



Comment on: Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list

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Comment on: Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list

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Sir,
We recently came across the study by Savoldi *et al.*¹ and would like to point out some potential problems associated with this and similar studies. It has hopefully now become clear to almost everybody that antimicrobial resistance (AMR) is a major threat to global

human health and that appropriate interventions are highly needed. Up until now the focus of intervention has been on simply reducing antimicrobial use; however, as pointed out in several recent studies, other epidemiological drivers are likely as important or even more important.^{2,3}

In the present study the authors examined the association between a single pre-selected epidemiological variable and reported occurrences of AMR using a simple univariate linear regression model. In this way they risk examining a confounding epidemiological variable and have a biased estimate of the regression coefficient, possibly overlooking other more specific variables that might be more important.

For example, in the study by Collignon *et al.*² they examined the association between AMR among *Escherichia coli*, nationwide antimicrobial usage (AMU) and a limited number of pre-selected country-specific parameters for governance, education, gross domestic product (GDP) per capita, healthcare spending and community infrastructure. They found that, while AMR might be associated with each of these in a univariate analyses, it was only significantly associated with governance and infrastructure (sanitation) in the multivariate model. Importantly, when compared with the study by Savoldi *et al.*,¹ they did not identify income as a significant explanatory variable when including the other variables.

In Hendriksen *et al.*³ we recently used metagenomics to determine the complete resistome in urban sewage and, rather than using a limited set of pre-selected assumed drivers, we associated AMR abundances with all available World Bank data (more than 1500 variables) for all countries, AMU and flight connections around the world. We identified 18 different significant clusters of variables that each explained part of the AMR abundances observed. In contrast to Collignon *et al.*² we still found AMU to be significant, but of more limited importance than the remaining drivers. Most drivers identified were associated with sanitation, health, education and governance, but additional potential interesting details were revealed. Again, when also including other parameters in a multivariate model, income was, by itself, not significant.

We do think that studies such as the one just published by Savoldi *et al.*¹ have relevance in pointing out potential interventions other than reducing AMU when trying to deal with AMR and we do acknowledge that we cannot wait for all causal links to be established before taking action. However, we should remember to take a scientifically critical look at other potential explanations and not only look at income in simple univariate analyses as the solution for everything.

There is no doubt that income and having money for interventions is important. However, when it comes to reducing AMR, it is more important how the scientific community advises and where governments decide to spend the money rather than just having a high gross national income.

Transparency declarations

None to declare.

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Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list—authors' response

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Sir,

We thank Aarestrup and van Bunnik¹ for their comment on our work² and for drawing our attention to their recently published study that came to slightly different conclusions. In their study, the authors used a metagenomic approach on urban sewage samples collected from 79 sites in 60 countries; the authors matched antimicrobial resistance (AMR) gene abundances with 1503 country-specific indicators and found that socioeconomic factors (especially sanitation, education and governance) strongly correlated with AMR, while income status *per se* was not significant.³

Conversely, in our paper, we found a significant correlation between the prevalence of seven distinct antibiotic-resistant bacteria and lower income status.²

We do agree with the authors that the spread of AMR results from a complex interaction of multiple factors, many of which are still to be evaluated, and our paper certainly does not intend to simplify the phenomenon of AMR and limit the causal relationship only between income status and AMR rates. As stated in our goals, our study aimed at providing an updated picture of the current surveillance coverage and to assess the global distribution of the most clinically relevant antibiotic-resistant bacterial phenotypes, according to the 2017 WHO pathogen priority list.⁴ In addition, we chose *a priori* the variable 'income' as an immediate and reasonable proxy of poverty and inequality in order to raise global attention to the issue for easy identification of places where promotion of hospital-level antimicrobial stewardship and infection control interventions are most needed. Of course, low income may be a proxy for other factors to be addressed at national and international levels, such as improved sanitation and, as such, we would see our paper as being complementary to the findings of Hendriksen *et al.*³

Third, although the use of metagenomics on urban sewage seems to be a flexible and reliable tool for surveying AMR, we consider that focusing the AMR burden exclusively on a healthy human population might be a limitation and that the clinical relevance of the 'AMR abundance' needs to be further investigated. Conversely, our study focused on clinically significant data by including exclusively data on invasive isolates and on clinically relevant resistance patterns.

We trust that the article of Hendriksen *et al.*³ brings new evidence and contributes, together with our results, to advocating a specific public health intervention to overcome resistance at both hospital and national levels and in particular in low- and medium-income countries.

Transparency declarations

None to declare.

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