance over time and across locations is difficult because resistance of pathogens to individual drugs must be aggregated to assess overall burden. Here, we take a first step towards the development of resistance indices, summarizing resistance at the level of the infectious agent.

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The results indicate that although clinicians have been able to adapt to increasing resistance in *E. coli* by switching to antibiotics that remain active, as indicated by the divergence between the static-use and adaptive DRI, they have had fewer alternatives in the case of *Acinetobacter* spp., where resistance is increasing to nearly all agents.

Although we have not presented data by disease condition, *E. coli* represents the vast majority of UTIs. Therefore, the DRI for *E. coli* is a useful proxy as a DRI for UTIs. However, for other pathogens, infections in different sites of the body represent different challenges and may not be well represented by a single index. For instance, pneumococcal infection of the bloodstream or lungs may be a different challenge than pneumococcal disease in

cerebrospinal fluid, which few drugs penetrate. The index should be based on the most recent and updated clinical breakpoints (S, I and R). These take into account the clinical effectiveness of a drug for a given infection. Clinical resistance in this context is determined by a careful analysis of all available data by international committees such as the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) in the USA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Thereby, the success of a given drug is defined not only by the bacterium's susceptibility to the drug, but also by its pharmacology with regards to the time course of the drug concentration in the human body (pharmacokinetics) and the biological effect of the drug at these concentrations on the bacteria (pharmacodynamics), and whenever available, by information on clinical outcomes.

Ultimately, the robustness of the resistance index will depend on the quality of surveillance systems that generate the underlying data on susceptibility and antibiotic use. Laboratory capacity remains inadequate in many parts of the world, although surprisingly large amounts of quality data are generated but remain underutilized due to the lack of dedicated surveillance systems. Susceptibility data are more likely to be reported from largely tertiary care facilities, where problems of resistance tend to be greater than in smaller, regional hospitals and could also vary by time of specimen collection (Laupland, Ross et al. 2007). Thus, trends are likely to be more accurate than absolute levels. However, data-related challenges are not unique to resistance; they confront government agencies charged with computing the consumer price index as well. DRIs could motivate better reporting of resistance data from smaller facilities and provide an impetus to surveillance in both developed and developing countries.

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National and regional data on antibiotic sales are increasingly available through companies like IMS Health, although in some countries, hospital prescriptions are not included. Gathering accurate data on antibiotic sales is particularly challenging in countries with a large informal pharmaceutical sector. Here, sales from the formal sector may be indicative of trends and likely mirror sales in the informal sector. A feasible, immediate application of DRIs may be at the scale of the hospital, where data on both resistance and antibiotic use are likely to be available.

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The resistance index takes a first, important step towards making trends in resistance intelligible to nonexperts and useful to experts. Policymakers, particularly in developing countries, are interested in the implications of any public health intervention for morbidity, mortality and current and future drug procurement budgets. We need to translate susceptibility into metrics that policymakers can understand and care about. A further step would be to tie the resistance index to estimates of actual disease burden. For instance, how important is resistance to *Acinetobacter,* which typically causes fewer infections or deaths than *E. coli*? Translating the DRI into disease burden requires a careful, unbiased assessment of clinical outcomes of resistant infections, but in absence of these data morbidity and mortality rates of untreated infections may well suffice. Correlation between resistance levels and severity of infection does not imply that the direction of causality runs from resistance to poor outcomes. These and other methodological challenges should be the subject of future efforts.

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Conflict of interest statement

We declare that we have no conflict of interest.

Contributors

RL initiated the research. RL and KK coordinated the research. RL conducted the analysis. RL and KK wrote the manuscript. Both authors saw and approved the final version.

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References

Cooke, R. (1991). Experts in Uncertainty: Opinion and Subjective Probability in Science. Oxford, Oxford University Press.

ECDC. (2010). "Antimicrobial resistance surveillance in Europe 2009." Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, ECDC. Accessed January 16, 2011 http://www.ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf

Khan, W., S. Ross, et al. (1974). "Haemophilus influenzae type B resistant to ampicillin. A report of two cases." Jama **229**(3): 298-301.

Laupland, K. B., T. Ross, et al. (2007). "Investigation of sources of potential bias in laboratory surveillance for anti-microbial resistance." Clin Invest Med **30**(4): E159-166.

McConnell, J. (2004). "Giving identity to the faceless threat of antibiotic resistance." Lancet Infect Dis **4**(6): 325.

Sahm DF, Marsilio MK, Piazza G. (1999). "Antimicrobial resistance in key bloodstream bacterial isolates: electronic surveillance with the surveillance network database—USA". Clin Infect Dis. 1999;29 (1):259–63.

Taur, J. and Smith, M. A. (2007). "Adherence to the Infectious Diseases Society of America Guidelines in the Treatment of Uncomplicated Urinary Tract Infection". Clin Infect Dis. 44(6): 769-774 doi:10.1086/511866

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ECDC [Internet]. "Antimicrobial resistance surveillance in Europe 2009." Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: European Centre for Disease Prevention and Control ; 2010 [updated 2010 Nov 24; cited 2011 Jan 16]. Available from: http://www.ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf ¶
Khan W, Ross S, Rodriguez W, Controni G, and Saz AK . Haemophilus influenzae type B resistant to ampicillin. A report of two cases. Jama. 1974; **229**(3): 298-301.¶
Laupland KB, Ross T, Pitout JD, Church DL, and Gregson DB. Investigation of sources of potential bias in laboratory surveillance for anti-microbial resistance. Clin Invest Med. 2007; **30**(4): E159-166.¶
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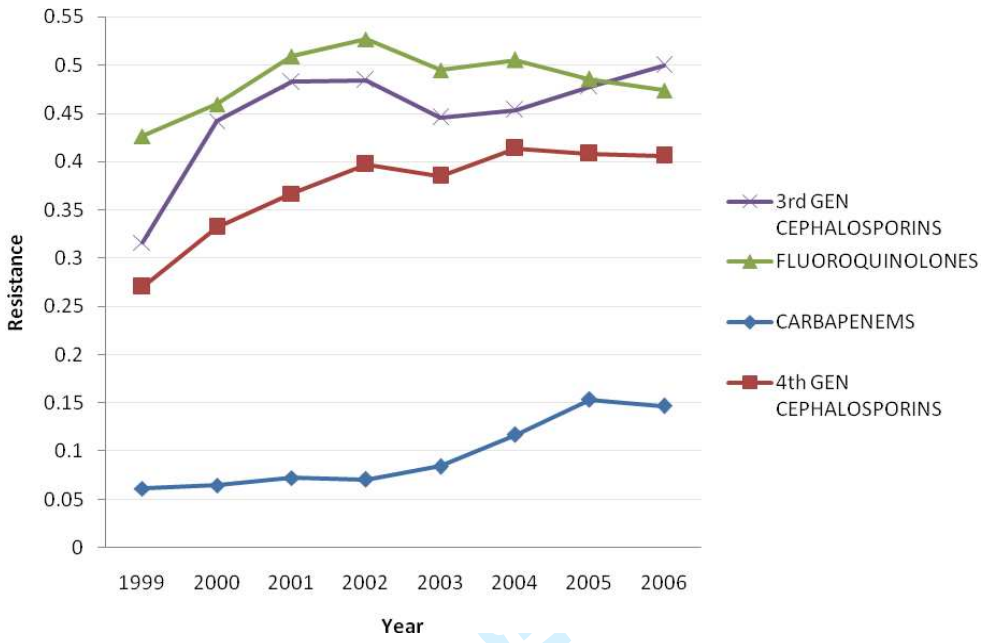
Figure 1a: Resistance rates of *Acinetobacter* spp. to four antibiotic classes in the United States, 1999–2006



Note: The following drugs were used to test for resistance to antibiotic classes: 3rd generation cephalosporins - ceftriaxone, ceftazidime; fluoroquinolones - ciprofloxacin, levofloxacin; carbapenems – imipenem; 4th generation cephalosporins – cefepime;

Source: Author's calculations using susceptibility data from The Surveillance Network® (TSN)

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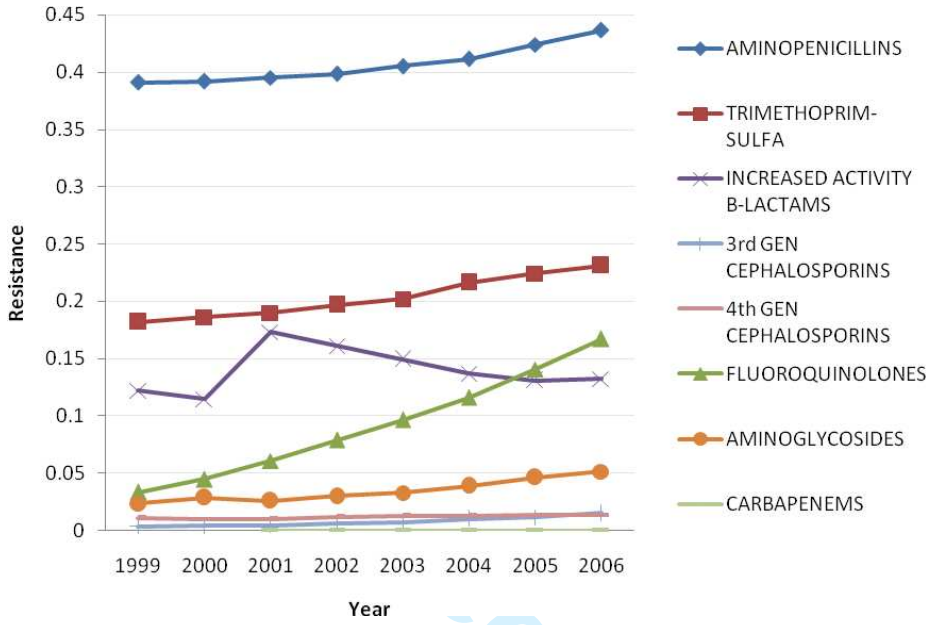
Figure 1b: Resistance rates of *Escherichia coli* to eight antibiotic classes in the United States, 1999–2006



Note: The following drugs were used to test for resistance to antibiotic classes: aminopenicillins – ampicillin; trimethoprim-sulfa – co-trimoxazole; increased activity beta-lactams – ampicillin/sulbactam, aztreonam, piperacillin; 3rd generation cephalosporins - ceftriaxone, ceftazidime; 4th generation cephalosporins – cefepime; fluoroquinolones - ciprofloxacin, levofloxacin; aminoglycosides – gentamicin, tobramycin; carbapenems – imipenem;

Source: Author's calculations using susceptibility data from The Surveillance Network® (TSN)

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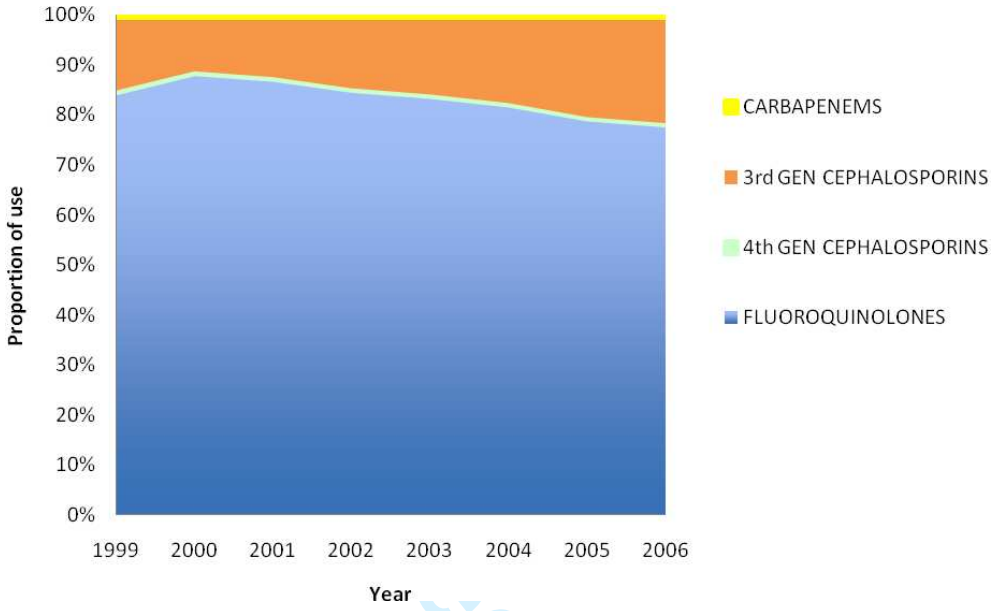
Figure 2a: Proportions of most-common antibiotic classes used to treat infections caused by *Acinetobacter* spp. in the United States, 1999–2006



Source: Author's calculations with prescription data derived from IMS Health Xponent™ January 1999-December 2007, IMS Health Incorporated.

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Figure 2b: Proportions of most-common antibiotic classes used to treat infections caused by *E. coli* in the United States, 1999–2006

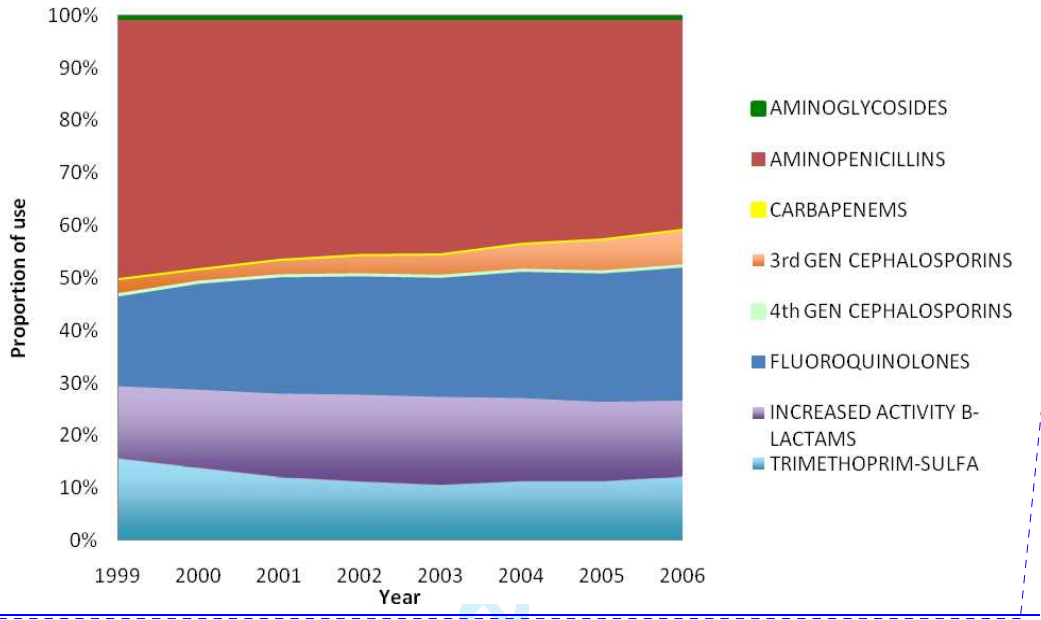

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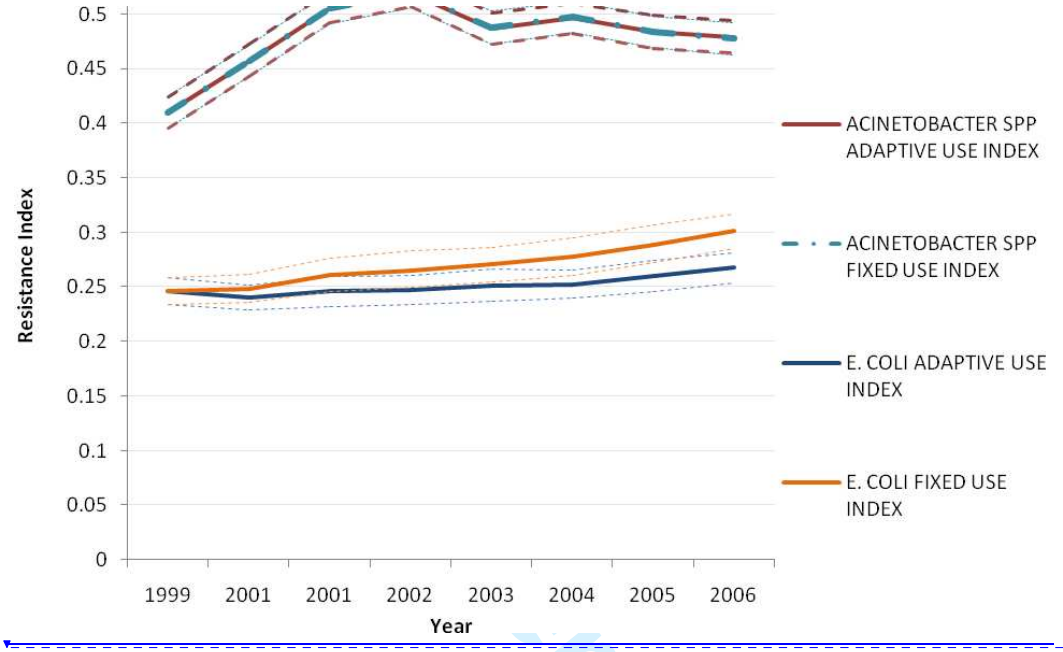
Figure 3: Static- and adaptive use DRIs for *Acinetobacter* spp. and *E. coli* in the United States, 1999–2006



Note: Dotted lines represent 95% confidence intervals (CIs); CIs for resistance and use proportion components derived using a bootstrap method with m=1000 simulations. A t-test showed that the difference of means from the bootstrap distribution was statistically significant at 1% level

Source: Author's calculations using susceptibility data from The Surveillance Network® (TSN) and prescription data derived from IMS Health Xponent™ January 1999-December 2007, IMS Health Incorporated.

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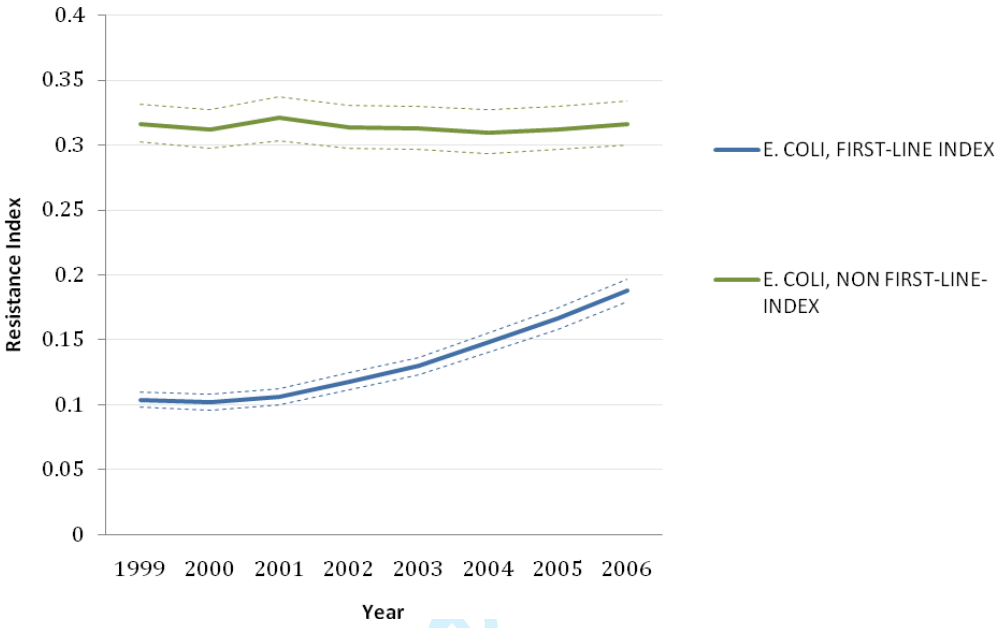
Figure 4: Adaptive DRIs for first-line therapy *E. coli* in the United States, 1999–2006



Note: a) Dotted lines represent 95% confidence intervals (CIs); CIs for resistance and use proportion components derived using a bootstrap method with m=1000 simulations.

b)Trimethoprim-sulfa and oral fluoroquinolones used as first-line therapies against *E. coli* urinary tract infections based on Taur and Smith (2007)

Source: Author's calculations using susceptibility data from The Surveillance Network® (TSN) and prescription data derived from IMS Health Xponent™ January 1999-December 2007, IMS Health Incorporated.

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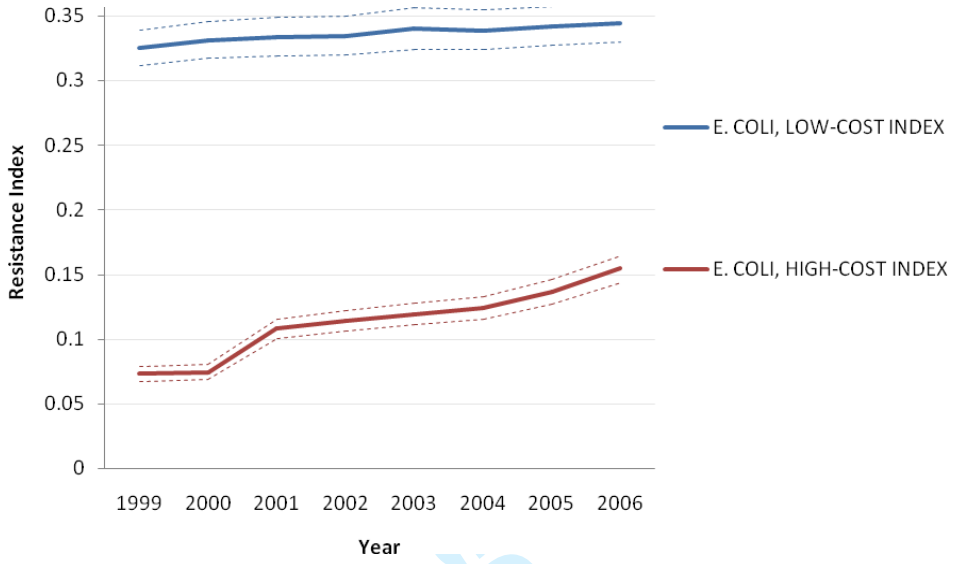
Figure 5: Adaptive affordability DRIs for *E. coli* in the United States, 1999–2006



Note: a) Dotted lines represent 95% confidence intervals (CIs); CIs for resistance and use proportion components derived using a bootstrap method with m=1000 simulations.

b) Low and high cost indices are based on daily cost at or under $30 and exceeding $30 respectively. Cheap drug classes include aminoglycosides, aminopenicillins, 3rd generation cephalosporins and trimethoprim-sulfamethoxazole; expensive drug classes include 4th generation cephalosporins, carbapenems, fluoroquinolones and increased activity beta-lactams.

Daily drug cost data were obtained from Cornell University's Weill Medical College.[2]

Source: Author's calculations using susceptibility data from The Surveillance Network® (TSN) and prescription data derived from IMS Health Xponent™ January 1999-December 2007, IMS Health Incorporate

[2] http://www-users.med.cornell.edu/~spon/picu/referenc/abxcost.htm. Accessed in December 2010

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Deleted: ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, imipenem, nitrofurantoin, and piperacillin. Cheap and expensive indices are based on daily cost at or under $100 and exceeding $100, respectively, in the case of *Acinetobacter* species. For *Acinetobacter* spp., cheap drugs were cefepime, ceftazidime, ceftriaxone and ciprofloxacin; expensive drugs include imipenem.
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Conflict of interest statement