Machine Learning for Worldwide Antibiotic Usage and Resistance Prediction: A Longitudinal Study on Effective Environmental, Economic, and Social Predictors

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ABSTRACT

Antibiotic resistance (ABR) is a growing global health concern that threatens the future of human wellbeing. The leading causes of increased ABR—excessive and inappropriate use of antibiotics—can be linked to a diverse array of multidisciplinary environmental factors, largely those related to the healthcare, agricultural, and food industries. Here, we employ machine learning to understand antibiotic resistance trends, utilizing a dataset of 804 socioeconomic, environmental, and demographic indicators to identify the most effective predictors of and factors contributing to ABR, and predict antibiotic resistance for years with available data using the model. We predicted that machine learning would be able to accurately predict antibiotic resistance and that the significant predictors would be diverse, though primarily environmental-related. We found that global antibiotic use and resistance risk has predictables trends by means of machine learning, with our models' accuracy being above 95%. We also found that the best predictors of ABR were most often environmental factors. Nonetheless, the significance of a diverse array of factors indicates that antibiotic use and resistance is an inherently multidisciplinary issue. Overall, our study can be used to inform policymakers across all disciplines to implement measures to mitigate the rise of antibiotic resistance.

INTRODUCTION

As a leading global health concern, antibiotic resistance warrants a coordinated plan of action to address its threat to human health (Lee et al., 2013). Antibiotics inhibit the growth and survival of bacteria while dealing minimal harm to the patient (Singh et al., 2014). However, bacteria can acquire resistance to these drugs through diverse biological mechanisms—such as target modification, permeability reduction, and metabolic alteration—typically induced by mutations deemed antibiotic-resistance genes (ARGs) (Van Hoek et al., 2011; Zhang & Cheng, 2022). Excessive use and antibiotic mismanagement—namely in the healthcare, agricultural and food industries—are the leading causes of increased antibiotic resistance (Lopez‑Vazquez et al., 2012; Manyi-Loh et al., 2018).

The loss of antibiotics as an effective treatment option would negate much of the medical achievements of the past century and prove disastrous for human health by rendering the practice of many medical procedures unsafe (Andersson & Hughes, 2010; Smith & Coast, 2013). Currently, developed and developing nations are already witnessing climbing death tolls (Murray et al., 2022). In 2019, antimicrobial resistant bacterial infections accounted for 1.27 million direct fatalities worldwide, forecasted to reach 10 million annually by 2050 (Murray et al., 2022; Tang et al., 2023).

Disease outbreaks tied to extreme weather events, particularly in developing nations, can exacerbate ABR among climate-impacted communities (McMichael, 2015). Moreover, anthropogenic changes in the environment such as global warming and pollution may accelerate the spread of ABR (Buelow et al., 2021; MacFadden et al., 2018). Runoff of antibiotics from contaminated animal manure, farmland, and pharmaceutical waste feed the persistence of ARGs in impacted ecosystems (CDC, 2022; Zainab et al., 2020). However, the environment's role in spreading ABR to human pathogens beyond acting as a reservoir of

ARGs remains unclear (Lepper et al., 2022). Understanding how ABR circulates between the environment, livestock, and humans is imperative and lies at the core of the "One-Health" perspective, which stresses the interconnectivity of human, environmental and domestic animal health with respect to ABR (Aslam et al., 2021; Larsson et al., 2018).

As a testament to the relevance of One-Health, a number of ARGs originally from the environment, transfer to human pathogens via animal hosts, a process reinforced by world trade, conflict, animal migration and human travel (Aslam et al., 2021; Hernando-Amado et al., 2019). Increasing dependency on antibiotics, has equally favored the spread of antibiotic-resistance (Fletcher, 2015).

The use of artificial intelligence (AI) has proven useful in the struggle against ABR. In clinical settings, AI has been used to assist clinicians in diagnosing antibiotic-resistant infections, designing personalized antibiotic regimens for patients, and applying appropriate measures to limit unnecessary antibiotic usage or improper dosage of administered antibiotics (Sakagianni et al., 2023). AI-assisted decision-making can help clinicians adhere to antibiotic stewardship programs by limiting reliance on broad-spectrum antibiotics that promote the spread of resistance (Kanjilal et al., 2020). Furthermore, machine learning models have been used to analyze patterns and identify global hotspots of ABR (Fallach et al., 2020; Nsubuga et al., 2024; OneHealthTrust, 2024; Tong et al., 2024). Overall, the use of machine learning helps healthcare providers, policymakers, and public healthcare authorities to respond quickly to outbreaks and act to reduce the global burden of ABR (Ali et al., 2023).

Our study aims to elucidate global ABR trends by using a machine learning model to identify the factors driving this phenomenon and predict antibiotic usage and ABR statistics for future years. Our model used a dataset of 804 indicators from the World Bank—including environmental, social, economic, and demographic factors—to predict antibiotic consumption per country, a proxy for antibiotic resistance, in 145 regions across the world

over a period of 20 years. Given the multifaceted nature of ABR, we hypothesize that our machine learning model will identify a range of strongly associated predictors of antibiotic use and resistance from different domains, however, environmental factors will be the most important predictors. Moreover, we hypothesize that the model will yield an accurate global picture of future antibiotic usage, provided that sufficient data is available for each region. Overall, by finding the effective predictors of antibiotic resistance in past and future years, our model can pave the way for future studies to advise policy makers in planning and implementing cost-effective interventions to prevent and control antibiotic resistance.

METHODS

Data processing

Inputs. ABR is a multi-faceted problem that covers the interaction between health, social, economic, and environmental factors. We here consider 804 statistical time series covering the aforementioned categories for 145 countries worldwide from 2003 to 2022 from the *World Development Indicators* and the *Health, Nutrition and Population Statistics* databases from the World Bank[1] (World Bank Open Data, 2024). This includes 79 indicators related to the environment; 8, to climate change[2]. (See Appendix I for the full list of categories, indicators and regions). The 717 other indicators serve as contextual factors used to aid the training of the machine learning model. We applied z-score standardization on a per-factor-basis as many of the indicators were on different scales (percentages, dollars, population, etc.). The 6.99% of the database values that were unavailable were assigned a neutral z-score of zero, which attenuates the influence of missing data in the model training as a neutral value does not bias prediction.

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[1] Initially, due to the unavailability of 45.77% of the factors either over time or for specific regions, filtering was done to improve data quality. 52.23% (879/1683) of the indicators and 45.49% (121/266) of the regions were therefore removed from the initial database due to incomplete data. We moved forward with the remaining 804 indicators and 145 regions.
[2] Notable environmental factors include: *Urban land area where elevation is below 5 meters (sq. km), People practicing open defecation (% of population), People using at least basic drinking water services, rural (% of rural population), People with basic hand washing facilities including soap and water, urban (% of urban population), Urban population (% of total population), etc.*

Outputs. The most recent worldwide antibiotic usage data for each of the 145 regions from 2003 to 2018 was obtained from the group of Global Research on Antimicrobial Resistance (Browne et al. 2021). Defined daily dose per 1,000 people per day (DDD/1,000/day) was used as a measure of drug utilization, an internationally standardized unit used to examine worldwide trends and compare drug usage over time, matching the intentions of our analysis (Defined Daily Dose (DDD), 2024). A defined dose is the average maintenance dose for adults for a prescribed drug (ATC/DDD Index, 2024). The total antibiotic usage per region was determined by the total usage in DDD/1,000/day of 8 antibiotic types[3]. To facilitate the machine learning training, we used equal width binning to categorize total antibiotic usage and resistance risk into five intervals: low, medium-low, medium, medium-high and high[4]. We use antibiotic consumption as a proxy for resistance (Olesen et al., 2018).

Machine learning

Model architecture. We used a multilayer perceptron classifier (MLP) (Murtagh, 1991) composed of 804 inputs (matching each of the indicators), a dropout layer, a hidden layer composed of 405 nodes on which the hyperbolic tangent activation function was applied, and 5 output layers (matching each of the categories) on which the softmax activation function was applied. Bayesian optimization was used to optimize for the model's hyperparameters (Frazier, 2018). (See Appendix II for specifics on the model design choices and technical details.) MLP was chosen for its simplicity in training, and ease of understanding of the links between input and output, which is necessary for our results analysis and to determine influence of specific factors on antibiotic usage. A softmax output was chosen; the model returns the probability of a country being in one of the five total

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[3]Tetracyclines (J01A), amphenicols (J01B), penicillins (J01C), other beta-lactams (J01D), sulfonamides and trimethoprim (J01E), macrolides (J01F), lincosamides & streptogramins (J01G), aminoglycosides, and quinolones (J01M).
[4]Low (≤ 11.42), medium-low (11.42, 20.04], medium (20.04, 28.66], medium-high (28.66, 37.28], and high (> 37.28), in DDD/1,000/day.

antibiotic usage categories, when given the context of the 804 indicators associated with that country during a year.

  Training. For the input, the model was repeatedly contextualized with sets of 804 indicators which pertained to one of the 145 studied regions during one of the years between 2003 to 2017. By its output, the machine learning model therefore attempted to infer which of the five categories a given country's antibiotic consumption level would land in. When compared with the known output category, the model could improve upon its predictions over time and learn patterns in the training data. To verify its learning accuracy, the model was contextualized with sets of 804 indicators which pertained to each of the 145 regions during the year 2018—testing data the model has not seen before during the training phase.

  Result processing. As the most recent antibiotic usage data ends in 2018, the trained model was applied on the contexts of each of the 145 countries from 2019 to 2022 in order to predict their total antibiotic usage. 95% was chosen as a threshold for a high prediction accuracy. Once the model was established to be accurate, we determined effective correlations between each of the 804 inputs and a high total antibiotic usage using the integrated gradients method (Sundararajan et al., 2017). Each factor received its associated attribution, an importance value, normalized to a range of [-1, 1], measuring its contribution to a high total antibiotic usage. The importance of each of the 87 environmental factors, and the top 100 indicators, was then established by a numerical ordering of the attributions.
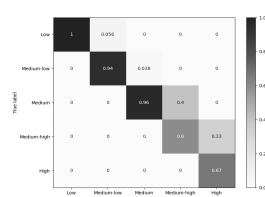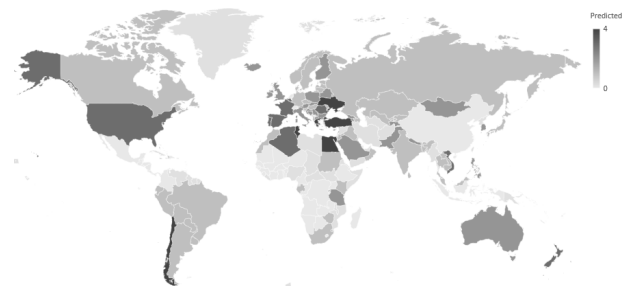
RESULTS[5]

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[5] For additional visualizations and maps, please refer to: https://thataquarel.github.io/health/.
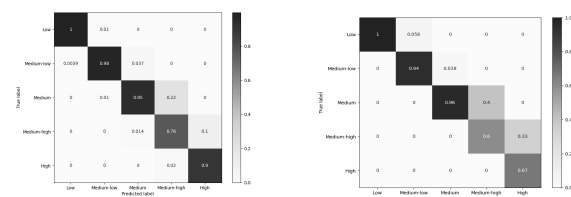
Figure 1. Predicted and actual total antibiotic usage category confusion matrix for training data (2003 to 2017).

Figure 2. Predicted and actual total antibiotic usage category confusion matrix for testing data (2018).

Figure 3. Predicted total antibiotic usage category (low, medium-low, medium, medium-high, high) per country by machine learning in 2022. Chile, Egypt, Greece, Tunisia, Turkey, Ukraine have a high antibiotic usage and resistance risk.

We achieved a 97.74% accuracy in predicting the category of training data (Fig. 1), and a 95.17% accuracy in predicting the category of testing data (Fig. 2), allowing the model to confidently discern between the five categories in total antibiotic usage. We were therefore convinced in applying the model to make future predictions (Fig. 3) and to obtain the most effective predictors of high antibiotic usage (Table 1). See Appendix III for visualizations.

Table 1. Most effective predictors of high antibiotic usage sorted by type of correlation.

High total antibiotic usage predictors	
Positively linked	**Negatively linked**
People using at least basic sanitation services (% of population)	Adjusted net savings, excluding particulate emission damage (% of GNI)
People using at least basic sanitation services, rural (% of rural population)	Adjusted net savings, including particulate emission damage (% of GNI)
People using at least basic sanitation services, urban (% of urban population)	Adjusted savings : gross savings (% of GNI)
People using at least basic drinking water services (% of population)	Adjusted savings : net national savings (% of GNI)
People using at least basic drinking water services, rural (% of rural population)	Urban population growth (annual %)
People using at least basic drinking water services, urban (% of urban population)	Population growth (annual %)
People using safely managed sanitation services (% of population)	Probability of dying among adolescents ages 10-14 years (per 1,000)
Access to electricity (% of population)	Probability of dying among youth ages 20-24 years, male (per 1,000)
Access to clean fuels and technologies for cooking (% of population)	Mortality rate, neonatal (per 1,000 live births)
Total natural resources rents (% of GDP)	Adolescent fertility rate (births per 1,000 women ages 15-19)
Urban population	Employment to population ratio, ages 15-24, female (%) (modeled ILO estimate)
Agricultural land (% of land area)	Employment to population ratio, ages 15-24, total (%) (modeled ILO estimate)

DISCUSSION

In this study, we utilized machine learning to forecast and interpret global antibiotic resistance trends. In agreement with our initial hypothesis, which expected a diverse array of effective predictors, our findings revealed that environmental indicators—followed by health, education, economy, growth, and social development factors—played a significantly influential role in predicting high total antibiotic usage and resistance risk. For environmental predictors, the significance of factors such as access to basic sanitation services, access to basic drinking water services, access to clean fuels and technologies for cooking, access to electricity, and the percentage of the population using safely managed sanitation services

revealed the correlation between sanitation-related environmental and a high antibiotic usage. The positive correlation between the sanitation-related environmental factors and antibiotic usage can be linked to the fact that developed healthcare systems—in this case, implied by established sanitation measures—are heavily dependent on the use of antibiotics (Cecchini,et al., 2015). Therefore, countries with developed healthcare systems are more at risk of having increased levels of antibiotic resistance, and thus warrant informed measures to prevent and control the development of ABR. Our study contradicts some previous studies that have associated improved sanitation with a decrease in antimicrobial resistance (Fuhrmeister et al., 2023; Essack, 2021).

Our results found that the indicators most positively correlated with high levels of antibiotic consumption—and thus, by proxy, ABR—in all disciplines were associated with more developed countries. In the domain of health, the significant correlation of the percentage of population immunized to measles and the percentage of the population aged 80 and older who are female with antibiotic usage suggest higher rates of immunization and higher life expectancy, which are indicative of better healthcare and overall development in that country. Similarly, in the education category, higher completion and enrollment rates indicate a more educated population, which is associated with social development in the Human Development Index (HDI) (Dasic et al., 2020). In the economy and growth categories, factors such as the share of communications and financial services in imports and exports reflect a country's integration into the global economy and its economic resilience. The positive correlation found in the social development category with the employment-to-population ratio among ages 15-24 suggests higher paid work opportunities for youth, which positively points to a country being economically developed. These findings correlate with previous studies which have found that, on average, higher-income countries consume more antibiotics (Browne et al., 2021; Eili Y. Klein et al., 2018).

Conversely, the countries with the lowest antibiotic usage are typically less developed nations. These countries include: the Ivory Coast, Niger, Nicaragua, El Salvador, Namibia, Ethiopia, and the Democratic Republic of Congo. In these countries, lower rates of immunization, lower life expectancy, less access to education, lower economic resilience, and less developed healthcare systems have contributed to lower overall antibiotic usage for less developed countries. According to the most effective predictors, as these countries develop, they are likely to consume more antibiotics, leading to increased ABR. Consequently, this underscores the global need for applied measures to counter antibiotic resistance.

To refine the methods of our study, further research should aim to redefine the following limitations. Firstly, using antibiotic usage as a proxy for antibiotic resistance may not be applicable in specific cases. Antibiotic usage is not only influenced by the antibiotic resistance of a country, but can also be the result of 1) economic factors such as the lack of healthcare funding, 2) lack of health policies and healthcare professional's concern about antibiotic resistance (Coco et al., 2009; Mangione-Smith et al., 2001; Pechere, 2001). Further research may need to consider using a wider range of output factors, such as the prevalence of the MDR1 gene, in order to address the limitations in countries where antibiotic usage is heavily influenced by socio-economic factors (Catalano et al,. 2022).

Secondly, the antibiotic usage dataset for each country is presented as the daily defined doses per one thousand people per day. Since the metric is normalized by population size, despite a countries' high total consumption of antibiotics, when that consumption is divided by the population size, the per capita consumption may appear lower than that of smaller countries with similar total consumption but smaller populations. This may lead to larger countries, such as India and China being labeled as low risk for antibiotic resistance, even though they may have high absolute antibiotic consumption.

Thirdly, antibiotic resistance is not only influenced by human usage but also by antibiotic consumption in agriculture and livestock, which was not considered in our output dataset containing only human antibiotic usage data. Antibiotics used for disease prevention and growth promotion in animals can lead to emergence of resistant bacteria that can be transmitted to humans through the food chain or environmental pathways (Manyi-Loh et al., 2018). To more accurately assess the relationship between antibiotic usage and antibiotic resistance, future research should consider integrating data on antibiotic usage in agriculture and livestock into the existing model to provide a more comprehensive picture of the factors contributing to ABR.

Fourthly, the integrated gradients method used to determine the importance of each factor on ABR can only determine statistical links and not causal relationships (Sundararajan, Taly, & Yan, 2017). With the advancement of computationally powerful tools, further research could enhance the integrated gradients method by incorporating causal inference techniques to establish causal relationships between input factors and antibiotic resistance (ABR).

Overall, based on the success rates of our machine learning prediction model, we have demonstrated that machine learning can effectively determine significant antibiotic usage and resistance factors, and forecast trends. While our current model may not establish causality between these factors and antibiotic resistance (ABR), it provides a crucial foundation for future research. By pinpointing the key determining factors, we have set the stage for future studies to address our limitations and delve into investigating causality more thoroughly. Furthermore, our findings highlight the importance of considering environmental factors in policy making and healthcare strategies aimed at combating antibiotic resistance—an intrinsically multidisciplinary problem, as suggested by our machine learning model.

Policymakers, healthcare providers, and researchers can utilize our study's insights to develop more targeted and effective approaches to address the antibiotic resistance crisis.

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Appendix I: List of studied categories, factors and regions

Studied factors: 804 total factors, including 79 environmental factors and 8 climate change factors.

Studied categories: 18 categories of factors.

Environment	Science & Technology
Climate Change	Education
Public Sector	Infrastructure
Private Sector	Aid Effectiveness
Financial Sector	External Debt
Economy & Growth	Energy & Mining
Health	Agriculture & Rural Development
Poverty	Social Development
Gender	Urban Development

Studied regions: 145 countries.

Appendix II : Model design choices

We use PyTorch for model training, Ray Tune for hyperparameter training, and Pandas for data wrangling in Python 3.11.

- Hyperparameter training was done with Bayesian optimization over 128 different samples.

- 2, 4, 8, 16, 32, 64, and 128 were tried as batch sizes. 8 was determined to be the most performant based on mean accuracy.

- The number of hidden nodes were randomly and uniformly sampled between 5 and 1608 (the double of the inputs). 405 was determined to be the most performant based on mean accuracy.

- As stochastic gradient descent was used as the optimizer, learning rate and momentum were randomly and uniformly sampled between the intervals of [1e-4, 1e-2] and [0.1, 0.9], respectfully. Learning rate was determined to be 0.00210655; momentum, 0.595350287.

- The hyperbolic tangent function was selected as the non-linear activation function as it is a function centered around zero. Both negative and positive inputs are therefore equally favored. Determining the attributions and significance of each factor by integrating gradients is therefore unbiased, a considerable advantage compared to if we used ReLU, or its derivatives, as the activation function.
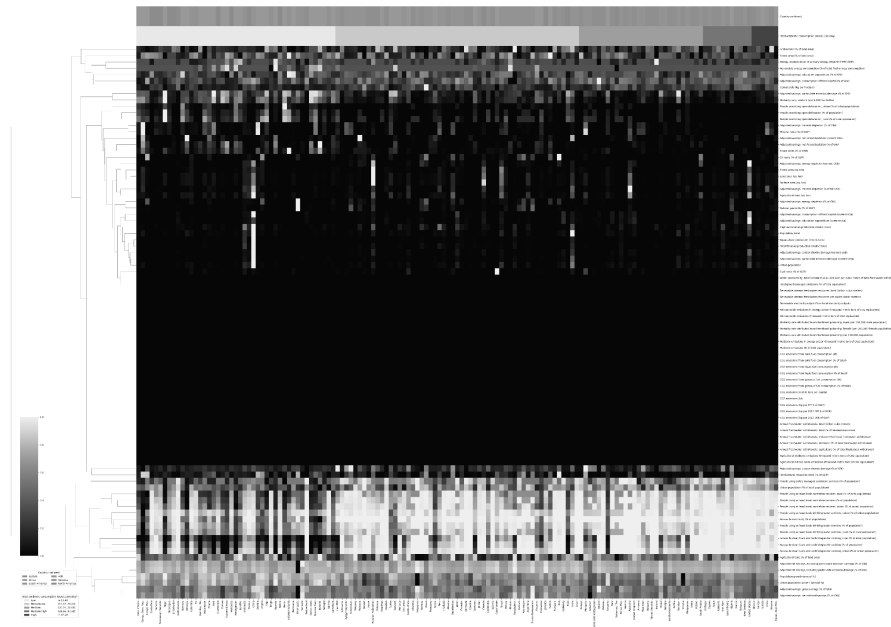
For further model design details, please refer to the source code.

For visualizations and results, please refer to our website.

Appendix III:

Comprehensive correspondence between top significant environmental indicators (n=87) and total antibiotic usage worldwide (n=145 regions), 2022

Comprehensive correspondence between top significant indicators (n=100) and total antibiotic usage worldwide (n=145 regions), 2022