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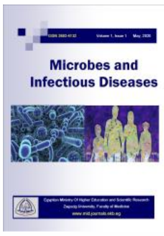

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Original article

Exploring determinants of antimicrobial resistance: A comprehensive analysis of health, socio-economic, and environmental factors

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ABSTRACT

Background: Antimicrobial resistance (AMR) is considered one of the key health challenges facing the globe. It has various implications for shaping the future of the health and healthcare industries. **Aim**: This study aims to explore potential socioeconomic and health system factors shaping the AMR burden globally. **Methods**: This secondary data-analysis study was conducted during the period from 2022 to 2023 between Cairo and Copenhagen. Data from the "global sewage surveillance project" in addition to several published datasets were composed, validated, and cleaned. Several exploratory data analyses were applied to examine the relationship between AMR and different factors, especially health system-related and socio-economic conditions and environmental and behavioral-related factors. Mathematical modeling using generalized multiple mixed models (GLMM) modeling techniques was applied to shape and describe these relations. The dependent variable was AMR burden measured by the number of resistant genes in the sewage sample that were expressed by FPKM; the independent variables were more than forty, covering various proposed factors. **Results**: The stepwise multiple fixed effects modeling showed that the proportion of the population with basic drinking water, care for newborns index, and the number of all health workers in the 10,000 population are the main determinants with negative coefficients. When a random effect model was fitted, it showed a significant association between AMR burden and region ($p < 0.001$). **Conclusion**: This study highlights the importance of basic hygienic measures and the empowered healthcare system in reducing the burden of antimicrobial resistance globally. Regional variations in AMR prevalence emphasize the need for tailored interventions that address specific regional contexts to combat this global health challenge effectively.

Introduction

Antimicrobial resistance (AMR) is a critical health issue facing the globe. It has various implications for shaping the future of the health and healthcare industries. AMR is not only a health concern but a multifaceted problem as well. The burden of AMR is heavier on low-middle-income countries like Egypt [1]. Identifying the existence and potential impact of AMR in Egypt and in agreement with the commitment in the World Health Organization Resolution (WHA 68.7), Egypt

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initiated the drafting of its national action plan (NAP) (2018-2022), which was coordinated by the MOHP with assistance from WHO. In the same context, a national healthcare-associated infection surveillance program started in Egypt in May 2011 [2].

According to the institute for Health Metrics and evaluation (IHME), Egypt in 2019, had approximately 16,100 deaths attributable to AMR and 56,600 deaths, and is considered to rank the 147th highest age-standardized mortality rate per 100,000 population associated with AMR across 204 countries [3].

According to the WHO, in 2014, data from 4 countries in the Eastern Mediterranean region (EMR) on *Escherichia coli (E. coli)* and *Klebsiella pneumonia* resistance to 3rd generation cephalosporins were obtained with an overall range of resistant proportion from 22 to 63% and 22 to 50% respectively. In addition, the global report on surveillance highlighted that the antibacterial resistance among other bacteria in the region is 0-93%. To fight AMR, we must understand the underlying contributing factors which are under-examined so far [4]. For a long time, we thought AMR was only related to antibiotic misuse; however, factors like economic, social, and various other predictors are still being discovered [5]. Such a breakthrough was made possible because the whole genomic sequencing (WGS) techniques go hand in hand with statistical modeling using artificial intelligence (AI) techniques [6].

Genomic data on resistant genes (resistomes) are being collected by the Danish Technical Institute team and analyzed using WGS techniques. The goal of the Global Sewage Surveillance Project, which was started in 2016 by the Danish Technical University, is to investigate the viability of using sewage for ongoing AMR monitoring. The study is based on analyzing these data using an AI mixed model to examine the possible macro-level factors contributing to AMR around the globe, including Egypt.

Statistical modeling is continuing to grow in a multidisciplinary field. Its importance was drawn from public health policies being multi-factorial issues [7]. Furthermore, as AMR is a complex problem, mathematical models are one of the best choices for analyzing related data to provide evidence-based policymaking [8].

This study aims to explore potential socioeconomic and health system factors shaping the AMR burden globally.

Methods

Data sources collection

This study is of secondary data analysis studies that depend on several published data. Our study was conducted from April 2022 to May 2023 as a collaboration between the public health and community medicine department, the faculty of medicine, Cairo University, Egypt, and the genetics epidemiology department at the Danish Technical Institute. The study utilizes data from the following sources: a) the global sewage surveillance project at the Food Institute at the Danish Technical University; b) The open-access database of the World Bank; c) the Global Burden of Disease (GBD) project data of The Institute for Health Metrics and Evaluation and d) the Oxford open-access databases.

The outcome variable for this study is the AMR burden represented by the number of resistant gene abundance or bacterial resistomes, measured in fragments per kilobase of exon per million mapped fragments (FPKM [9]. Such data were data collected in 2017; samples of domestic sewage were taken from 79 locations in seven geographical regions and 74 cities in 60 countries, and data for the rest of the countries were generated as predicted values. The predictors representing social, economic, demographic, environmental, and health system variables were obtained from the abovementioned databases (Appendix). countries classification into regions and super regions based on the global burden of diseases (GBD)classification of the world into 21 regions and seven super regions [10-12].

Data analysis

The data was checked for validity to ensure that the data matches the year and localities obtained from the global sewage surveillance database and the accuracy in defining each variable. Also, the completeness of the different variables is present in the databases. To examine the relationships between AMR burden and the predictors, exploratory data analysis and generalized linear mixed model (GLMM) regression. FPKM was used to predict the AMR burden. The exploratory data analysis included visualizations such as scatter plots with and without fitted lines, histograms, and facets graphs to identify potential relationships between the variables. Stepwise regression analysis was used to select the most critical fixed terms to include in the model, using forward and backward methods. The Akaike Information Criterion (AIC), significant level (SL), and Schwarz Bayesian Criterion (SBC) were used to select the best model. Mixed effects models were used to account for the variation in the outcome variable not accounted for by the fixed effects. The random effects were assumed to be normally distributed with a mean of zero and a variance specific to each level of the grouping variable (region according to the IHME classification). The model was fitted with and without fixed effects. The software used for data management and analysis included Microsoft Excel 365, a CSV file, R Studio (Studio 4.0.3), and various R packages such as StepReg for stepwise regression and lme4 and Haven for the GLMM, Ggplot2 for graphs, Caret for machine learning. Ethical approval was obtained from the Ethical Committee at Kasr Alainy School of Medicine, Cairo University under the number MD-163-2021.

Results

Exploratory data analysis

Pairwise correlations

The results show that several factors are significantly correlated with AMR burden, including open defecation, out-of-pocket expenditure, antibiotic consumption, MCV1 coverage, DTP3 coverage, basic sanitation, physicians, basic drinking water, internet use, Universal Health Coverage (UHC) effective coverage index, antenatal, postpartum, and postnatal care for mothers, all health workers, antenatal, peripartum, and postnatal care for newborns, SDI, under-five mortality, domestic general government health expenditure, and share of population covered by health insurance. Other predictors showed significant correlations, yet they were not part of the model for several reasons **(Appendix).**

The strongest correlations with AMR burden were found for factors such as basic sanitation, number of physicians, nursing and midwifery personnel, and SDI, which were negatively correlated with AMR burden. Meanwhile, factors such as open defecation and out-of-pocket expenditure were positively correlated with AMR burden.

Multi-level scatter plots

The multilevel scatter plot with linear regression lines shown in **figure (1)** illustrates the relationship between the number of all health workers per 10,000 population and AMR burden by FPKM across different super regions. The scatter plot shows a negative association between the two variables, with higher numbers of health workers associated with lower AMR burden. The regression lines for each super region also suggest a negative association between the two variables, although there is some variation in the strength of the association across regions.

General linear model

This study used six fixed effects linear models to identify the most important factors associated with global AMR burden in forward and backward stepwise manners. The results showed that the care for newborns index, the number of all health workers per 10,000 population, and the percentage of the population with basic drinking water were statistically significant predictors of AMR burden across different models, and all had negative coefficients. Other variables appeared to have effects when included in some of the models as follows.

The high middle-income group, percent of the population who have basic drinking water, percent of the population who practice open defecation, antibiotic consumption (DDD/1,000/day), UHC effective coverage index, care for newborns index, DTP3 coverage, and met need for family planning with modern contraception index, number of nursing and midwifery personnel per 10,000 population and pharmaceutical personnel per 10,000 population, socio-demographic index and total health expenditure as percentage of GDP were statistically significant predictors of AMR burden. The high middle-income group, antibiotic consumption (DDD/1,000/day), and met need for family planning with modern contraception index had positive coefficients, while the rest of the significant predictors had negative coefficients.

Multilevel (mixed effect) model

A linear mixed effects model was used to investigate the association between AMR burden and geographic region while controlling for the effects of other potential confounders. The model included a random intercept for region, accounting for clustering observations within regions. The results showed a significant association between AMR burden and region ($p < 0.001$), with an estimated variance of the random intercept for region indicating substantial heterogeneity in AMR burden across regions. The intra-cluster cross-correlation (ICC) was calculated to be 0.614, indicating that 61.4% of the total variance in AMR burden can be attributed to differences between regions **(Appendix).**

We also investigated the association between AMR burden and access to basic drinking water using a linear mixed effects model with a random intercept for region. The results showed a significant association between access to basic drinking water and AMR burden ($p < 0.001$), with regions having better access to basic drinking water having lower AMR burden **(Table 1)**. The estimated variance of the random intercept for region was 3123.55, indicating substantial heterogeneity in AMR burden across regions that the fixed effect of access to basic drinking water could not explain. The ICC of our model was calculated to be 0.47, indicating that 47% of the total variance in AMR burden can be attributed to differences between regions **(Table 2)**.

Our findings highlight the importance of geographic region as a predictor of AMR burden and the need for interventions and surveillance efforts that consider regional differences in AMR prevalence and patterns of antimicrobial use. Access to basic drinking water was also found to be an important predictor of AMR burden, suggesting that improving access to clean water may be an effective strategy in mitigating the burden of antimicrobial resistance.

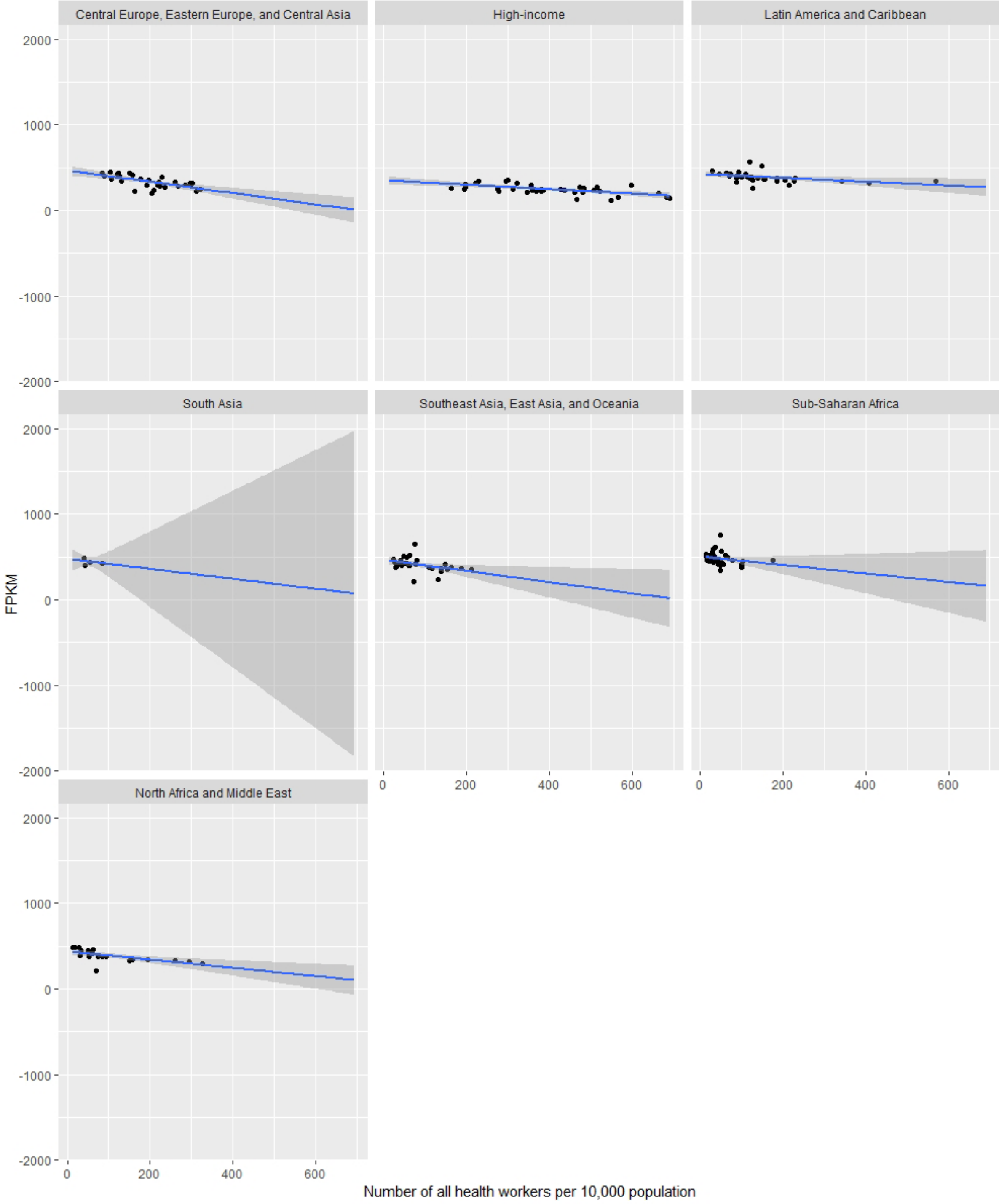
Table 1. Shows the mixed effects regression results with random intercept only.

	AMR burden		
Predictors	**Estimates**	**CI**	***P***
Intercept	375.53	338.85-412.20	<0.001
Random Effects			
σ^2	4097.82		
τ 00 Region	6507.14		
ICC	0.61		
N Region	21		
Observations	198		
Marginal R^2 / Conditional R^2	0.000/0.614		

Table 2. Shows the mixed effects regression results with random intercept and a fixed effect.

	AMR burden		
Predictors	**Estimates**	**CI**	***P***
Intercept	375.53	338.85-412.20	<0.001
Basic Drinking water	-2.94	-3.78- -2.10	<0.001
Random Effects			
σ^2	3586.31		
τ 00 Region	3123.55		
ICC	0.47		
N Region	21		
Observations	195		
Marginal R^2 / Conditional R^2	0.250/0.599		

Figure 1. scatter plot showing the relationship between the number of all health workers per 10,000 population and antimicrobial resistance (amr) burden in different super regions. Each panel represents a different region, with the scatter plot and linear regression



Discussion

Antimicrobial resistance is an enormous public health challenge that requires global attention in order to halt the spread of resistant infections [13]. Most of the literature on this subject has focused on irrational antimicrobial agent use, ignoring the fact that this is primarily human behavior. Furthermore, it reflects the efficacy of the health-care systems [14]. This study explored socioeconomic and health system determinants that may be involved in AMR. The findings of this study can provide insights for policymakers and health practitioners to develop effective strategies for reducing the burden of AMR.

This study highlighted the pivotal role of 3 factors as predictors in determining AMR: the availability of basic potable water, the number of health workers per 10000 people, and the index of newborn care availability. This agreed with **Booth *et al.*** in a 2022 study where lack of access to sanitary water was identified as a predictor for AMR [15]. In addition, according to **Alvarez-Uria *et al.*,** it was found that a certain country's income can predict this country's levels of AMR, for example, with an 11.3% decrease in the prevalence of *E. coli* resistant to broad-spectrum cephalosporins, there is an increase in the log of Gross National Income (GNI) per capita [16].

This would be explained as follows: low-income countries have a higher population density, suboptimal sewage systems, poor sanitation, and lack of access to clean water as well as inadequate antimicrobial stewardship programs, low vaccination rates, and lower education levels.

Moreover, according to **Booth et al.** it was demonstrated that healthcare access and quality were significantly associated with blood culture QREC (%) levels [15]. This was in accordance with the results of the current study, where the number of all health workers per 10,000 population (proxy of healthcare accessibility) was a statistically significant predictor of AMR burden across different models. Regarding the healthcare workforce, whether the ratio of health workers per 10,000 people was given as the total number of health workers or as the number of a certain group of health workers, it was significant in most models in different ways and almost always had a negative correlation. Whenever the number of health workers increases, the AMR burden will decrease. The role of the health workforce, especially in developing countries, may also be controversial, especially for pharmaceutical personnel, as there might be no guidelines for dispensing antibiotics [17] or poor knowledge about the risks of dispensing antibiotics without a prescription, as it is a common healthcare practice in a lot of developing countries [18]. Therefore, it is crucial to provide education and training to healthcare workers on the appropriate use of antibiotics and infection prevention measures.

The index of effectiveness of antenatal, perinatal, and postnatal care for newborn babies is an index used by the GBD team to measure service provision. It reflects the service provision block in health system block models. This predictor was significant in almost all the models with negative coefficients, which reflects a simple but powerful fact: Wherever there is a lack of basic health services like newborn care, the burden of AMR will be higher.

Antibiotic consumption, which was expressed in defined daily doses (DDD) per 1000 inhabitants per day, was a significant predictor in a backward selection model. This predictor was selected to be among the project dataset as it was thought to be a confounding variable because many literature and policy papers believe that high antibiotic consumption is one of the main factors behind the antimicrobial resistance burden [19]. Antibiotic consumption was a significant positive predictor, meaning that with the increase in antibiotic consumption, the burden of AMR increases. In agreement with the existing literature and policy papers, it is important to promote the rational use of antibiotics and implement effective antibiotic stewardship programs [20, 21].

The need for family planning with modern contraception is one of the effective coverage indicators that is used by the GBD team. It represents the health promotion services for a significant population (females at their reproductive age). The use of modern contraception has been shown to reduce maternal mortality, unintended pregnancies, and unsafe abortions. Therefore, increasing the coverage of family planning services can positively impact the health and well-being of women and their families. In the backward selection, this predictor was significant with a positive coefficient, and in the univariate regression, it showed a negative correlation. This may be due to the presence of certain confounding factors or leverage points.

The GBD team calculated the UHC effective coverage index [22]. They chose 23 "effective coverage indicators" representing health service types. To approximate access to quality care, "effective coverage indicators" were standing on intervention coverage or "outcome-based measures" e.g. mortality-to-incidence ratios. Then, "outcome-based measures" were converted to values on a scale of 0–100 that is based on percentiles (the 25th and 975th of location-year values). They created the UHC effective coverage index in a way that used the weight of each "effective coverage indicator" following each indicator's potential health gains. For example, they were measured by disability-adjusted life-years for each location-year and population-age group. As a predictor for AMR burden, it was significant yet with positive coefficients as well, although, in the univariate analysis, it was in negative correlation with AMR burden, which reflects possible mathematical controversy—either confounding or mediating factors or interaction terms.

Created by GBD researchers, the socio-demographic Index (SDI) is a compounded indicator of the status of development. It is calculated using the mean of the following indices; total fertility rate among those under the age of 25 (TFU25), mean education for those 15 years of age and older (EDU15+), and lagged distributed income (LDI) per capita. SDI as a predictor was significant with a negative coefficient, and it had the highest coefficient among other significant predictors. With one unit change in SDI, the AMR burden will change to 350 FPKM. Since it is a composite indicator that includes fertility, education, and income, that means that with the increase in the level of socioeconomic development of a certain country, the burden of AMR will decrease. Therefore, investing in improving the socioeconomic development of a country can be an effective strategy to combat AMR.

Income group is a classification done by the World Bank Group based on the gross domestic product (GDP)[10]. As a categorical predictor, only one group was significant (the high-middle-income countries) with a positive coefficient compared to the reference group, which is the low-income countries group.

Limitations

The study collected data on the AMR burden (AMR burden) from over 60 countries, but some nations, like Egypt, were improperly sampled, resulting in the use of predicted values in the model. The data was collected from various databases, with each country represented by one entry representing the average predictor for that country. This means the models produced cannot describe or predict beyond the average values of each country, and the results cannot be generalized to the populations of these countries. Data-related problems include different institutions making the collection and cleaning process, which may have different criteria and depend on state-related national census authorities. The data collected from middle and low-income countries seems insufficient, resulting in projections. The data used in the outcome variables was collected in 2017, while the predictors variable may vary in years around 2017.

Conclusion

High AMR burden is measured by the number of resistant genes in the sewage sample that FPKM measured. This can be explained through different possibilities: incompetent health systems and poor service delivery represented in weak health care services for newborns or lack of the proper number of the health workforce. In addition, poor potable water supply and related hygienic measures represent environmental and behavioral elements that can play a role in antimicrobial resistance. Hence, comprehensive national policies under the auspices of the international cooperation framework should be adopted to compact AMR. Such policies may include social, economic, and environmental aspects and strengthen the health system to achieve universal health coverage. Furthermore, regional variations in AMR prevalence emphasize the need for tailored interventions that address specific regional contexts to combat this global health challenge effectively.

Recommendations

The following recommendations, if implemented, can help mitigate the burden of antimicrobial resistance and enhance health outcomes, especially in Low and Low-Middle-Income Countries:

a. Accelerating the implementation of (UHC) in Low and - Low-Middle Income Countries is crucial for ensuring universal health and mitigating AMR.

b. The health workforce's training is critical for enhancing the appropriate use of antibiotics and reducing the risk of AMR.

c. Socio-economic factors like poverty and limited healthcare access are crucial in reducing the burden of AMR.
d. Strengthening local capacity through data collection, analysis, quality improvement, accessibility, and use can sustain data systems, inform policy, and enhance decision-making at all levels.
e. Further research is needed to deeply investigate the identified factors as AMR predictors.

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Conflict of interest

NO financial or personal relationships with other people or organizations that could inappropriately influence (bias) the authors' actions.

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