

August 31, 2011

Mr. Richard Sands  
Managing Editor, BMJ Open  
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Dear Mr. Sands,

We are grateful for the opportunity to revise our manuscript “Communicating Trends in Resistance Using a Drug Resistance Index”. The revised version takes on board the valuable comments of the three reviewers. Reviewer 1 (Andreas Heddini) is primarily concerned with availability of antibiotic consumption data. We have previously recognized this caveat and have expanded its discussion in the revised version. Reviewer 2 (Christophe Fraser) would like the methods section to be expanded and confidence intervals introduced. We have done so. Reviewer 3 (Tom O’Brien) is primarily concerned with the usefulness of the index for empiric therapy, a task to which the index is not well suited. Finally, we have modified the title of the paper slightly.

Although the original idea for an index was mine, conversations with DrsKlugman and Grundmann have helped deepen the concept and bring it to its current shape and form. Therefore, I would like to retain them as co-authors on this paper. In addition, two research assistants, Itamar Megiddo and Nikolay Braykov, who implemented the bootstrap procedure, have been included as authors as well.

I realize that this paper is coming to you after the two-week deadline for resubmissions. However, we have done our best to turn this around expeditiously given the August vacation season, when none of the authors have been around. I hope you will take the timing of this request into consideration.

Sincerely,

Ramanan Laxminarayan

## **Response to Andreas Heddini**

This paper provides a thought-provoking and highly interesting model for better assessment of the burden incurred by resistant bacterial infections. The authors have developed a model, which serves as a useful tool to begin to capture and translate available resistance data into more comprehensible estimates of burden. However, as pointed out by the authors themselves, one important limitation is the scarcity and uncertainty of data on antibiotic consumption. This will be particularly challenging in low- and middle-income countries where sometimes 50 % or more of the total pharmaceutical sector is catered for by informal actors and data on antibiotic consumption are generally scarce. Having said this, the model is nevertheless likely to be most useful and serves as an excellent starting point to create aggregated and comparable data on the seriousness and burden of antibiotic resistance.

*We agree that antibiotic consumption data, though scarce, are becoming increasingly available. These are measured in terms of retail sales but can be verified against wholesaler purchases, which are generally observable. Our model only requires consistency in trends in antibiotic consumption. Unless there are systematic, time variant bias in measuring consumption through sales in formal sector outlets, the resistance index is likely to be a consistent measure. We have explained this further in the revision.*

## Response to Christophe Fraser

This paper is interesting, and addresses a current policy debate. Simplifying and synthesising the complex data on antibiotic resistance is a worthy task that may indeed aid communication of a complex multifactorial problem to a wider audience.

As a step in this direction, the authors propose some drug resistance indices, namely the weighted percentage resistance to drugs used. Different indices result from different stratifications of antibiotic use, by current usage, past usage, price, and first versus second-line.

This seems like a sensible way to summarise the data currently available, though strictly speaking I am not sure it is best described an 'index' (as in a stock market index) since it is an aggregate % resistant score.

*We use the term "index" in the sense that it is a "measure".*

The data sources are not well described or sufficiently referenced, and in particular the denominator/sample sizes do not seem to be described at all.

*We have expanded our description of data sources in the revision in the Methods section.*

I also think the authors should consider setting up a cached date-stamped copy of the web-sources they used as an SI of this paper, as websites have a nasty habit of being updated or deleted.

*This has been done.*

The manuscript would also benefit from a statistical analysis, e.g. presenting bootstrap confidence intervals for the indices.

*We agree and confidence intervals have now been provided.*

## Response to Thomas F. O'Brien

The indices described here by Laxminarayan et al. incorporate data on the antibiotics used to treat various pathogens into presentations of the resistance of those pathogens to the antibiotics. They are meant to make the presentations more informative and also clearer to policymakers. A reader might be helped, however, by more description of methods, of the data elements and linkages needed in available microbiology and pharmacy databases to relate the indices to the phases of antibiotic treatment.

A sick, febrile patient commonly gets initial empirical antibiotic therapy targeting many possible pathogens and guided, at best, by their overall past antibiotic susceptibilities summarized in a local antibiogram. The specific pathogen infecting that patient and its susceptibility to antibiotics may then be reported by a laboratory two days later. At that point the caregiver switches from not knowing which pathogen's past resistance prevalences are applicable, because the pathogen has been unknown, to not caring any more because the identified pathogen's susceptibilities are now explicitly known and an antibiotic can be chosen from them without reference to, or possibly now contradictory to, the local antibiogram. If the identified pathogen were an *Escherichia coli* susceptible to sulfamethoxazole-trimethoprim, for example, the drug to which the antibiogram showed *E. coli* to be most often resistant, it might now be preferred here. While using it may promote further resistance to it and further diminish its by-now largely discounted value for empirical therapy, it spares use of other antibiotics still useful for empirical therapy. While data for this knowledge-based treatment sequence may exist only where there are more resources, so also as the authors point out may the databases to support indices depending on similar data.

The identity and antibiotic susceptibility of the pathogen infecting a patient is likely to be in a database generated by a microbiology laboratory, or by a network of them like the Surveillance Network Database used here. The antibiotics used to treat that patient may be filed in electronic pharmacy records. If "resistance of a pathogen to a specific drug should be weighted by the extent to which that drug is used for treating the pathogen" then linking pathogen in one database to its treatment in another would seem necessary. Treatment may be the harder of the two to sort out. Pharmacy files may not distinguish multiple antibiotics used provisionally to treat the many possible pathogens needing to be "covered" during empirical therapy from the more focused treatment of an identified pathogen that may replace the empirical therapy if the pathogen is identified.

More details about how this was done for these studies and might be done for others might help a reader better see the significance of the indices and how to apply them.

*We have tried to make clear the data elements and linkages needed in available microbiology and pharmacy databases. However, the resistance index is not intended individual patient management for empiric therapy.*