Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis

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Summary

Introduction The decreasing effectiveness of antimicrobial agents is a growing global public health concern. Low-income and middle-income countries are vulnerable to the loss of antimicrobial efficacy because of their high burden of infectious disease and the cost of treating resistant organisms. We aimed to assess if copayments in the public sector promoted the development of antibiotic resistance by inducing patients to purchase treatment from less well regulated private providers.

Methods We analysed data from the WHO 2014 Antibacterial Resistance Global Surveillance report. We assessed the importance of out-of-pocket spending and copayment requirements for public sector drugs on the level of bacterial resistance in low-income and middle-income countries, using linear regression to adjust for environmental factors purported to be predictors of resistance, such as sanitation, animal husbandry, and poverty, and other structural components of the health sector. Our outcome variable of interest was the proportion of bacterial isolates tested that showed resistance to a class of antimicrobial agents. In particular, we computed the average proportion of isolates that showed antibiotic resistance for a given bacteria-antibacterial combination in a given country.

Findings Our sample included 47 countries (23 in Africa, eight in the Americas, three in Europe, eight in the Middle East, three in southeast Asia, and two in the western Pacific). Out-of-pocket health expenditures were the only factor significantly associated with antimicrobial resistance. A ten point increase in the percentage of health expenditures that were out-of-pocket was associated with a 3·2 percentage point increase in resistant isolates (95% CI 1·7–5·1; p=0·002). This association was driven by countries requiring copayments for drugs in the public health sector. Of these countries, moving from the 20th to 80th percentile of out-of-pocket health expenditures was associated with an increase in resistant bacterial isolates from 17·76% (95% CI 12·54–22·97) to 36·27% (31·16–41·38).

Interpretation Out-of-pocket health expenditures were strongly correlated with antimicrobial resistance in low-income and middle-income countries. This relation was driven by countries that require copayments on drugs in the public sector. Our data suggest cost-sharing of antimicrobials in the public sector might drive demand to the private sector in which supply-side incentives to overprescribe are probably heightened and quality assurance less standardised.

Funding National Institutes of Health.

Introduction Antimicrobial resistance is a growing global public health challenge that could undo decades of progress in decreasing morbidity and mortality from infectious diseases. Common bacterial pathogens have increasingly developed resistance to most available antibiotics. This phenomenon, coupled with a dry antibiotic pipeline, has led WHO to warn of a “post-antibiotic era, in which common infections and minor injuries can kill.”

Resistant organisms are more difficult to treat and are associated with higher morbidity and mortality than their susceptible counterparts.2 3 The US Centers for Disease Control and Prevention (CDC) estimates that at least 2 million illnesses and 23 000 deaths a year in the USA were caused by antibiotic resistance.4 The economic burden of antimicrobial resistance is difficult to calculate because of insufficient data and the need to account for externalities.5 However, estimates of the effect of antimicrobial resistance on the US economy are exceedingly high, including $20 billion (estimated in 2008) in direct health-care costs with additional indirect costs as high as $25 billion per year.6

The concern over rising antimicrobial resistance is not restricted to high-income countries. Okeke and colleagues7 document accelerating rates of resistance in enteric, respiratory, and sexually transmitted pathogens in low-income and middle-income countries. Several factors have been proposed as contributing to the spread of antimicrobial resistance.8 9 Socioeconomic status also affects what antibiotic agents are prescribed and is posited to be associated with resistance.10 11 Byarugaba12 points to a direct effect of poverty on antimicrobial use, whereas others13 suggest that rising incomes in low-income and middle-income countries...
might be an important factor. Okeke and colleagues\textsuperscript{14,16} have studied links between poverty and resistance and have identified several plausible pathways. First, people living in low-income and middle-income countries are more exposed to infectious diseases than people living in high-income countries and might be more susceptible because of malnutrition or immunodeficiency, and subsequently have a greater need for antimicrobial therapy. Second, impoverished individuals might be more at risk of being exposed to sub-inhibitory doses of antimicrobial agents because poverty can encourage shorter courses of treatment, drug sharing, or use of lower quality or expired drugs.\textsuperscript{7} Third, access to appropriate medical care can be more limited in developing countries, thus encouraging individuals to self-medicate or seek care from less tightly regulated, for-profit providers.

Out-of-pocket health expenditures are a major source of health-care financing in low-income and middle-income countries. Pharmaceutical purchases (including antimicrobial agents) constitute an estimated 70% of out-of-pocket health expenditures in India and 43% in Pakistan.\textsuperscript{18–21} In the sample of low-income and middle-income countries used in our main analysis, on average 49% of health expenditures are private. Most private health expenditures (76%) are out-of-pocket. Consistent with other reports, most out-of-pocket expenditures in low-income and middle-income countries (63%) were for drugs.\textsuperscript{21}

Traditionally, cost-sharing in the form of copayments has been viewed as a way to curtail the overuse of medical care. However, in many low-income and middle-income countries, copayments in the public sector can have an unintended consequence. Most developing economies have a robust informal private health-care sector that operates alongside the more traditional public health sector. If the public and private health sectors serve as substitutes for one another to some degree, the prediction from consumer theory is that raising the price (via a higher copayment) in the public health sector for a drug will shift more consumers into the private sector, depending on the elasticity of substitution and transaction costs associated with purchase in the public sector.\textsuperscript{22}

Motivated by this theoretical prediction, we aimed to assess with a mathematical economic model whether copayments in the public sector would promote the development of antibiotic resistance by inducing patients to purchase antibiotic treatment from less well regulated private providers who have financial incentives to inappropriately prescribe antibiotics, offer shortened courses of treatment, or use lower quality formulations. Even if total consumption of antibiotics were unchanged, the shift of more patients to less-regulated providers could lead to more antibiotic resistance.

Because of the scarcity of available data, few empirical studies have been done to assess the importance of out-of-pocket payments and copayments on antimicrobial resistance in low-income and middle-income countries.\textsuperscript{14–20} Here we use a recently published dataset\textsuperscript{1} collected by WHO to assess the role of such payments, while adjusting for other key proposed predictors on the prevalence of antimicrobial resistance across a sample of low-income and middle-income countries.

### Methods

#### Data sources

The main data source for antimicrobial resistance was the WHO global report on antimicrobial resistance, published in April, 2014.\textsuperscript{1} This report represented the “first attempt by WHO to assemble the accessible information on national ABR [antibacterial resistance] surveillance and on ABR data for a set of common pathogenic bacteria”. WHO sent questionnaires to member states, of which 129 responded and 114 provided data. The questionnaire was designed to probe each country on the prevalence of nine bacteria-antimicrobial resistance combinations including: *Escherichia coli* (resistance to third-generation cephalosporins, resistance to fluoroquinolones), *Klebsiella pneumoniae* (resistance to third-generation cephalosporins, resistance to carbapenems), *Staphylococcus aureus* (resistance to meticillin [MRSA], resistance, or non-susceptibility, to penicillin), non-typhoidal salmonella (resistance to fluoroquinolones), *Shigella* species (resistance to fluoroquinolones), and *Neisseria gonorrhoeae* (decreased susceptibility to third-generation cephalosporins). If data from national sources were incomplete or unavailable, WHO accessed data from national and international surveillance networks. If data from these two sources combined were still incomplete (<30 isolates tested), WHO sought data from the scientific literature published after 2007 to further broaden the sample. The report provides further details on the WHO method.\textsuperscript{1} Our outcome variable of interest was the proportion of bacterial isolates tested that showed resistance to a class of antimicrobial agents. In particular, we computed the average percent of isolates that showed antibiotic resistance for a given bacteria-antibacterial combination in a given country.

We took data for poverty (the percent poverty gap at $2 a day), sanitation (the percent of population with access to improved sanitation facilities), the percent of health expenditures that are paid out-of-pocket, and livestock and hospital bed density from the World Bank Indicators.\textsuperscript{22} The livestock production index includes meat, dairy products, and other derivatives directly from livestock.

We also included data for copayments for drugs in the public sector. In the sensitivity analyses (appendix), we included other features of the health sector such as copayments on consultations, physician density, and whether private providers could dispense drugs. We calculated physician density using the World Bank Indicators. The other variables listed were taken from the...
WHO pharmaceutical sector country profile reports. The variables included in the analysis were indicator variables equal to one if a copayment was required or dispensing by private physicians was admissible, or otherwise zero. Our sample included 47 countries (23 in Africa, eight in the Americas, three in Europe, eight in the Middle East, three in southeast Asia, and two in the western Pacific). The appendix lists the countries included in the analysis and the sources and precise definitions of all variables.

Statistical analysis

The dataset for the main analysis was a longitudinal panel of bacteria-antimicrobial resistance pairs at the country level. Bacterial-antimicrobial resistance combinations were aggregated within-country across data sources by use of the arithmetic average. Because the threshold to develop antimicrobial resistance against a given agent varies across pathogens, we modelled these differences with bacteria-antimicrobial combinations and region-specific slopes (holding constant fixed effects, a set of nine indicator variables, one for each of the nine bacteria-antimicrobial combinations and a set of five indicator variables for each of the different regions). Statistical testing rejected the hypothesis that these dummy variables were not confounders in understanding the association between environmental and health-care predictors and resistant bacterial isolates (F-test $\chi^2$ 23·46; p<0·001).

Our main findings are not derived on the basis of comparisons of different bacteria. The inclusion of indicator variables for each bacterial-antibacterial pair in our regression specifications allowed us to identify the statistical association between the percent of health expenditures that were out-of-pocket and the percent of isolates that were resistant, within (not across) a given bacterial-antibacterial pair. We estimated country-level linear regression models with percent of tested isolates that were resistant to a given antimicrobial agent as the outcome. Multivariate regression models added environmental and structural health-care characteristics believed to affect antimicrobial resistance.

Therefore, our basic linear fixed effects statistical model was:

$$\% \text{ Isolates} = \alpha + 0X + \beta_{\text{OOP Health Expenditures}} + \gamma + \delta + \epsilon_{\text{res}}$$

where $b$ is bacteria-antibacterial resistance pair, $c$ is country, and $r$ represents region. The outcome of interest is the percent of bacterial isolates tested that are classified as resistant. $X$ is a column vector of socioeconomic and environmental variables that vary at the country-level and have been implicated as factors that are accelerating resistance such as sanitation, livestock, and poverty. Standard errors were clustered by country to acknowledge the fact that countries were not sampled independently.

The appendix shows results that weight by population and weight the outcome by number of isolates and the addition of additional health-care characteristics such as physician density, log of income per person, and log of total health expenditures. We also averaged bacteria-antimicrobial combinations to the country level (appendix p 9). Finally, we expanded our sample to all countries with data for resistance and the World Development Indicators even if they did not have data for copayment structure (appendix p 10). We substituted countries for region indicator variables in the regression so that we estimated the association between out-of-pocket expenditures and resistance with only within-country variation (appendix p 11). Our results are not sensitive to these changes in the main specification.

We also ran separate regressions with resistance isolates for each bacterial group as the dependent variable (rather than the index resistance measure). We analysed data with Stata (version 12.1) (College Park, TX, USA).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The median antimicrobial resistance in isolates in our sample of countries was 15·0%. Table 1 shows summary statistics. Livestock production, hospital bed density, and poverty were not statistically different across the two groups. The percent of health expenditures that were out-of-pocket was statistically higher in the upper 50th percentile of antimicrobial resistance. To explore whether these simple differences remained significant conditional on other factors, we used multivariate regression. Resistance of bacterial isolates exceeded 20% in each region (figure 1). In our sample of countries, private health expenditures comprised about half of total health expenditures. Most of these private health expenditures were out-of-pocket (figure 2). Consistent with other

<table>
<thead>
<tr>
<th>All groups</th>
<th>Resistance lower than median</th>
<th>Resistance median or greater</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out-of-pocket expenditures, % of total health expenditures</td>
<td>35 87 (16·79)</td>
<td>33 01 (15·88)</td>
<td>38 58 (17·24)</td>
</tr>
<tr>
<td>Sanitation, % of population with access to improved facilities</td>
<td>52 45 (28·21)</td>
<td>49 20 (28·06)</td>
<td>55 53 (28·11)</td>
</tr>
<tr>
<td>Poverty gap, % &lt;$2 a day</td>
<td>44 48 (29·49)</td>
<td>47 06 (29·78)</td>
<td>42 03 (29·12)</td>
</tr>
<tr>
<td>Livestock index</td>
<td>125 67 (18·41)</td>
<td>124 68 (21·28)</td>
<td>126 61 (15·23)</td>
</tr>
<tr>
<td>Hospital bed density</td>
<td>19 78 (19·30)</td>
<td>19 78 (18·78)</td>
<td>19 77 (19·85)</td>
</tr>
</tbody>
</table>

Data are mean (SD). *Compares median or greater resistance with below median resistance.
reports, most out-of-pocket payments in low-income and middle-income countries were spent on drugs (figure 2).21

Figures 3 and 4 show the results of the multivariate analysis. Figure 3 shows the partial effect of a given predictor variable on antibacterial resistance after adjustment for other variables. We noted a positive relation between out-of-pocket spending on health care and antimicrobial resistance. A ten point increase in the percentage of out-of-pocket health expenditures was associated with a 3.2 percentage point increase in resistant bacteria (95% CI 1.17–5.15; p=0.002), representing roughly 15% of the sample average of resistance. This estimate was taken directly from the regression results (figure 3), and was obtained by multiplying the adjusted effect of the percent of health expenditures out of pocket on antibiotic resistance and its confidence interval by ten to represent a ten, as opposed to a one, unit increase. None of the other predictor variables (including sanitation) were significant.

Table 2 shows estimates from regressions with percent resistant isolates for each separate organism as the outcome variable. These estimates are imprecise because of small sample sizes. Nevertheless, the marginal effect of the percent of health expenditures that are out of pocket was significant and statistically indistinguishable from that provided using the summary resistance index measure (presented in figure 3 in all but one instance). The one exception was for the category Neisseria gonorrhoeae resistant to fluoroquinolones that had the smallest number of results (n=21). We believe this provides a strong justification for the summary index and we limit further analyses to the summary measure.

Of countries that required copayments, moving from the 20th to the 80th percentile of out-of-pocket health expenditures was associated with an increase in the bacterial isolates that were resistant from 17.76 (95% CI 12.54–22.97) to 36.27 (31.16–41.38) percentage points. Of countries that had no such requirement, moving from the 20th to the 80th percentile of out-of-pocket health expenditures was not associated with a change in the percentage of bacterial isolates that were resistant (19.54 [95% CI 12.91–26.12] to 19.48 [11.78–27.18]). Findings of an analysis done at the country level to assess factors that vary at that level showed that copayments for drugs strongly positively predicted the percent of health expenditures that are out of pocket, whereas copayments on consultation did not (appendix). This finding could relate to the fact that drugs seem to account for most out-of-pocket payments for health in low-income and middle-income countries (figure 1); it is difficult to know for certain how much of this out-of-pocket expenditure increase represents quantity versus price.

One threat to the validity of our analysis is that copayments in the public sector are not randomly assigned. It

Figure 1: Antimicrobial resistance by region
Antimicrobial resistance is calculated as the mean over data sources, bacterial–antimicrobial combinations, and over low-income and middle-income countries within a given region. The appendix shows the formula.

Figure 2: Out-of-pocket health expenditure (as a proportion of private health expenditures; A) and out-of-pocket spending on drugs (B)
is plausible that the level of public copayments is associated with other, unrecorded determinants of antibiotic resistance, thus changing the interpretation of our results. For instance, countries that have low infection control, poor infrastructure, or inadequately trained personnel for health care more generally, and thus more antibiotic resistance, could require higher copayments in their public sector clinics as a way to supplement their underfunded and overall poor health-care system. Thus, the omitted variable could be infection control practices or hospital infrastructure or aggregate (public and private) health expenditures.

Although we cannot randomly assign copayments on drugs in the public sector across countries, we checked whether countries with copayments are statistically indistinguishable from those without them. We assessed whether countries without public sector copayments were more likely to have poor sanitation, high levels of poverty, large numbers of livestock, a high density of hospitals, etc (since countries with these latter characteristics are a priori more likely to have high levels of antibiotic resistance).

Our results are not supportive of that view (appendix)—none of the predictors of antibiotic resistance are correlated with the presence of copayment and there is no difference between the marginal effects between the two groups. These results suggest countries with copayments on medications in the public sector are not observationally different than countries that do not have copayments.

**Discussion**

The control of the spread of resistant bacterial pathogens is an urgent global public health priority. Our results highlight an underappreciated policy lever to address this problem—the rolling back of cost-sharing arrangements for drugs in the public sector. In our study, we noted that out-of-pocket health expenditures are significantly more important than any other country-level environmental factors (including poverty, livestock production, access to sanitation, and other institutional features of the health sector) in predicting patterns of antimicrobial resistance across low-income and middle-income countries. Importantly, we noted that the association between out-of-pocket expenditures and resistance is driven by countries that require a copayment for drugs in the public sector.

Although no previous research has assessed the association between out-of-pocket payments and antibiotic resistance in low-income and middle-income countries, our findings are consistent with results that showed that suppliers-induced demand is an important determinant for excess use of health care. Data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) suggest a link between higher outpatient antimicrobial use and antimicrobial resistance. Although public use data for antibiotics consumption in low-income and middle-income countries, our findings are consistent with results that showed that suppliers-induced demand is an important determinant for excess use of health care. Data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) suggest a link between higher outpatient antimicrobial use and antimicrobial resistance. Although public use data for antibiotics consumption in low-income and middle-income countries, our findings are consistent with results that showed that suppliers-induced demand is an important determinant for excess use of health care. Data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) suggest a link between higher outpatient antimicrobial use and antimicrobial resistance.
**Panel: Research in context**

**Systematic review**

We searched Google Scholar and PubMed for scientific literature on antibiotic resistance in low-income and middle-income countries with the keywords “antibiotic resistance”, “antibiotic consumption”, “out-of-pocket health expenditures”, and “low- and middle-income countries.” We did not use a specific language or date filter. We assessed the “antibiotic consumption”, “out-of-pocket health expenditures”, and “low- and middle-income countries” in low-income and middle-income countries with the keywords “antibiotic resistance”, “out-of-pocket health expenditures”, and “low- and middle-income countries.” We used ordinary least squares to estimate the association between out-of-pocket health expenditures and percent resistant isolates for each separate organism as the outcome (the organisms are given as column headings). All models include the variables in equation 1 of the main analysis (e.g., livestock, sanitation, poverty, or hospital bed density). A Wald test of equality between the separate regression coefficient estimates and the preferred specification fails to reject the null for all but one instance. The results presented above are very similar to the preferred estimates use the summary index. Robust standard errors clustered at the country level are in brackets and are reported below the coefficient estimates. *p<0.05.

<table>
<thead>
<tr>
<th>Out-of-pocket health expenditures, mean (95%CI)</th>
<th>Meticillin-resistant Staphylococcus aureus</th>
<th>Escherichia coli</th>
<th>Klebsiella pneumoniae</th>
<th>Non-typhoidal salmonella</th>
<th>Shigella species</th>
<th>Fluoroquinolone-resistant Neisseria gonorrhoeae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of observations, n</td>
<td>36</td>
<td>79</td>
<td>58</td>
<td>33</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>p value of Wald test of equality with baseline coefficient estimate</td>
<td>0.974</td>
<td>0.199</td>
<td>0.396</td>
<td>0.209</td>
<td>0.189</td>
<td>0.001</td>
</tr>
</tbody>
</table>

We found several site-specific studies on the emergence of a particular antibiotic resistance pathogen in low-income and middle-income countries.

**Interpretation**

We find that the percent of health expenditures that are out-of-pocket strongly correlate with antimicrobial resistance in low- and middle-income countries. This relation was driven by countries that require copayments on drugs in the public sector. Our results suggest cost-sharing of antimicrobials in the public sector might shift demand from the public to the private sector where supply-side incentives to overspend are likely heightened and quality assurance less standardised. Our findings have two broader implications: first the standard one-sector model of demand for health care is not completely inelastic.30

However, when two sectors are selling the same or similar products, an increase in the price of one does not necessarily reduce overall quantity demanded, and can in fact increase resistance for the same overall consumption level if consumption in the private sector leads to greater resistance. To make this point clear, we developed a formal model (appendix). Briefly, in a spatial differentiation model, patients can substitute between the two sectors according to their own convenience or transaction costs. Heterogeneity between consumers (in terms of willingness and ability to trade off travel, wait time, and uncertainty about quality) lead to some demand in each sector even with different out-of-pocket prices for exactly the same product. An increase in one price might simply shift the marginal consumer from one sector to the other. For example, increasing the copayment in the public sector, on top of travel and waiting costs, might push consumers to use ubiquitous private pharmacies instead. More interestingly, total resistance might increase even if total consumption stays the same or decreases (up to a point) if the resistance generated per pill is sufficiently higher in the private sector. This assumption is plausible in view of the fact that shortened courses of treatment are common in the private sector, but drive resistance.

Our results have important limitations. First, data for antimicrobial resistance across resource-limited countries suffer from reporting bias and were most likely derived from hospital settings. Although reporting bias is a problem for all comparative health analyses, it is probably especially problematic for our outcome of interest. We have attempted to mitigate reporting bias by including indicator variables for regions. Therefore, the multivariate regression analysis compares a set of countries within the same region, and such countries are probably subject to similar constraints on data collection. Accurate surveillance that is standardised across geographical units would be the most direct way to eliminate reporting bias and should be a global health priority. More data for community-associated resistance might suggest that environmental predictors are more important than our study suggests. Second, our study focused on cross-country differences. Several studies have noted important geographical variation within a given country.19 The comparison of cross-country and within-country predictors of resistance should be an important focus of future research. Finally, what we have presented is a correlation and not definitive evidence of a causal mechanism.

The key insight of our analysis is that cost-sharing on drugs in the public sector might shift individuals into a less well regulated, often informal private sector. This situation is by contrast with the standard health economics view, which was developed for a one-sector system whereby cost-sharing tends to decrease demand.
To our knowledge, we are the first to point out this important distinction for low-income and middle-income countries. Bolstering the capacity of the public sector to diagnose, prescribe, and provide subsidised, high-quality antimicrobial agents could deter individuals from seeking medical care from self-employed private providers from whom they might receive lower quality or inappropriate dosage of antibiotics. For instance, research done by Onwujekwe and colleagues in Nigeria found that 78% of low-quality drugs came from private facilities compared with public facilities. Paruk and colleagues noted that patients receiving antibiotics in the private sector were more likely to receive a shortened course of antimicrobial therapy compared with those in the public sector. Because the same individual in the private sector often does prescribing and dispensing activities and quality controls on drugs are often absent, pulling patients into a strengthened public health sector for treatment of communicable disease could reduce the use of inappropriate or low quality antimicrobial agents and thus decrease the spread of resistant organisms. Pharmaceutical companies can have a role too. For instance, they could work to prevent counterfeit versions of their product by introducing scratch off labels and text messaging for verification as has been done in some low-income and middle-income countries.

The strategy of reducing cost barriers associated with drugs in the public sector is being proposed by the Health Ministry of India and has already been implemented in China. Whether such strategies slow the rate of antimicrobial overuse and resistance will be of their product by introducing scratch off labels and text messaging for verification as has been done in some low-income and middle-income countries.

Multiple antibiotic resistance and efflux.

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