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Population-level Analysis of Public Health Surveillance and Global Progress to Estimate the Burden of Antimicrobial Resistance

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Master of Public Health

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Bachelor of Science

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2017

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Abstract

Population-level Analysis of Public Health Surveillance and Global Progress to Estimate the Burden of Antimicrobial Resistance

By Michael P Kozuch

Purpose: Gaps remain in our ability to understand and quantify the scope of antimicrobial resistance (AMR). To assess the intersection between public health surveillance (PHS) and the global burden of disease associated with AMR, data were examined to capture the unique context within each country reporting to the Global Antimicrobial Resistance Surveillance System (GLASS). This investigation addressed whether two priority pathogens, *K. pneumonia* and *E. coli*, with demonstrated resistance in humans, animals, and the environment, exerted detectable effects at the national level.

Methods: Data in this ecological study were obtained using multiple, publicly available datasets from 2018. Countries were grouped by Human Development Index (HDI). Burden was measured using disability adjusted life years (DALYs) occurring from all causes. Questions from the Tripartite Antimicrobial Resistance Country Self-Assessment Survey capturing multi-sectoral approaches and country progress on national action plans (NAPs) on AMR were dichotomized in the analysis. Resistance profiles for *K. pneumoniae* and *E. coli* were calculated using the mean proportion of resistant antimicrobial susceptibility testing (AST) results by antibiotic-pathogen pair. Linear regression models were used to examine the relationship between markers of AMR and country-level disability burden.

Results: Data were available from 52 countries reporting to GLASS: 13 (25%) had low or medium HDI, 10 (19%) had high HDI, and 29 (56%) had very high HDI. The regression for Model 1 of 4 showed a significant positive association between the proportion of resistant *K. pneumoniae* ASTs and the rate of all-cause DALYs per 100,000 populations (β = 154.9; 95% CI: 30.6, 279.1). Reductions in burden were observed in countries reporting multisectoral AMR working groups (β = -10731.0; 95% CI: -17263.1, -4198.9) or with developed NAPs on AMR (β = -6292.1; 95% CI: -11832.7, -751.5).

Conclusion: The proportion of resistant *K. pneumoniae* and AMR national strategies are associated with the country-level burden of disease. Despite its potential predictive value, the proportion of resistant *E. coli* did not exert a discernable effect. Particularly during the scale-up of global efforts in AMR surveillance, our framework synthesizes the relationship between population-level factors, AMR, and risk of disability.

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†JRR Tolkien, *Lord of the Rings*

Table of Contents

List of Abbreviations

AMR	Antimicrobial Resistance
AST	Antimicrobial Susceptibility Testing
DALYs	Disability adjusted life years
FAO	Food and Agricultural Organization of the United Nations
GBD 2019	Global Burden of Disease Study 2019
GLASS	Global Antimicrobial Resistance Surveillance System
HDI	Human Development Index
LMIC	Low and Middle Income Countries
NAP	National Actional Plan
OIE	World Organisation for Animal Health
PHS	Public Health Surveillance
TrACSS	Tripartite Antimicrobial Resistance Country Self-Assessment Survey
WHO	World Health Organization
YLDs	Years of life lived with disability
YLLs	Years of life lost

MANUSCRIPT

Introduction

The emergence and increasing prevalence of antimicrobial resistance (AMR) present new and threatening challenges to human health. Although much is known about the mechanisms of AMR emergence and spread, considerable gaps remain in our ability to understand and quantify the scope of the AMR problem.[1,2] AMR constitutes a significant burden of disease by prolonging illness, increasing risk of disability and death, and requiring greater treatment costs.[3–9]

Klebsiella pneumonia and *Escherichia coli* – both components of normal intestinal floral – were identified by World Health Organization (WHO) as two priority AMR pathogens.[1,10] AMR in these pathogens exacerbate urinary tract and bloodstream infections and necessitate treatment with increasingly aggressive (or even last-resort) drugs.[1,11,12] Owing to complex interactions between humans, animals, and the environment, AMR in *K. pneumonia* and *E. coli*, as well as other pathogens, highlights the need for multisectoral public health and healthcare collaboration using a One Health approach.[13–17]

Antibiotics are a cornerstone of modern medicine.[18] The causes of global morbidity and mortality are trending away from infectious disease in adults and children.[19,20] Antibiotic usage among humans has steadily increased since their earliest use in clinical practice with sulphonamides in 1935 and penicillin in 1941.[21] The resulting downward trend in infectious disease mortality came to characterize the early successes of antibiotic therapy in the 20th century.[22–25] For example, infectious disease mortality in the United States fell from 283 deaths per 100,000 in 1937 to just 59 deaths per 100,000 in 1996.[23]

Similarly, the increasing availability of antibiotics in low- and middle-income (LMIC) countries (e.g. oral azithromycin in Malawi, Niger, Tanzania) is associated with reduction in child mortality to 13.5%.[26] Broader assertions linking an estimated 114% increase in antibiotic consumption in LMIC from 2000 to 2015 with reduced child mortality rate stir debate over ethical considerations in balancing AMR with reducing burden of disease.[27–29] Other types of medical care also came to rely on the abundance of antibiotics in the mid-20th century. But as the proverbial *golden age* of antibiotic discovery brought about dramatic changes to both clinical and agricultural practices, selective pressures facilitated the evolution of resistant phenotypes among bacterial strains.[19,21,22,27,30]

Three factors proposed by Wenzel and Edmond drive the extent of antibiotic resistance: (1) antibiotic resistance introduced to a population; (2) spontaneously selected or enhanced resistance from suboptimal antibiotic use; and (3) the proportion of human-human transmission.[31] Their assertions based on human populations are also relevant to One Health. These factors can also be applied in the context of growing proximity between humans and agriculture, including trends in antibiotic use in animal husbandry and aquaculture. In the United States, for example,160 million antibiotic prescriptions totaling over 22.7 million kg are split evenly between human and non-human use.[31]

In a landmark study, a direct link was demonstrated between tetracycline supplemented feed and the emergence of tetracycline-resistant gut flora in farm members and livestock alike.[32] Through continued patterns of antimicrobial use in agriculture, there is increased selective pressure for strains of antimicrobial-resistant pathogens.[33] Antibacterial resistance can also arise from plasma-mediated transfer between bacteria

where horizontal gene transfer facilitates bacterial adaptation.[33,34] This mode of transmission is important for both cases of animal-human transmission and human transmission where enzyme-mediated resistance via carbapenemases are horizontally transferred.[16,35] With continued suboptimal antibiotic use, growing proximity between humans and animals, and continued human-human transmission, there is ever-greater risk for the emergence and dissemination antimicrobial-resistant pathogens.

Integrated One Health public health surveillance (PHS) programs should incorporate warning systems for emerging resistance in humans, animals, and the environment. However, current PHS are either limited by national capacity,[1,13,36–38] heterogeneity of data collection,[1,39–41] or the lack of integration.[1,10,13] Consisting of WHO, the World Organisation for Animal Health (OiE), and the Food and Agriculture Organization of the United Nations (FAO), a tripartite was conceived to systematically address issues of AMR using a One Health framework.[41–44] In conjunction with the WHO's Global Action Plan on Antimicrobial Resistance, nations are to develop national action plans (NAPs) that include national PHS for antimicrobial resistance.[14] In particular, nations contribute to global PHS efforts by incorporating standardized data collection methods and reporting to the Global Antimicrobial Resistance Surveillance System (GLASS) for priority pathogens including *K. pneumonia* and *E. coli*.[14,45] Other factors such as the timely monitoring and evaluation of national progress create early opportunities to address issues during implementation of AMR action plans.

To assess the intersection between the quality of PHS data and the global burden of disease associated with the emergence and dissemination of AMR, data were examined to capture the unique context within each country reporting to GLASS.

Specifically, this investigation addressed whether two priority pathogens, *K. pneumonia* or *E. coli*, with demonstrated resistance in humans, animals, and the environment, exerted detectable effects at the national level. Burden was measured using disability adjusted life years (DALYs) occurring from all causes. Considerations for a One Health framework were included to evaluate the potential impacts from varying levels of national progress in addressing AMR.

Methods

Data in this ecological study of the impacts of AMR on the risk of disability and death were obtained using multiple, publicly available datasets from 2018. Human Development Index (HDI) data were incorporated to approximate country capabilities to address AMR.[46,47] GLASS provided standardized antimicrobial susceptibility testing (AST) data as a marker of AMR.[48,49] Resistance profiles for *K. pneumoniae* and *E. coli* were calculated using the mean proportion of resistant AST results by antibiotic-pathogen pair. The Tripartite Antimicrobial Resistance Country Self-Assessment Survey (TrACSS) offers monitoring and evaluation of the global action plan on AMR.[50,51]

Questions on a 5-point scale (A to E) capturing multi-sectoral approaches and country progress on NAPs on AMR were dichotomized to improve statistical efficiency (Appendix A).[52] Estimated DALYs per 100,000 from the Global Burden of Disease Study 2019 (GBD 2019) were calculated as the sum of years of life lost (YLLs) and years of life with disability (YLDs) divided by mid-year population.[53–55]

Simple and multiple linear regression models were used to examine the relationship between markers of AMR and country-level mortality and disability burden. Four models analyzed the association of *K. pneumoniae* resistance, *E. coli* resistance, TrACSS question 4.1 on multi-sector and One Health collaboration/coordination, and TrACSS question 5.1 on country progress with development of a NAP on AMR with DALYs from all causes (Appendix B). Countries were grouped by HDI category and models included the proportion of adults over 65 years old to generate adjusted measures of association.[56,57] Results of linear models were expressed as beta-coefficients with and the corresponding 95% confidence intervals. Model fit is captured via adjusted

coefficients of determination (adjusted R-squared). All statistical analyses were performed using R version 4.0.2.[58]

Results

Of the 52 countries reporting to GLASS, 13 had low or medium HDI, 10 had high HDI, and 29 had very high HDI (Table 1). Countries with low or medium human development also had smaller proportions of their population > 65 years old (4.5%, standard deviation [SD] 1.7%) than high (7.5%, SD 3.2%) or very high HDI countries (15.9%, SD 6.9%). The proportion of resistant AST results for *K. pneumoniae* in low and medium HDI countries was 51.9% (SD 13.6%), 42.9% in high HDI (SD 16.5%), and 26.5% in very high HDI countries (SD 18.2%). A similar trend was evident for *E. coli*. Across all countries, only 7 of 52 (13.5%) answered either A or B to question 4.1 in TrACSS compared to 15 of 47 (31.9%) answering A or B to question 5.1.

Individually, all predictors except for % > 65 years old were significantly associated with all-cause burden of disease (Table 2). In the multivariable models, there was a weak but statistically significant linear association between the proportion of resistant *K. pneumoniae* ASTs and all-cause DALYs in Model 1 (Figure 1a; adjusted $R^2 = 0.39$). For each 1% increase in the rate of resistant *K. pneumoniae*, the DALYs a country experiences increases, on average, by 154.9 per 100,000 population (Table 3.a; CI: 30.6, 279.1) after adjusting for other variables in the model. Neither of the associations between *K. pneumoniae* or *E. coli* resistance and DALYs was statistically significant in Models 2-4 (Table 3a-3b). Multi-sector and One Health collaboration/coordination was significantly associated with reductions in DALYs in both Model 1 (β = -10731.0; CI: -17263.1, -4198.9) and Model 2 (β = -8265.6; CI: -15251.4, -1279.8). Conversely, country progress with development of a NAP was associated with a DALYs in Model 3 (β = -6292.1; CI: -11832.7, -751.5) but not in Model 4 (β = -5814.0; CI: -11533.6, -94.3).

In all models, high and very high HDI categorization was significantly associated with reductions in DALYs when compared against low and medium HDI countries.

Discussion

This analysis demonstrated the extent to which the proportion of resistant pathogens, national strategies in AMR, and country capabilities to address AMR continue to drive trends in the risk of death and disability. Of particular note, we observed that higher proportions of resistant *K. pneumoniae* as reported to the WHO GLASS were associated with greater burden of disease measured by DALYs occurring from all causes. Despite ostensible potential role in predicting the burden of disease at the country level, resistant *E. coli* as measured by ASTs did not exert a discernable effect when considered along with other factors. This study provided estimates for the effect of age using the % > 65 years old as proxy for countries' overall age structure. However, older populations, on average, only predicted greater disease burden when in conjunction with data on the proportion of resistant *K. pneumoniae*.

Our results highlighted the potential value in ongoing monitoring and evaluation of the AMR global action plan. Namely, we observed large reductions in estimated DALYs in countries reporting, at a minimum, functioning multisectoral AMR working groups. Countries with developed, approved, and funded AMR action plans tended to experience fewer DALYs than those without. However, country progress on NAPs was less conclusive as a predictor of disability and death. HDI consistently predicted DALYs across all scenarios, with low and middle HDI countries contributing most to the burden of disability and death compared to high and very high HDI countries.

The results of this investigation should be considered within the context of available literature. Many studies estimate the economic burden of AMR, yet few systematically examine predictors of health impacts across regional or national levels.[59–61]

Nevertheless, previous attempts to estimate AMR-attributable burden using population-level data report a twofold increase from 2007 to 2015 in the proportion of DALYs due to *K. pneumoniae* and *E. coli*.[62] As a component of HDI, socioeconomic factors such as gross national income per capita are known to be inversely associated with the prevalence of infections by resistant pathogens.[63] Drivers of AMR identified in our study, including NAPs for AMR and multisectoral One Health strategies, were also reported in a study of AMR in Pacific Island countries and territories.[64] Contrasting existing studies, our study did not reliably conclude whether AMR-attributable burden increased with age among adults.[62]

Estimates of the global burden of disease associated with the emergence and dissemination of AMR are still debated. Several review studies highlight evolving methods to adjust for confounding in studies estimating the global health impact of AMR, yet heterogeneity in both predictor and outcome measures still contribute to uncertainty.[40,65] Measuring the burden of disease using DALYs was a methodological consideration previously employed to enable further assessment and comparisons of countries or health conditions.[66] It also drew upon reliable population health indicators in the GBD Study.

This study contributed to the literature by providing a framework analysis that incorporated transdisciplinary approaches in One Health. This analysis is the first to assess the global burden of disease associated with the emergence and dissemination of AMR by consolidating data across multiple global initiatives. Specifically, the relationship between data from GLASS, TrACSS, and GBD 2019 had not been investigated. The population-level approach using DALYs occurring from all causes also

mitigated fragmented data collection methods capturing the burden of disease. For instance, low and middle HDI countries balance resource limitations with standardized data reporting procedures. Outcomes data from GBD 2019 provide a more inclusive framework to include countries as their participation in GLASS or TrACSS increases. Particularly during the scale-up of global efforts in AMR surveillance, our proposed framework retains the ability to accommodate extended analyses as data become available. It also suggested an analytical platform to facilitate crosstalk among disciplines in One Health.

Our analysis had limitations. The availability and quality of AMR PHS data is subject to national capacity with participation in GLASS skewed towards higher HDI countries. In general, countries implement GLASS protocols in a standardized, step-wise fashion as resources permit. The resulting data sparsity and heterogeneity within GLASS contributed to limited statistical power. We synthesized the proportion of resistant *K. pneumoniae* and *E. coli* across all reported ASTs. Consequently, we sacrificed the potential to investigate pathogen-specific, antibiotic resistance. HDI was selected to approximate a country's overall capabilities to enact strategies in combatting AMR. But as a composite measure, it may potentiate multiple collinear factors associated with the risk of death and disability. Results from this ecological study using country-level population units cannot be used to make inferences smaller subgroups or even individuals. There is the potential for bias arising from incomplete reporting in the source data. The corresponding bias analysis would require additional data collection to ascertain the direction and magnitude of the effect.

AMR threatens to undermine major global health success in combatting infectious diseases. However, factors contributing to trends in AMR are complex. Global health strategies should be multifaceted to minimize the emergence and spread of AMR in humans, animals, and the environment. While the global action plan creates a framework for countries to combat AMR, it requires investment from nations and global stakeholders to bridge gaps actively identified during implementation. Here we proposed a framework analysis that describes the relationship between population-level factors, AMR, and risk of death and disability. Future direction should include ongoing review of monitoring and evaluation data on country progress in AMR. Additionally, understanding the longitudinal relationship between adherence to NAPs, disease burden, and rates of AMR can better inform policy decisions. Health outcomes relevant to animals and the environment should be used in tandem with measures of the health impact of AMR in humans.

REFERENCES

1. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*.; 2014:1-256.

2. Abat C, Rolain J-M, Dubourg G, Fournier P-E, Chaudet H, Raoult D. Evaluating the clinical burden and mortality attributable to antibiotic resistance: the disparity of empirical data and simple model estimations. *Clin Infect Dis*. 2017;65(Suppl 1):S58-S63. doi:10.1093/cid/cix346

3. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057-1098. doi:10.1016/S1473-3099(13)70318-9

4. Ammerlaan HSM, Harbarth S, Buiting AGM, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. *Clin Infect Dis*. 2013;56(6):798-805. doi:10.1093/cid/cis1006

5. Lim C, Takahashi E, Hongsuwan M, et al. Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. *eLife*. 2016;5:e18082. doi:10.7554/eLife.18082

6. Roberts RR, Hota B, Ahmad I, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis*. 2009;49(8):1175-1184. doi:10.1086/605630

7. Moreno CÁ, Rosenthal VD, Olarte N, et al. Device-associated infection rate and mortality in intensive care units of 9 colombian hospitals: findings of the international nosocomial infection control consortium. *Infect Control Hosp Epidemiol*. 2006;27(4):349-356. doi:10.1086/503341

8. Cuellar LE, Fernandez-Maldonado E, Rosenthal VD, et al. Device-associated infection rates and mortality in intensive care units of Peruvian hospitals: findings of the International Nosocomial Infection Control Consortium. *Pan Am J Public Health*. 2008;24:16-24. doi:10.1590/S1020-49892008000700002

9. Rosenthal VD, Guzman S, Orellano PW. Nosocomial infections in medical-surgical intensive care units in Argentina: attributable mortality and length of stay. *Am J Infect Control*. 2003;31(5):291-295. doi:10.1067/mic.2003.1

10. Tacconelli E, Magrini N. *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics*. World Health Organization; 2017:1-7.

11. Zhen X, Stålsby Lundborg C, Sun X, Zhu N, Gu S, Dong H. Economic burden of antibiotic resistance in China: a national level estimate for inpatients.

Antimicrob Resist Infect Control. 2021;10(5):1-9. doi:10.1186/s13756-020-00872-w

12. Tillotson GS, Zinner SH. Burden of antimicrobial resistance in an era of decreasing susceptibility. *Expert Rev Anti Infect Ther*. 2017;15(7):663-676. doi:10.1080/14787210.2017.1337508

13. Queenan K, Häsler B, Rushton J. A One Health approach to antimicrobial resistance surveillance: is there a business case for it? *Int J Antimicrob Agents*. 2016;48(4):422-427. doi:10.1016/j.ijantimicag.2016.06.014

14. World Health Organization. *Global Action Plan on Antimicrobial Resistance*.; 2015:1-12.

15. Zinsstag J, Schelling E, Waltner-Toews D, Tanner M. From “one medicine” to “one health” and systemic approaches to health and well-being. *Prev Vet Med*. 2011;101(3-4):148-156. doi:10.1016/j.prevetmed.2010.07.003

16. Radhouani H, Silva N, Poeta P, Torres C, Correia S, Igrejas G. Potential impact of antimicrobial resistance in wildlife, environment and human health. *Front Microbiol*. 2014;5(23):1-12. doi:10.3389/fmicb.2014.00023

17. Guerra B, Fischer J, Helmuth R. An emerging public health problem: acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds. *Vet Microbiol*. 2014;171(3):290-297. doi:10.1016/j.vetmic.2014.02.001

18. Smith R, Coast J. The true cost of antimicrobial resistance. *Br Med J*. 2013;346:f1493. doi:10.1136/bmj.f1493

19. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1151-1210. doi:10.1016/S0140-6736(17)32152-9

20. Institute for Health Metrics and Evaluation (IHME). GBD Compare. Published 2015. Accessed March 23, 2021. http://vizhub.healthdata.org/gbd-compare

21. Aminov R. History of antimicrobial drug discovery: major classes and health impact. *Biochem Pharmacol*. 2017;133:4-19. doi:10.1016/j.bcp.2016.10.001

22. Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *The Lancet*. 2016;387(10014):168-175. doi:10.1016/S0140-6736(15)00474-2

23. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA*. 1999;281(1):61-66. doi:10.1001/jama.281.1.61

24. Podolsky SH. *Pneumonia Before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America*. JHU Press; 2006.

25. Tomasz A. Antibiotic resistance in Streptococcus pneumoniae. *Clin Infect Dis*. 1997;24(Suppl 1):S85-S88. doi:10.1093/clinids/24.Supplement_1.S85

26. Keenan JD, Bailey RL, West SK, et al. Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. *N Engl J Med*. 2018;378(17):1583-1592. doi:10.1056/NEJMoa1715474

27. Klein EY, Boeckel TPV, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci*. 2018;115(15):E3463-E3470. doi:10.1073/pnas.1717295115

28. Klein EY, Levin SA, Laxminarayan R. Reply to Abat et al.: Improved policies necessary to ensure an effective future for antibiotics. *Proc Natl Acad Sci*. 2018;115(35):E8111-E8112.

29. Abat C, Gautret P, Raoult D. Benefits of antibiotics burden in low-income countries. *Proc Natl Acad Sci U S A*. 2018;115(35):E8109-E8110. doi:10.1073/pnas.1809354115

30. Lewis K. Platforms for antibiotic discovery. *Nat Rev Drug Discov*. 2013;12(5):371-387. doi:10.1038/nrd3975

31. Wenzel RP, Edmond MB. Managing antibiotic resistance. *N Engl J Med*. 2000;343(26):1961-1963. doi:10.1056/NEJM200012283432610

32. Levy SB, FitzGerald GB, Macone AB. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *N Engl J Med*. 1976;295(11):583-588. doi:10.1056/NEJM197609092951103

33. Butaye P, van Duijkeren E, Prescott JF, Schwarz S. Antimicrobial resistance in bacteria from animals and the environment. *Vet Microbiol*. 2014;171(3-4):269-272. doi:10.1016/j.vetmic.2014.04.009

34. Hasegawa H, Suzuki E, Maeda S. Horizontal plasmid transfer by transformation in Escherichia coli: environmental factors and possible mechanisms. *Front Microbiol*. 2018;9:1-6. doi:10.3389/fmicb.2018.02365

35. Meletis G. Carbapenem resistance: overview of the problem and future perspectives. *Ther Adv Infect Dis*. 2016;3(1):15-21. doi:10.1177/2049936115621709

36. Takaya S, Hayakawa K, Matsunaga N, et al. Surveillance systems for healthcare-associated infection in high and upper-middle income countries: a scoping review. *J Infect Chemother*. 2020;26(5):429-437. doi:10.1016/j.jiac.2020.01.001

37. Perez F, Villegas MV. The role of surveillance systems in confronting the global crisis of antibiotic-resistant bacteria. *Curr Opin Infect Dis*. 2015;28(4):375-383. doi:10.1097/QCO.0000000000000182

38. Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR surveillance in low and middle-income settings - a roadmap for participation in the Global Antimicrobial Surveillance System (GLASS). *Wellcome Open Res*. 2017;2(92):1-18. doi:10.12688/wellcomeopenres.12527.1

39. Tacconelli E, Sifakis F, Harbarth S, et al. Surveillance for control of antimicrobial resistance. *Lancet Infect Dis*. 2018;18(3):e99-e106. doi:10.1016/S1473-3099(17)30485-1

40. Pezzani MD, Tornimbene B, Pessoa-Silva C, et al. Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. *Clin Microbiol Infect*. Published online January 13, 2021. doi:10.1016/j.cmi.2021.01.004

41. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. *Monitoring Global Progress on Addressing Antimicrobial Resistance: Analysis Report of the Second Round of Results of AMR Country Self-Assessment Survey*.; 2018:1-30.

42. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. *The FAO-OIE-WHO Collaboration*.; 2010:1-8.

43. Food and Agriculture Organization of the United Nations. *Evaluation of FAO's Role and Work on Antimicrobial Resistance (AMR)*.; 2021.

44. World Organisation for Animal Health. The OIE strategy on antimicrobial resistance and the prudent use of antimicrobials.

45. World Health Organization. *Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: Early Implementation 2020*.; 2020.

46. United Nations Development Programme. Human Development Index (HDI). Human Development Reports. http://hdr.undp.org/en/content/human-development-index-hdi

47. United Nations Development Programme. Human Development Index (HDI) Indicators. Human Development Reports. http://hdr.undp.org/en/indicators/137506

48. World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS). Published 2021. http://www.who.int/glass/en/

49. World Health Organization. *Global Antimicrobial Resistance Surveillance System: Manual for Early Implementation*.; 2015.

50. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. Guidance note to accompany the global monitoring questionnaire on AMR. Published online October 1, 2017.

51. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. Global Database for the Tripartite Antimicrobial Resistance (AMR) Country Self-assessment Survey (TrACSS). Published 2018. http://amrcountryprogress.org/

52. World Health Organization, Food and Agriculture Organization of the United Nations, World Organisation for Animal Health. Global Monitoring of Country Progress on Antimicrobial Resistance (AMR): Country Self-Assessment Questionnaire. Published online September 10, 2017. https://amrcountryprogress.org/download/Tripartite-antimicrobial-resistance-country-self-assessment%20survey-2017-2018-English.pdf

53. Institute for Health Metrics and Evaluation (IHME). GBD Results Tool. Global Health Data Exchange. Published 2021. http://ghdx.healthdata.org/gbd-results-tool

54. Global Burden of Disease Collaborative Network. *Global Burden of Disease Study 2019 (GBD 2019) Population Estimates 1950-2019*. Institute for Health Metrics and Evaluation (IHME); 2020.

55. Global Burden of Disease Collaborative Network. *GBD 2019 Data and Tools Overview*. Institue for Health Metrics and Evaluation; 2020.

56. Rosenbaum PR, Rubin DB. Difficulties with regression analyses of age-adjusted rates. *Biometrics*. 1984;40(2):437-443.

57. Guo H-R. Age adjustment in ecological studies: using a study on arsenic ingestion and bladder cancer as an example. *BMC Public Health*. 2011;11:820. doi:10.1186/1471-2458-11-820

58. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021.

59. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect*. 2014;20(10):973-980. doi:10.1111/1469-0691.12798

60. Naylor NR, Pouwels KB, Hope R, et al. The health and cost burden of antibiotic resistant and susceptible Escherichia coli bacteraemia in the English hospital setting: A national retrospective cohort study. *PloS One*. 2019;14(9):e0221944. doi:10.1371/journal.pone.0221944

61. Eliopoulos GM, Cosgrove SE, Carmeli Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. *Clin Infect Dis*. 2003;36(11):1433-1437. doi:10.1086/375081

62. Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2019;19(1):56-66. doi:10.1016/S1473-3099(18)30605-4

63. Savoldi A, Carrara E, Gladstone BP, Azzini AM, Göpel S, Tacconelli E. Gross national income and antibiotic resistance in invasive isolates: analysis of the top-ranked antibiotic-resistant bacteria on the 2017 WHO priority list. *J Antimicrob Chemother*. 2019;74(12):3619-3625. doi:10.1093/jac/dkz381

64. Loftus M, Stewardson A, Naidu R, et al. Antimicrobial resistance in the Pacific Island countries and territories. *BMJ Glob Health*. 2020;5(4). doi:10.1136/bmjgh-2020-002418

65. Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control*. 2018;7:58. doi:10.1186/s13756-018-0336-y

66. Mangen M-JJ, Plass D, Havelaar AH, et al. The Pathogen- and Incidence-Based DALY Approach: An Appropriated Methodology for Estimating the Burden of Infectious Diseases. *PLoS ONE*. 2013;8(11). doi:10.1371/journal.pone.0079740

TABLES

Table 1. Distribution of Country-level Characteristics, by Human Development Index, 2018

Characteristic	Human Development Index: Low and Medium (n=13)		High (n=10)		Very High (n=29)	
	n (%) or Mean (SD)		n (%) or Mean (SD)		n (%) or Mean (SD)	
% of Resistant ASTs for *K. pneumoniae*[a]	51.91	(13.55)	42.89	(16.47)	26.51	(18.21)
% of Resistant ASTs for *E. coli*	54.28	(11.03)	38.82	(14.91)	19.47	(10.02)
% of Population > 65 Years Old	4.45	(1.70)	7.47	(3.22)	15.85	(6.88)
Disability Adjusted Life Years (DALYs) per 100,000	38101.50	(12915.18)	29896.00	(7929.91)	28547.64	(5878.47)
Multi-sector and One Health Collaboration/Coordination						
EITHER (A) No formal multi-sectoral governance or coordination mechanism exists OR (B) Multi-sectoral working group(s) or coordination committee on AMR established with Government leadership	4	(7.69)	2	(3.85)	1	(1.92)
EITHER (C) Multi-sectoral working group(s) is (are) functional, with clear terms of reference; regular meetings, and funding for working group(s). Activities and reporting/accountability arrangements are defined OR (D) Joint working on issues including agreement on common objectives, including restriction of use of critically important antimicrobials OR (E) Integrated approaches used to implement the national AMR action plan	9	(17.31)	8	(15.38)	28	(53.85)
Country Progress with Development of a National Action Plan on AMR[b]						
EITHER (A) No National AMR Action Plan OR (B) National AMR action plan under development	6	(12.77)	4	(8.51)	5	(10.64)
EITHER (C) National AMR action plan developed OR (D) National AMR action plan approved by government that reflects Global Action Plan objectives, with an operational plan and monitoring arrangements OR (E) National AMR action plan has funding sources identified, is being implemented and has relevant sectors involved with a defined monitoring and evaluation process in place	6	(12.77)	4	(8.51)	22	(46.81)

[a]GLASS data on *K. pneumoniae* available from only 50 countries in 2018; [b]TrACSS data on National Action Plans only available from 47 countries from 2017-2018; **AST:** Antimicrobial susceptibility testing

Table 2. Univariable Linear Regression Analyses of Predictors for Country-level Burden of Disease, 2018

Predictor	Estimate	95% CI	*P* Value
% of Resistant ASTs for *K. pneumoniae*[a]	188.55	(69.56, 307.54)	0.003
% of Resistant ASTs for *E. coli*	151.63	(20.58, 282.69)	0.028
% of Population > 65 Years Old	-14412.68	(-48760.16, 19934.80)	0.415
Human Development Index (HDI) Category			
Low and Middle	Ref.		
High	-8205.20	(-15207.59, -1202.80)	0.026
Very High	-9553.85	(-15110.44, -3997.27)	0.001
Multi-sector and One Health Collaboration/Coordination			
EITHER (A) No formal multi-sectoral governance or coordination mechanism exists OR (B) Multi-sectoral working group(s) or coordination committee on AMR established with Government leadership	*Ref.*		
EITHER (C) Multi-sectoral working group(s) is (are) functional, with clear terms of reference; regular meetings, and funding for working group(s). Activities and reporting/accountability arrangements are defined OR (D) Joint working on issues including agreement on common objectives, including restriction of use of critically important antimicrobials OR (E) Integrated approaches used to implement the national AMR action plan	-9949.86	(-16869.85, -3029.87)	0.007
Country Progress with Development of a National Action Plan on AMR[b]			
EITHER (A) No National AMR Action Plan OR (B) National AMR action plan under development	*Ref.*		
EITHER (C) National AMR action plan developed OR (D) National AMR action plan approved by government that reflects Global Action Plan objectives, with an operational plan and monitoring arrangements OR (E) National AMR action plan has funding sources identified, is being implemented and has relevant sectors involved with a defined monitoring and evaluation process in place	-6479.77	(-12148.77, -810.77)	0.030

[a]GLASS data on *K. pneumoniae* available from only 50 countries in 2018; [b]TrACSS data only available from 47 countries from 2017-2018

Table 3a. Multiple Linear Regression of Country-level Burden of Disease and Multi-Sectoral Approaches, 2018

	Model 1			Model 2		
Predictor	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
% of Resistant ASTs for *K. pneumoniae*[a]	154.87	(30.64, 279.11)	0.019			
% of Resistant ASTs for *E. coli*				60.06	(-151.88, 272.00)	0.581
% of Population > 65 Years Old	58938.88	(20659.61, 97218.14)	0.004	45248.09	(1075.81, 89420.38)	0.051
Human Development Index (HDI) Category						
Low and Middle	*Ref.*			*Ref.*		
High	-7938.35	(-14216.04, -1660.66)	0.017	-7755.02	(-15173.17, -336.86)	0.046
Very High	-9911.65	(-16770.30, -3053.00)	0.007	-10363.75	(-19772.23, -955.27)	0.036
Multi-sector and One Health Collaboration/Coordination						
EITHER (A) No formal multi-sectoral governance or coordination mechanism exists OR (B) Multi-sectoral working group(s) or coordination committee on AMR established with Government leadership	*Ref.*			*Ref.*		
EITHER (C) Multi-sectoral working group(s) is (are) functional, with clear terms of reference; regular meetings, and funding for working group(s). Activities and reporting/ accountability arrangements are defined OR (D) Joint working on issues including agreement on common objectives, including restriction of use of critically important antimicrobials OR (E) Integrated approaches used to implement the national AMR action plan	-10731.02	(-17263.12, -4198.92)	0.002	-8265.61	(-15251.38, -1279.84)	0.025
R-squared		0.455			0.314	
Adjusted R-squared		0.393			0.239	
No. Observations		50			52	

[a]GLASS data on *K. pneumoniae* available from only 50 countries in 2018

Table 3b. Multiple Linear Regression Analyses of Country-level Burden of Disease and Progress with National Action Plans, 2018

	Model 3			Model 4		
Predictor	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
% of Resistant ASTs for *K. pneumoniae*[a]	121.19	(-26.39, 268.77)	0.116			
% of Resistant ASTs for *E. coli*				-47.15	(-285.07, 190.78)	0.700
% of Population > 65 Years Old	59671.08	(14305.35, 105036.80)	0.014	43417.32	(-6964.46, 93799.10)	0.099
Human Development Index (HDI) Category						
Low and Middle	*Ref.*			*Ref.*		
High	-9387.44	(-16864.00, -1910.87)	0.018	-10218.11	(-18507.64, -1928.58)	0.020
Very High	-11801.24	(-19718.88, -3883.60)	0.006	-14686.98	(-24613.60, -4760.36)	0.006
Country Progress with Development of a National Action Plan on AMR[b]						
EITHER (A No National AMR Action Plan OR (B) National AMR action plan under development	*Ref.*			*Ref.*		
EITHER (C) National AMR action plan developed OR (D) National AMR action plan approved by government that reflects Global Action Plan objectives, with an operational plan and monitoring arrangements OR (E) National AMR action plan has funding sources identified, is being implemented and has relevant sectors involved with a defined monitoring and evaluation process in place	-6292.08	(-11832.66, -751.49)	0.032	-5813.99	(-11533.64, -94.34)	0.053
R-squared		0.397			0.310	
Adjusted R-squared		0.319			0.226	
No. Observations		45			47	

[a]GLASS data on *K. pneumoniae* available from only 50 countries in 2018; [b]TrACSS data only available from 47 countries from 2017-2018

FIGURES

Figure 1a. Relationship Between Resistant *K. pneumoniae* and Country-level Burden of Disease, 2018

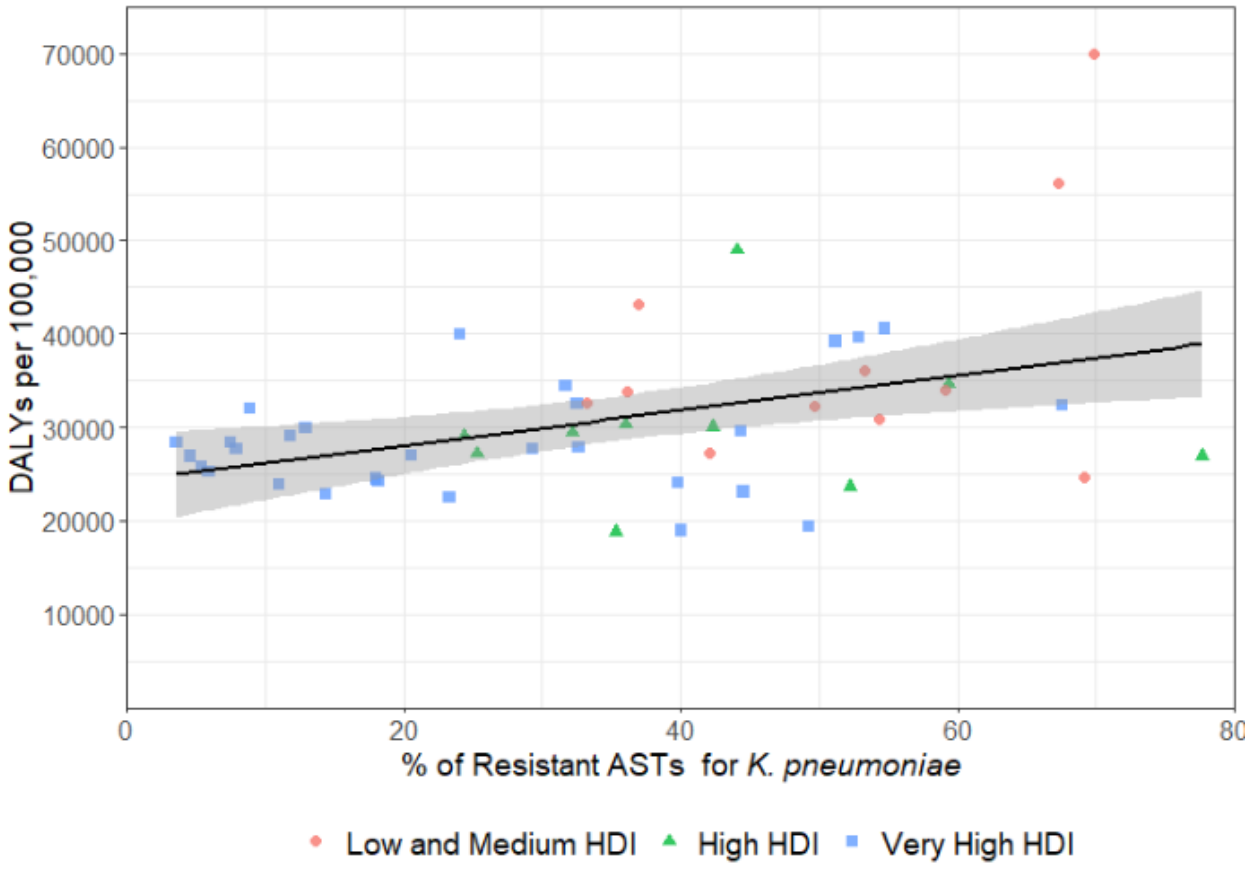
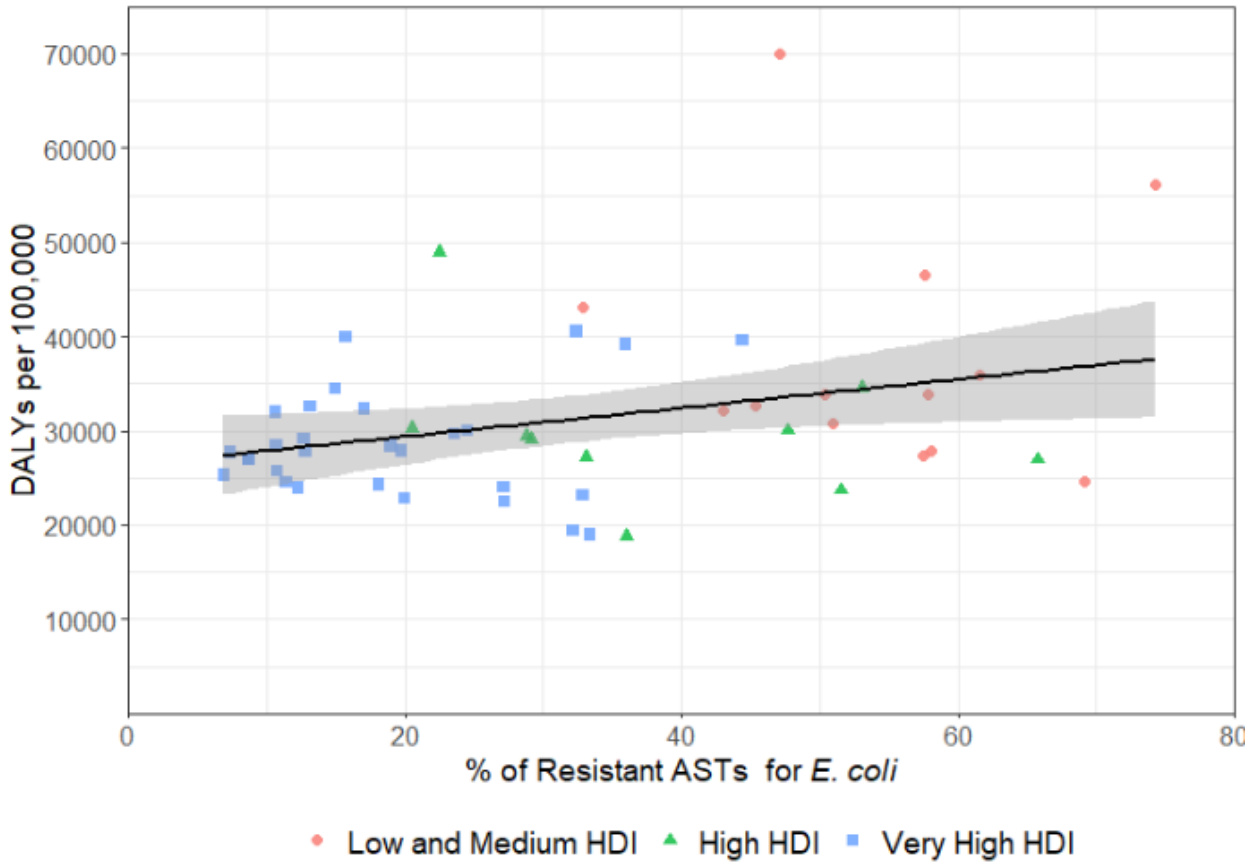


Figure 1b. Relationship Between Resistant *E. coli* and Country-level Burden of Disease, 2018



APPENDICES

Appendix A

TrACSS Questions 4.1 and 5.1

Global Monitoring of Country Progress on Antimicrobial Resistance (AMR): Country Self-Assessment Questionnaire (Version 2.0, 9 October 2017)

4. Multi-sectoral approach to addressing AMR

Please select one rating that most closely matches the country situation.

4.1 Multi-sector and One Health collaboration/coordination		
○	**A**	No formal multi-sectoral governance or coordination mechanism exists.
○	**B**	Multi-sectoral working group(s) or coordination committee on AMR established with Government leadership.
○	**C**	Multi-sectoral working group(s) is (are) functional, with clear terms of reference; regular meetings, and funding for working group(s). Activities and reporting/accountability arrangements are defined.
○	**D**	Joint working on issues including agreement on common objectives, including restriction of use of critically important antimicrobials.
○	**E**	Integrated approaches used to implement the national AMR action plan.

5. Country progress with development of a national action plan on antimicrobial resistance (AMR)

Please select one rating that most closely matches the country situation.

5.1 Country progress with development of a national action plan on AMR		
○	**A**	No national AMR action plan.
○	**B**	National AMR action plan under development.
○	**C**	National AMR action plan developed.
○	**D**	National AMR action plan approved by government that reflects Global Action Plan objectives, with an operational plan and monitoring arrangements.
○	**E**	National AMR action plan has funding sources identified, is being implemented and has relevant sectors involved with a defined monitoring and evaluation process in place.

Appendix B

Model 1: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + E$ where:

Y = All-cause disease burden (DALYs per 100,000)
X_1 = Rate of *K. pneumoniae* resistance (%)
X_2 = Response to TrACSS question 4.1 (0: A/B, 1: C/D/E)
X_3 = HDI category (Low/Middle, High, Very High)
X_4 = Proportion of population > 65 years old (%)
E = Random Error, assumed ~ $N(0,\sigma^2)$
β_0: true y-intercept, and β_i: regression coefficient (slope) for the *i*th predictor

Model 2: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + E$ where:

Y = All-cause disease burden (DALYs per 100,000)
X_1 = Rate of *E. coli* resistance (%)
X_2 = Response to TrACSS question 4.1 (0: A/B, 1: C/D/E)
X_3 = HDI category (Low/Middle, High, Very High)
X_4 = Proportion of population > 65 years old (%)
E = Random Error, assumed ~ $N(0,\sigma^2)$
β_0: true y-intercept, and β_i: regression coefficient (slope) for the *i*th predictor

Model 3: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + E$ where:

Y = All-cause disease burden (DALYs per 100,000)
X_1 = Rate of *K. pneumoniae* resistance (%)
X_2 = Response to TrACSS question 5.1 (0: A/B, 1: C/D/E)
X_3 = HDI category (Low/Middle, High, Very High)
X_4 = Proportion of population > 65 years old (%)
E = Random Error, assumed ~ $N(0,\sigma^2)$
β_0: true y-intercept, and β_i: regression coefficient (slope) for the *i*th predictor

Model 4: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + E$ where:

Y = All-cause disease burden (DALYs per 100,000)
X_1 = Rate of *E. coli* resistance (%)
X_2 = Response to TrACSS question 5.1 (0: A/B, 1: C/D/E)
X_3 = HDI category (Low/Middle, High, Very High)
X_4 = Proportion of population > 65 years old (%)
E = Random Error, assumed ~ $N(0,\sigma^2)$
β_0: true y-intercept, and β_i: regression coefficient (slope) for the *i*th predictor

LITERATURE REVIEW TABLE

INCLUDED	KEYWORDS (PUBMED AND EMBASE)	PUBMED MESH TERMS	EXCLUDED KEYWORDS
Concept 1: Antimicrobial	• antimicrobial[tw] • antibiotic*[tw] • fluoroquinolone*[tw] • carbapenem*[tw] • cephalosporin*[tw]	• fluoroquinolones • carbapenems • cephalosporin antibiotics	• Antifungal*[tw] • Antiparasitic*[tw] • Antiviral*[tw]
Concept 2: Resistance	• Resistance • Susceptibility • resist*[tw] • susceptib*[tw] • "beta-Lactam Resistance"[tw] • "Cephalosporin resistance" • "Carbapenem-Resistant Enterobacteriaceae" • fluoroquinolone*[tw] • "drug resistance, multiple, bacterial"	• drug resistance, bacterial • beta-Lactam Resistance • Cephalosporin resistance • Carbapenem-Resistant Enterobacteriaceae • fluoroquinolones • drug resistance, multiple, bacterial	
Concept 3: Setting (tied with Burden)	• Global • Countries • countr* • global • worldwide		
Concept 4: Burden (tied with Setting)	• death[tw] • "all-cause mortality"[tw] • DALY*[tw] • "Disability-adjusted life years"[tw] • burden*[tw] • cost*[tw] • incidence[tw]		

Concept 5: Country-level factors	• HDI[tw] • "Human Development Index"[tw] • TrACSS[tw] • Tripartite[tw] • GLASS[tw] • “G.L.A.S.S.”[tw] • "Global antimicrobial resistance and use surveillance system" • "Tripartite Antimicrobial Resistance (AMR) Country Self-Assessment Survey"		
EXCLUDED	**KEYWORDS (PUBMED AND EMBASE)**	**PUBMED MESH TERMS**	**EXCLUDED KEYWORDS**
***Excluded* Concept 1: Remaining Antimicrobials**	• Antifungals • Antiparasitics • Antivirals		
QUALIFIERS	**KEYWORDS (PUBMED AND EMBASE)**	**PUBMED MESH TERMS**	**EXCLUDED KEYWORDS**
Age	• None Specified		
Species	• None Specified		
Language	• English		
Date range	• None Specified		
Publication type	• None Specified		

Final Search Statements

PubMed = n = 204

Date: 3/15/2021

((antimicrobial[tw] or antibiotic*[tw] or fluoroquinolone*[tw] or carbapenem*[tw] or cephalosporin*[tw])

NOT (Antifungal*[tw] or Antiparasitic*[tw] or Antiviral*[tw]))

AND (resist*[tw] or susceptib*[tw] or "beta-Lactam Resistance"[tw] or "Cephalosporin resistance" or "Carbapenem-Resistant Enterobacteriaceae" or fluoroquinolone*[tw] or "drug resistance, multiple, bacterial")

AND (countr* or global or worldwide) and (death[tw] or "all-cause mortality"[tw] or DALY*[tw] or "Disability-adjusted life years"[tw] or burden*[tw] or cost*[tw] or incidence[tw])

AND (HDI[tw] or "Human Development Index"[tw] or TrACSS[tw] or Tripartite[tw] or GLASS[tw] or “G.L.A.S.S.”[tw] or "Global antimicrobial resistance and use surveillance system" or "Tripartite Antimicrobial Resistance (AMR) Country Self-Assessment Survey")

AND English[lang]