The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis

Antimicrobial Resistance Collaborators

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Summary

Background Antimicrobial resistance (AMR) is an urgent global health challenge and a critical threat to modern health care. Quantifying its burden in the WHO Region of the Americas has been elusive—despite the region's long history of resistance surveillance. This study provides comprehensive estimates of AMR burden in the Americas to assess this growing health threat.

Methods We estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with AMR for 23 bacterial pathogens and 88 pathogen–drug combinations for countries in the WHO Region of the Americas in 2019. We obtained data from mortality registries, surveillance systems, hospital systems, systematic literature reviews, and other sources, and applied predictive statistical modelling to produce estimates of AMR burden for all countries in the Americas. Five broad components were the backbone of our approach: the number of deaths where infection had a role, the proportion of infectious deaths attributable to a given infectious syndrome, the proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of pathogens resistant to an antibiotic class, and the excess risk of mortality (or duration of an infection) associated with this resistance. We then used these components to estimate the disease burden by applying two counterfactual scenarios: deaths attributable to AMR (compared to an alternative scenario where resistant infections are replaced with susceptible ones), and deaths associated with AMR (compared to an alternative scenario where resistant infections would not occur at all). We generated 95% uncertainty intervals (UIs) for final estimates as the 25th and 975th ordered values across 1000 posterior draws, and models were cross-validated for out-of-sample predictive validity.

Findings We estimated 569,000 deaths (95% UI 406,000–771,000) associated with bacterial AMR and 141,000 deaths (99,900–196,000) attributable to bacterial AMR among the 35 countries in the WHO Region of the Americas in 2019. Lower respiratory and thorax infections, as a syndrome, were responsible for the largest fatal burden of AMR in the region, with 189,000 deaths (149,000–241,000) associated with resistance, followed by bloodstream infections (169,000 deaths [94,200–278,000]) and peritoneal/intra-abdominal infections (118,000 deaths [78,600–168,000]). The six leading pathogens (by order of number of deaths associated with resistance) were *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Together, these pathogens were responsible for 452,000 deaths (326,000–608,000) associated with AMR. Methicillin-resistant *S. aureus* predominated as the leading pathogen–drug combination in 34 countries for deaths attributable to AMR, while aminopenicillin-resistant *E. coli* was the leading pathogen–drug combination in 15 countries for deaths associated with AMR.

Interpretation Given the burden across different countries, infectious syndromes, and pathogen–drug combinations, AMR represents a substantial health threat in the Americas. Countries with low access to antibiotics and basic health-care services often face the largest age-standardised mortality rates associated with and attributable to AMR in the region, implicating specific policy interventions. Evidence from this study can guide mitigation efforts that are tailored to the needs of each country in the region while informing decisions regarding funding and resource allocation. Multisectoral and joint cooperative efforts among countries will be a key to success in tackling AMR in the Americas.

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Articles

Research in context

Evidence before this study

The burden of drug-resistant infections is growing each year. The 2016 *Review on Antimicrobial Resistance* estimated that in 2050 there will be 317,000 annual deaths in North America and 392,000 in South America from resistant HIV, malaria, tuberculosis, and the most burdensome bacterial pathogens. The 2013 and 2019 Antibiotic Resistance Threats Reports from the Centers for Disease Control and Prevention (CDC) estimated 23,000 and 35,000 annual deaths in the USA attributable to drug resistance, respectively. A KPMG report estimated approximately one million additional deaths in North America and Latin America arising from antimicrobial resistance (AMR), mainly attributable to third-generation cephalosporin-resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus*. However, these studies do not report details regarding infectious syndrome, age group, or granular country-level estimates. We conducted a thorough search of articles available in PubMed, Medline, Web of Science, Scopus, and others covering exposure to resistant bacterial pathogens, seeking human-focused publications on AMR. Details on our literature review, including the search criteria used, are available in Appendix 1 (Section 2.5 pp 5–9). Despite a long history of AMR surveillance in the WHO Region of the Americas, surveillance still lacks clinical insights on patient presentation and outcome, which limits the assessment of AMR burden and its utility in informing strategies such as antimicrobial stewardship.

Added value of this study

To our knowledge, this analysis is the most comprehensive assessment of the burden of AMR in the Americas to date, providing estimates for 35 countries, 23 bacterial pathogens, and 88 pathogen–drug combinations in 2019. This study uses the major methodological innovations from the recent global burden of AMR study to quantify the burden of AMR in the Americas, with two different counterfactual scenarios as estimation endpoints (the burden directly attributable to bacterial resistance and the burden associated with bacterial resistance). This study additionally places AMR within the context of other notable causes of death by building on estimates of disease incidence, prevalence, and mortality from the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2019.

Implications of all the available evidence

In this study, we show that bacterial AMR is a critical public health problem in the Americas, with over half a million deaths associated with resistance. Six pathogens accounted for 79.5% of deaths (95% uncertainty interval [UI] 78.4–80.6) associated with bacterial AMR: *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. These estimates will not only inform efforts to combat bacterial AMR by guiding prevention strategies and providing insight on specific pathogen–drug combinations but may also illuminate the optimal approach on how to collect microbiological data to improve future estimation processes and overall scientific understanding of this enormous health threat.

Introduction

Antimicrobial resistance (AMR) is one of the most serious global public health threats of our time.[1] The frequently cited *Review on Antimicrobial Resistance* estimates that AMR could lead to the loss of ten million lives annually by 2050, in addition to significant clinical and economic consequences.[2] Although these forecasts were initially challenged,[3,4] the recent global burden of AMR study estimated 4.95 million deaths associated with and 1.27 million deaths attributable to resistance in bacteria in 2019.[5] This positions AMR as one of the most pressing challenges to global health and modern health care, requiring collaborative global, regional, and country-specific solutions informed by data.

Surveillance of AMR in the Americas was instituted more than three decades ago. These efforts were pioneered with the surveillance of sexually transmitted infections in the late 1980s, leading to the participation in the Gonococcal Antimicrobial Stewardship Programme in 1992.[6] The Regional System for Vaccines (SIREVA) was established with the leadership of the Pan-American Health Organization in 1993, and focuses on the surveillance of serotypes and antibiotic susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* with the aim of informing vaccine development. The Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA), established in 1996 as a response to a cholera outbreak in the region, aims to support national reference laboratories and collect information on AMR.[6] Most countries in the region have also provided information to the Global Antimicrobial Resistance and Use Surveillance System since 2015.

The USA also has a strong history of AMR surveillance. In 1996, the National Antimicrobial Resistance Monitoring System was founded as a collaborative programme of state and local public health departments, universities, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration, and the US Department of Agriculture.[7,8] During the past

decade in the USA, two national action plans for combating AMR have been released, a Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria has been formed, and the CDC's AMR Challenge has been launched to prompt global organisations into formal commitments.[9] Canada has also had some notable recent developments, releasing a high-level policy document in September 2017 entitled "Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action," with a primary focus on outlining strategic objectives on collaborative action against AMR.[10]

Notwithstanding the long history of AMR surveillance in the Americas, microbial and clinical surveillance mostly advanced as isolated endeavours until fairly recently.[11] As a result, only a handful of studies present a joint analysis of routine microbial surveillance, resistance, and the clinical cases/outcomes which are fundamental to understanding the attribution of health loss due to AMR, the limitations and bias of the available data, and the pathways of action to tackle this multifaceted problem. We aim to bridge this gap and describe the impact of AMR on health loss in the Americas (with both regional and country-level estimates in 2019) as a necessary step to understand the different challenges present in this region and its component countries, as well as to inform both clinical and policy decision-making in the coming years. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.[12]

Methods
This paper is part of a collection of studies that aim to describe a regional burden of AMR.[13] The methodological approach used here extends the results of our original study to provide more granular and country-specific estimates; however, our overall methodology is the same. As such, in an effort to provide a complete description of our analytic process, parts of this methods text are taken directly from our study, "The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis."[13]

Overview and input data
This study extends the results of the global burden of AMR study[5] and uses its methodological approach but provides more granular and country-specific estimates within the WHO Region of the Americas.[13] More specifically, based on the global estimation of all-age and age-specific deaths and disability-adjusted life-years (DALYs) (with DALYs calculated as the sum of years of life lost due to premature mortality and years of healthy life lost due to disability) for 204 countries and territories, here we present aggregated estimates for the entire WHO Region of the Americas in 2019, as well as country-level estimates. In certain analyses, countries belonging to the WHO Region of the Americas were grouped in accordance with GBD regions (ie, high-income North America, Southern Latin America, Andean Latin America, Caribbean, Central Latin America, and Tropical Latin America). Disease burdens associated with and attributable to AMR were estimated for 12 major infectious syndromes and one residual category, 23 bacterial pathogens, and 88 pathogen-drug combinations.

Our global input data consisted of 343 million individual records or isolates covering 11,361 study-location-years obtained from surveillance systems, hospital systems, systematic literature reviews, and other sources (Appendix 1 Sections 2.1–2.7 pp 4–9). Details on data specific to the Americas are presented in the Supplemental Material (Appendix 1 Table S5 p 60). All data inputs for our models were empirical data (ie, not modelled estimates), except for a custom vaccine probe data meta-analysis which we used to estimate the fraction of pneumonia caused by *Streptococcus pneumoniae*. Clinical and Laboratory Standards Institute (CLSI) clinical breakpoints and methodology were used as guidance for classification of isolates into categories of susceptible or resistant.[14]

Our overall approach can be divided into five broad components: the number of deaths where infection was implicated, the proportion of infectious deaths attributable to a given infectious syndrome, the proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antimicrobial drug of interest, and the excess risk of death or duration of an infection associated with this resistance.

We followed GATHER[15] guidelines (Appendix 1 pp 67–69).

Estimation steps and burden calculation
In our approach, ten estimation steps took place within the aforementioned five broad modelling components (Appendix 1 Section 3 pp 9–38).[13] In estimation steps one and two, we defined the number of deaths where infection was implicated by using the Global Burden of Disease (GBD) 2019 cause of death estimates[16] to determine the number of deaths by age, sex, and location for which either the underlying cause of death was of infectious origin or the pathway to death included sepsis. We considered infectious syndromes that played a role in the pathway of sepsis deaths, some of which may not have been the underlying cause of death. In estimation steps three and four, we used multiple data sources to estimate pathogen distributions for each infectious syndrome for deaths and incident cases for each age, sex, and location. In estimation steps five through seven, we estimated the prevalence of phenotypic resistance by country for each of 88 pathogen-drug combinations (Appendix 1 Section 3.5 pp 26–33).

In estimation steps eight and nine, we estimated the relative risk of death for a resistant infection compared with that of a drug-sensitive infection for each pathogen-drug combination. Availability of input data for the above estimation steps is documented in Appendix 1 Table S5 p 60.

To generate mutually exclusive burden estimates of multi-drug resistant pathogens, we estimated a population-attributable fraction (PAF) for the resistance profiles representing each possible combination of susceptibility and resistance to the drugs analysed (Appendix 1 Section 3.5.4 pp 30–31). This method considered prevalence of resistance, excess risk, and a redistribution of burden to each antibiotic based on the respective excess risk.

In estimation step ten, we computed two counterfactual scenarios to quantify the benefit of eliminating drug-resistant infections. In a scenario where drug-resistant infections are replaced with drug-susceptible ones, we consider the excess risk of resistance, known as the "attributable to AMR" counterfactual scenario. Deaths attributable to AMR were calculated by multiplying the number of deaths for each underlying cause by the fraction of these deaths where infection was implicated, followed by multiplying the fraction of infectious deaths attributable to each infectious syndrome. This was then multiplied by the fraction of infectious syndrome deaths attributable to each pathogen, and by the PAF for each location-year and pathogen-drug combination.

Under the no-infection counterfactual scenario, infections that are resistant would not occur; this is also termed the associated with AMR scenario. Calculations here closely follow the process described for the attributable to AMR counterfactual, except the PAF is replaced with the prevalence of resistance for each location-year and pathogen-drug combination. We used a similar approach to calculate DALYs for both counterfactual scenarios (Appendix 1 Section 3.7 pp 35–38).

Modelling tools and framework

Details on our modelling approach can be found in the global burden of AMR study[5] and in the Appendix of this paper (Appendix 1 Section 3 pp 9–38).[13] Briefly, for estimation steps three and four we used the Bayesian meta-regression tool MR-BRT to estimate case-fatality rates (CFRs) as a function of the Healthcare Access and Quality (HAQ) Index and various bias covariates. We used multinomial estimation with partial and composite observations to incorporate heterogeneous data in the estimation of pathogen distributions for each infectious syndrome. In estimation steps five through seven, we used a two-stage spatiotemporal modelling framework to estimate the prevalence of resistance in each pathogen-drug combination (a complete list of pathogen-drug combinations can be found in Appendix Tables S3.5.1.1 and S3.5.1.2 pp 27–28).

Given the relationship between antibiotic consumption levels and AMR rates,[17] we modelled antibiotic consumption at the national level to use as a covariate in the stage one models of prevalence of resistance, using an ensemble spatiotemporal Gaussian process regression model to combine antibiotic usage estimates with pharmaceutical sales data for low- and middle-income countries. In cross-country comparisons, the indicator metric "defined daily doses (DDD) per 1000 inhabitants per day" was used to report antibiotic consumption in the community and within the hospital setting by WHO Anatomical Therapeutic Chemical classification, which provided a rough estimate of the proportion of the population treated with antimicrobials on a daily basis. MR-BRT and a two-stage nested mixed effects meta-regression model were used in the estimation of both relative risk of death and excess risk of hospital stay for each pathogen-drug combination (Appendix 1 Section 3.6.2 p 33).

Uncertainty analysis

Consistent with GBD methods,[16] we propagated uncertainty from each step of the analysis into the final estimates of deaths and infections attributable to and associated with drug resistance by taking the 25th and 975th of 1000 draws from the posterior distribution of each quantity of interest.[13] The models were cross-validated for out-of-sample predictive validity (more details available in Appendix 1 Sections 3.2–3.6 pp 9–33).

Role of the funding source

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

Results

Burden of AMR by infections and infectious syndromes

We estimated 1,327,000 million (95% uncertainty interval [UI] 993,000–1,751,000) deaths and 38,595,000 million (28,843,000–50,344,000) DALYs involving at least one of the 12 infectious syndromes in the WHO Region of the Americas in 2019 (Appendix 1 Table S8 p 66). Of these, bacterial infections, for which the burden of AMR was assessed, caused 920,000 deaths (664,000–1,242,000 million) and 23,347,000 DALYs (16,810,000–31,528,000). Bacterial lower respiratory infections, which were present as either the intermediate or underlying cause for 293,000 deaths (233,000–375,000), were the infectious syndrome responsible for the most bacterial deaths. Bloodstream infections and intra-abdominal infections were involved in 266,000 (149,000–439,000) and 181,000 bacterial deaths (120,000–259,000), respectively. Urinary

tract infections were responsible for the fourth largest number of deaths caused by bacterial pathogens (80,000 [63,000–103,000]). Together, these four infectious syndromes accounted for 89.0% (85.3–91.8) of deaths related to bacterial infections in the region in 2019.

More than two of every five deaths that involved infection in the Americas in 2019 were associated with AMR (569,000 deaths [95% UI 406,000–771,000], Table 1). Of these, 141,000 deaths (99,900–196,000) were attributable to AMR. Among the 293,000 deaths involving bacterial lower respiratory infections, 189,000 deaths (149,000–241,000) were associated with and 45,700 deaths (33,700–60,900) were attributable to resistant bacteria. Of the 266,000 deaths caused by a bacterial bloodstream infection, 169,000 (94,200–278,000) were associated with and 42,600 (22,800–70,600) were attributable to AMR. Similarly, 118,000 deaths (78,600–168,000) which involved peritoneal/intra-abdominal infections were associated with AMR.[5]

Burden of AMR by pathogens and bacteria–drug combinations

Five bacterial pathogens each caused more than 50,000 deaths associated with AMR in the Americas in 2019 (Table 2). These were, in order of the number of associated deaths, *Staphylococcus aureus* (123,000 [91,300–163,000]), *Escherichia coli* (109,000 [78,800–149,000]), *Klebsiella pneumoniae* (66,100 [47,400–90,000]), *Streptococcus pneumoniae* (56,500 [45,800–70,200]), and *Pseudomonas aeruginosa* (51,000 [36,000–70,700]). Rankings of the leading pathogens with respect to burden attributable to resistance were similar, though included *Acinetobacter baumannii* in place of *S. pneumoniae*: *S. aureus* (30,700 [17,000–48,600]), *E. coli* (25,500 [17,700–36,300]), *K. pneumoniae* (18,100 [12,000–26,200]), *A. baumannii* (14,300 [7940–22,900]), and *P. aeruginosa* (12,500 [8040–18,700]).

Eight pathogen–drug combinations were each associated with more than 50,000 AMR deaths in the Americas in 2019 (Fig. 1). *E. coli* resistant to aminopenicillin was the combination with the largest number of associated AMR deaths, 99,900 (95% UI 72,000–136,000). It was also the combination with the largest number of associated AMR deaths in 15 of the 35 countries in the region (Appendix 1 Table S1 pp 53–54). The second, third, and eighth largest combinations with the greatest associated with AMR burden were resistant strains of *S. aureus*: macrolide-resistant *S. aureus* with 94,200 deaths (70,000–126,000), methicillin-resistant *S. aureus* (MRSA) with 87,800 deaths (65,000–120,000), and fluoroquinolone-resistant *S. aureus* with 54,700 deaths (40,000–75,000). *E. coli* strains resistant to β-lactam with β-lactamase inhibitors (77,000 deaths [55,000–105,000]), trimethoprim-sulfamethoxazole (67,000 deaths [49,000–90,000]), and fluoroquinolones (58,200 deaths [41,000–79,000]) represented the fourth, fifth, and sixth largest combinations associated with AMR fatalities. *K. pneumoniae* resistant to β-lactam with β-lactamase inhibitors, associated with 55,200 deaths [39,000–75,000],

Infectious syndrome	Associated with AMR				Attributable to AMR			
	Deaths		DALYs		Deaths		DALYs	
	Counts	Rate per 100k	Counts	Rate per 100k	Counts	Rate per 100k	Counts	Rate per 100k
All	569,000 (406,000–771,000)	56.3 (40.2–76.3)	14,100,000 (10,000,000–19,300,000)	1399.1 (992.2–1910)	141,000 (99,900–196,000)	13.9 (9.9–19.4)	3,480,000 (2,420,000–4,900,000)	344.5 (239.7–485.3)
BSI	169,000 (94,200–278,000)	16.7 (9.3–27.6)	4,680,000 (2,800,000–7,160,000)	462.8 (277.1–709.1)	42,600 (22,800–70,600)	4.2 (2.3–7)	1,170,000 (704,000–1,830,000)	116.2 (69.7–181.5)
Bacterial skin infections	18,200 (9150–34,200)	1.8 (0.9–3.4)	378,000 (193,000–706,000)	37.4 (19.1–69.9)	3840 (1760–7470)	0.4 (0.2–0.7)	79,600 (38,600–153,000)	7.9 (3.8–15.1)
Bone and joint infections	1910 (577–4440)	0.2 (0.1–0.4)	42,700 (12,600–99,700)	4.2 (1.2–9.9)	435 (126–1030)	0 (0–0.1)	9740 (2810–23,600)	1 (0.3–2.3)
CNS infections	3410 (2320–5300)	0.3 (0.2–0.5)	183,000 (125,000–273,000)	18.1 (12.3–27)	777 (515–1220)	0.1 (0.1–0.1)	41,500 (27,800–62,500)	4.1 (2.7–6.2)
Cardiac infections	12,000 (8260–15,600)	1.2 (0.8–1.5)	261,000 (189,000–338,000)	25.8 (18.7–33.4)	2990 (2030–3930)	0.3 (0.2–0.4)	64,800 (46,300–85,100)	6.4 (4.6–8.4)
Diarrhoea	556 (350–854)	0.1 (0–0.1)	35,500 (22,500–53,700)	3.5 (2.2–5.3)	126 (72–207)	0 (0–0)	7110 (4130–11,300)	0.7 (0.4–1.1)
Gonorrhoea and chlamydia	–	–	3600 (2110–5610)	0.4 (0.2–0.6)	–	–	356 (107–701)	0 (0–0.1)
Intra-abdominal infections	118,000 (78,600–168,000)	11.7 (7.8–16.6)	2,840,000 (1,830,000–4,140,000)	281.4 (181.1–409.4)	30,200 (19,700–43,300)	3 (2–4.3)	727,000 (463,000–1,070,000)	72 (45.9–105.8)
LRI and thorax infections	189,000 (149,000–241,000)	18.7 (14.8–23.9)	4,670,000 (3,620,000–6,020,000)	462.5 (358.3–596)	45,700 (33,700–60,900)	4.5 (3.3–6)	1,110,000 (823,000–1,480,000)	110.2 (81.5–146.7)
Tuberculosis	2420 (1520–3890)	0.2 (0.2–0.4)	87,500 (56,200–140,000)	8.7 (5.6–13.9)	1050 (253–2400)	0.1 (0–0.2)	35,000 (8290–79,800)	3.5 (0.8–7.9)
Typhoid, paratyphoid, and iNTS	68 (35–187)	0 (0–0)	3150 (1710–7240)	0.3 (0.2–0.7)	13 (3–35)	0 (0–0)	617 (187–1440)	0.1 (0–0.1)
UTI	53,300 (41,700–69,100)	5.3 (4.1–6.8)	950,000 (732,000–1,270,000)	94 (72.4–125.8)	12,800 (9780–17,100)	1.3 (1–1.7)	228,000 (170,000–318,000)	22.6 (16.9–31.4)

Data are estimates (95% uncertainty interval). Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. For gonorrhoea and chlamydia, we did not estimate the fatal burden, thus only the DALY burden is presented. AMR = antimicrobial resistance; BSI = bloodstream infection; CNS = central nervous system; DALYs = disability-adjusted life-years; iNTS = invasive non-typhoidal *Salmonella*; LRI = lower respiratory infection; UTI = urinary tract infection; UI = uncertainty interval; WHO = World Health Organization.

Table 1: Summary of deaths and DALYs by infectious syndrome for countries in the WHO Region of the Americas, 2019.

Pathogen	Associated with AMR				Attributable to AMR			
	Deaths		DALYs		Deaths		DALYs	
	Counts	Rate per 100k	Counts	Rate per 100k	Counts	Rate per 100k	Counts	Rate per 100k
All pathogens	569,000 (406,000–771,000)	56.3 (40.2–76.3)	14,100,000 (10,000,000–19,300,000)	1399.1 (992.2–1910)	141,000 (99,900–196,000)	13.9 (9.9–19.4)	3,480,000 (2,420,000–4,900,000)	344.5 (239.7–485.3)
Acinetobacter baumannii	45,300 (26,400–70,800)	4.5 (2.6–7)	1,080,000 (642,000–1,650,000)	106.5 (63.6–163)	14,300 (7940–22,900)	1.4 (0.8–2.3)	339,000 (191,000–542,000)	33.5 (18.9–53.6)
Citrobacter spp.	2330 (1530–3370)	0.2 (0.2–0.3)	65,400 (42,300–96,400)	6.5 (4.2–9.5)	666 (385–1070)	0.1 (0–0.1)	18,700 (10,500–30,400)	1.8 (1–3)
Enterobacter spp.	18,500 (12,500–25,900)	1.8 (1.2–2.6)	504,000 (336,000–717,000)	49.9 (33.2–71)	4240 (2750–6110)	0.4 (0.3–0.6)	116,000 (74,600–167,000)	11.4 (7.4–16.6)
Enterococcus faecalis	12,000 (7460–18,100)	1.2 (0.7–1.8)	312,000 (202,000–450,000)	30.9 (20–44.5)	3410 (1730–5750)	0.3 (0.2–0.6)	88,300 (46,600–145,000)	8.7 (4.6–14.3)
Enterococcus faecium	33,600 (21,300–49,100)	3.3 (2.1–4.9)	810,000 (508,000–1,190,000)	80.1 (50.2–118)	10,600 (6470–16,400)	1 (0.6–1.6)	254,000 (151,000–399,000)	25.1 (14.9–39.5)
Escherichia coli	109,000 (78,800–149,000)	10.8 (7.8–14.7)	2,470,000 (1,760,000–3,390,000)	244.8 (174–335.4)	25,500 (17,700–36,300)	2.5 (1.7–3.6)	581,000 (396,000–843,000)	57.5 (39.2–83.4)
Group A *Streptococcus*	3520 (1930–6290)	0.3 (0.2–0.6)	97,100 (59,000–164,000)	9.6 (5.8–16.2)	337 (0– 1220)	0 (0–0.1)	9240 (0–30,700)	0.9 (0–3)
Group B *Streptococcus*	14,200 (9780–20,000)	1.4 (1–2)	407,000 (273,000–583,000)	40.2 (27.1–57.7)	1780 (0– 4190)	0.2 (0–0.4)	52,200 (0– 121,000)	5.2 (0–11.9)
Haemophilus influenzae	2500 (1970–3190)	0.2 (0.2–0.3)	75,200 (57,000–96,500)	7.4 (5.6–9.5)	508 (148–903)	0.1 (0–0.1)	15,500 (5000–27,800)	1.5 (0.5–2.8)
Klebsiella pneumoniae	66,100 (47,400–90,000)	6.5 (4.7–8.9)	1,770,000 (1,250,000–2,410,000)	174.7 (124–238.6)	18,100 (12,000–26,200)	1.8 (1.2–2.6)	485,000 (322,000–700,000)	48 (31.9–69.3)
Morganella spp.	447 (325–611)	0 (0–0.1)	7490 (5280–10,600)	0.7 (0.5–1)	108 (60–175)	0 (0–0)	1790 (984–2950)	0.2 (0.1–0.3)
Mycobacterium tuberculosis	2420 (1520–3890)	0.2 (0.2–0.4)	87,500 (56,200–140,000)	8.7 (5.6–13.9)	1050 (253–2400)	0.1 (0–0.2)	35,000 (8290–79,800)	3.5 (0.8–7.9)
Neisseria gonorrhoeae	–	–	3600 (2110–5610)	0.4 (0.2–0.6)	–	–	356 (107–701)	0 (0–0.1)
Non-typhoidal *Salmonella*	142 (64–277)	0 (0–0)	8770 (3500–19,700)	0.9 (0.3–1.9)	29 (3–77)	0 (0–0)	1510 (273–3680)	0.1 (0–0.4)
Other *enterococci*	10,700 (7680–14,800)	1.1 (0.8–1.5)	246,000 (171,000–344,000)	24.4 (16.9–34.1)	2440 (1140–3970)	0.2 (0.1–0.4)	55,300 (24,600–92,200)	5.5 (2.4–9.1)
Proteus spp.	11,400 (8080–15,500)	1.1 (0.8–1.5)	229,000 (160,000–315,000)	22.7 (15.8–31.2)	1480 (838–2340)	0.1 (0.1–0.2)	29,500 (16,400–47,000)	2.9 (1.6–4.7)
Pseudomonas aeruginosa	51,000 (36,000–70,700)	5 (3.6–7)	1,230,000 (851,000–1,730,000)	122.1 (84.2–171.2)	12,500 (8040–18,700)	1.2 (0.8–1.9)	302,000 (194,000–457,000)	29.9 (19.2–45.2)
Salmonella Paratyphi	5 (3–7)	0 (0–0)	208 (128–352)	0 (0–0)	1 (0–2)	0 (0–0)	41 (8–86)	0 (0–0)
Salmonella Typhi	960 (515–1670)	0.1 (0.1–0.2)	52,700 (28,000–91,600)	5.2 (2.8–9.1)	189 (40–416)	0 (0–0)	10,400 (2110–22,400)	1 (0.2–2.2)
Serratia spp.	3980 (2470–6140)	0.4 (0.2–0.6)	122,000 (76,800–183,000)	12 (7.6–18.1)	1040 (585–1760)	0.1 (0.1–0.2)	32,100 (18,400–53,200)	3.2 (1.8–5.3)
Shigella spp.	182 (73–358)	0 (0–0)	11,500 (4670–21,500)	1.1 (0.5–2.1)	37 (3–95)	0 (0–0)	2090 (417–4870)	0.2 (0–0.5)
Staphylococcus aureus	123,000 (91,300–163,000)	12.2 (9–16.1)	2,800,000 (2,000,000–3,800,000)	277.3 (197.9–376.4)	30,700 (17,000–48,600)	3 (1.7–4.8)	698,000 (376,000–1,110,000)	69.1 (37.2–109.9)
Streptococcus pneumoniae	56,500 (45,800–70,200)	5.6 (4.5–6.9)	1,750,000 (1,370,000–2,220,000)	172.8 (135.8–220.2)	11,600 (7920–15,800)	1.1 (0.8–1.6)	356,000 (238,000–492,000)	35.2 (23.6–48.7)

Data are estimates (95% uncertainty interval). Count values are rounded to three significant figures, rate values are rounded to one decimal point. Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. For *Neisseria gonorrhoeae*, we did not estimate the fatal burden, thus only the DALY burden is presented. AMR = antimicrobial resistance; DALYs = disability-adjusted life-years; Group A *Streptococcus* = *Streptococcus pyogenes*; Group B *Streptococcus* = *Streptococcus agalactiae*; *Salmonella* Paratyphi = *Salmonella enterica* serovar Paratyphi; *Salmonella* Typhi = *Salmonella enterica* serovar Typhi; UI = uncertainty intervals; WHO = World Health Organization.

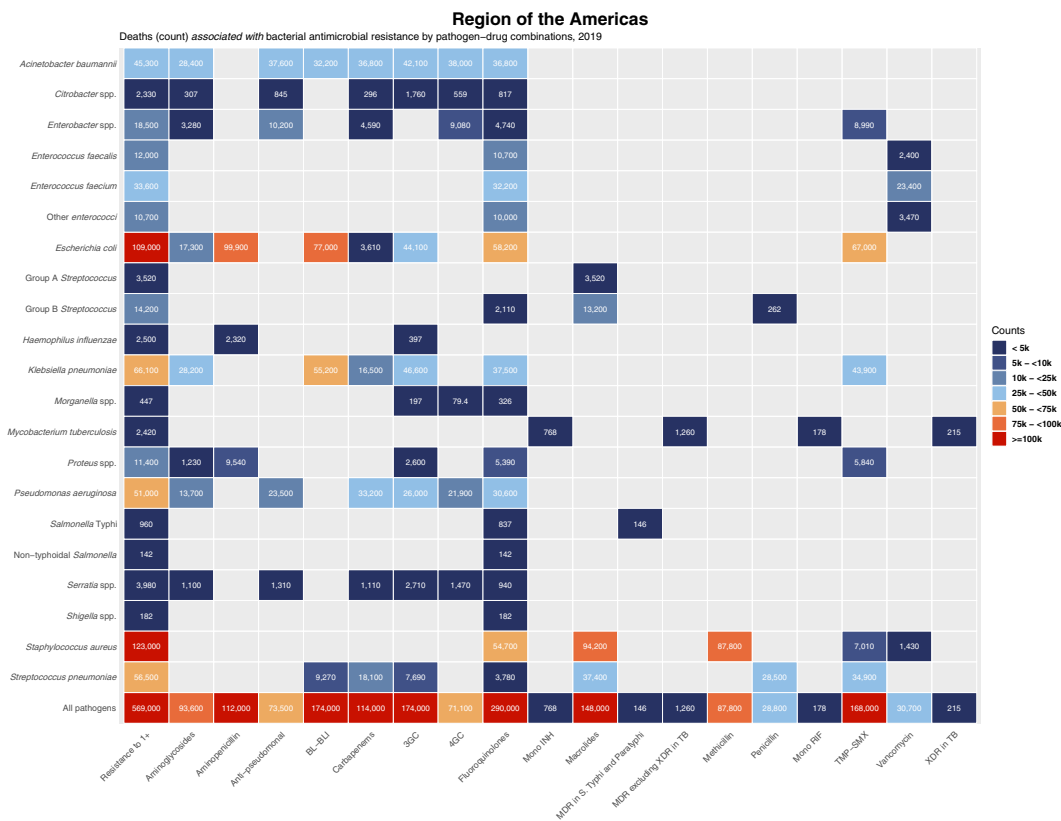***Table 2:* Summary of deaths and DALYs by pathogen in the WHO Region of the Americas, 2019.**

Region of the Americas
Deaths (count) *associated with* bacterial antimicrobial resistance by pathogen–drug combinations, 2019

	Resistance to 1+	Aminoglycosides	Aminopenicillin	Anti-pseudomonal	BL-BLI	Carbapenems	3GC	4GC	Fluoroquinolones	Mono INH	Macrolides	MDR in S. Typhi and Paratyphi	MDR excluding XDR in TB	Methicillin	Penicillin	Mono RIF	TMP-SMX	Vancomycin	XDR in TB
Acinetobacter baumannii	45,300	28,400		37,600	32,200	36,800	42,100	38,000	36,800										
Citrobacter spp.	2,330	307		845		296	1,760	559	817										
Enterobacter spp.	18,500	3,280		10,200		4,590		9,080	4,740							8,990			
Enterococcus faecalis	12,000								10,700									2,400	
Enterococcus faecium	33,600								32,200									23,400	
Other *enterococci*	10,700								10,000									3,470	
Escherichia coli	109,000	17,300	99,900		77,000	3,610	44,100		58,200								67,000		
Group A *Streptococcus*	3,520										3,520								
Group B *Streptococcus*	14,200								2,110		13,200				262				
Haemophilus influenzae	2,500		2,320				397												
Klebsiella pneumoniae	66,100	28,200			55,200	16,500	46,600		37,500								43,900		
Morganella spp.	447					197		79.4	326										
Mycobacterium tuberculosis	2,420									768			1,260			178			215
Proteus spp.	11,400	1,230	9,540				2,600		5,390							5,840			
Pseudomonas aeruginosa	51,000	13,700		23,500		33,200	26,000	21,900	30,600										
Salmonella Typhi	960								837			146							
Non–typhoidal *Salmonella*	142								142										
Serratia spp.	3,980	1,100		1,310		1,110	2,710	1,470	940										
Shigella spp.	182								182										
Staphylococcus aureus	123,000								54,700		94,200			87,800			7,010	1,430	
Streptococcus pneumoniae	56,500				9,270	18,100	7,690		3,780		37,400				28,500		34,900		
All pathogens	568,000	93,600	112,000	73,500	174,000	114,000	174,000	71,100	290,000	768	148,000	146	1,260	87,800	28,800	178	168,000	30,700	215

Counts
- < 5k
- 5k – <10k
- 10k – <25k
- 25k – <50k
- 50k – <75k
- 75k – <100k
- >=100k

Fig. 1: **Heatmap representing deaths associated with bacterial antimicrobial resistance by pathogen–drug combination in the WHO Region of the Americas, 2019.** Values are rounded to three significant figures. Results for *Salmonella enterica* serovar Paratyphi excluded from this figure due to no appreciable AMR burden for this pathogen in the Region of the Americas (see Table 2). 3GC = third-generation cephalosporins; 4GC = fourth-generation cephalosporins; Anti-pseudomonal = anti-pseudomonal penicillins with or without β-lactamase inhibitors; BL-BLI = β-lactams with β-lactamase inhibitors; Group A *Streptococcus* = *Streptococcus pyogenes*; Group B *Streptococcus* = *Streptococcus agalactiae*; MDR = multidrug resistance; Mono INH = isoniazid mono-resistance; Mono RIF = rifampicin mono-resistance; Resistance to 1+ = resistance to one or more drugs; S Typhi = *S. enterica* serovar Typhi; TB = tuberculosis, TMP-SMX = trimethoprim-sulfamethoxazole; XDR = extensive drug resistance.

was the seventh leading combination and the only one not related to resistance among *S. aureus* or *E. coli* species.

MRSA, responsible for 23,400 deaths [95% UI 10,000–39,000] attributable to resistance, was the only pathogen–drug combination with more than 10,000 attributed deaths (Fig. 2). The six combinations following MRSA in attributable mortality all had greater than 5000 deaths attributable to AMR and included five distinct pathogens, a far more diverse set than was found in the leading associated combinations. These were, ranked in decreasing order of attributable deaths: fluoroquinolone-resistant *E. coli* (6420 [4330–8960]), third-generation cephalosporin-resistant *E. coli* (6270 [2730–11,000]), carbapenem-resistant *A. baumannii* (6160 [3160–10,900]), carbapenem-resistant *P. aeruginosa* (5840 [3800–8700]), vancomycin-resistant *Enterococcus faecium* (5750 [3100–9500]), and third-generation cephalosporin-resistant *K. pneumoniae* (5390 [1900–10,200]).

Burden of AMR by location and age
The proportion of all-cause mortality that involved infection differed widely across the countries in the Americas, as did the degree to which infectious deaths involved resistant pathogens. Infections represented the smallest share of mortality in Canada (with 13.7% of deaths involving infection [95% UI 9.9–18.6]), and the largest share of deaths in Haiti (where 33.6% of deaths were infectious in nature [27.0–40.8]) (Appendix 1 Table S6 pp 61–63). By contrast, Haiti had the lowest proportion of infectious deaths that were associated with a resistant pathogen (30.3% [27.1–33.4]), while Chile had the highest (48.2% [46.0–50.3]). Fig. 3a shows that five countries had an age-standardised mortality rate associated with AMR greater than 90 deaths per 100,000 person-years: Haiti, Bolivia, Guatemala, Guyana, and Honduras (ranked from highest to lowest). The countries with the lowest age-standardised mortality rate
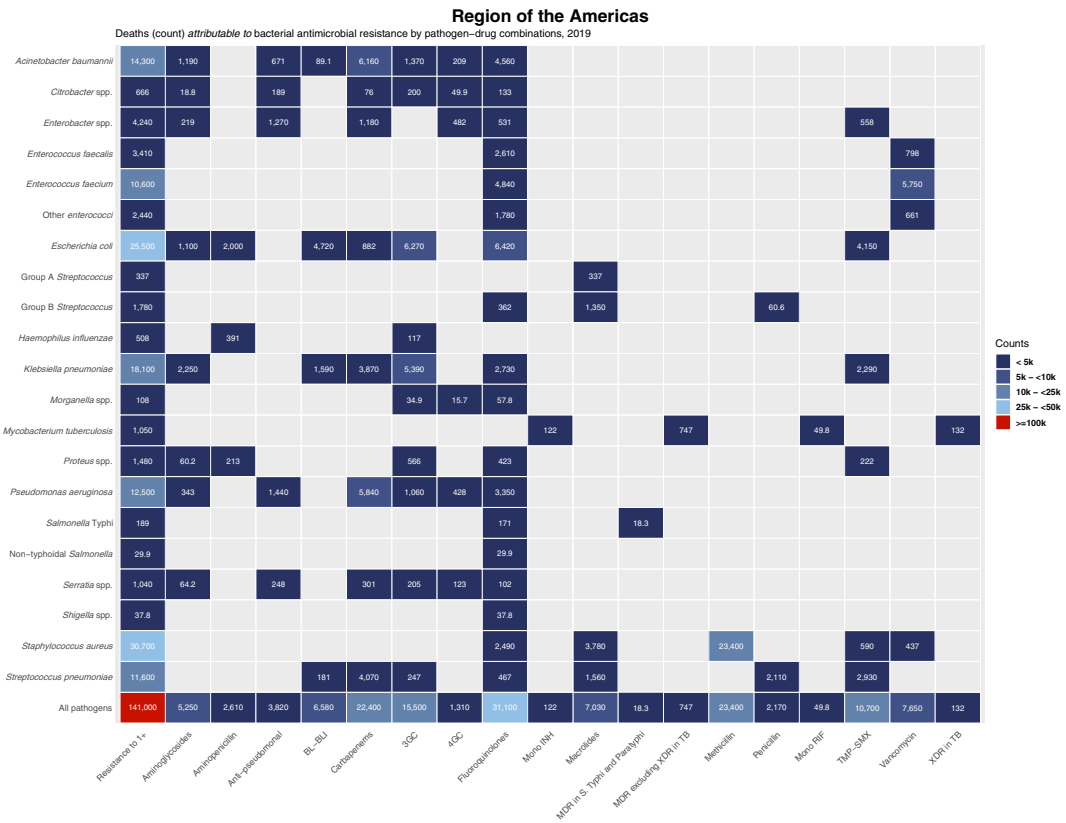
Region of the Americas

Deaths (count) *attributable to* bacterial antimicrobial resistance by pathogen–drug combinations, 2019

	Resistance to 1+	Aminoglycosides	Aminopenicillin	Anti-pseudomonal	BL-BLI	Carbapenems	3GC	4GC	Fluoroquinolones	Mono INH	Macrolides	MDR in S. Typhi and Paratyphi	MDR excluding XDR in TB	Methicillin	Penicillin	Mono RIF	TMP-SMX	Vancomycin	XDR in TB
Acinetobacter baumannii	14,300	1,190		671	89.1	6,160	1,370	209	4,560										
Citrobacter spp.	666	18.8		189		76	200	49.9	133										
Enterobacter spp.	4,240	219		1,270		1,180		482	531								558		
Enterococcus faecalis	3,410								2,610									798	
Enterococcus faecium	10,600								4,840									5,750	
Other *enterococci*	2,440								1,780									661	
Escherichia coli	25,500	1,100	2,000		4,720	882	6,270		6,420								4,150		
Group A *Streptococcus*	337										337								
Group B *Streptococcus*	1,780								362		1,350				60.6				
Haemophilus influenzae	508		391				117												
Klebsiella pneumoniae	18,100	2,250			1,590	3,870	5,390		2,730								2,290		
Morganella spp.	108					34.9	15.7	57.8											
Mycobacterium tuberculosis	1,050									122			747			49.8			132
Proteus spp.	1,480	60.2	213			566			423								222		
Pseudomonas aeruginosa	12,500	343		1,440		5,840	1,060	428	3,350										
Salmonella Typhi	189								171			18.3							
Non–typhoidal *Salmonella*	29.9								29.9										
Serratia spp.	1,040	64.2		248		301	205	123	102										
Shigella spp.	37.8								37.8										
Staphylococcus aureus	30,700								2,490		3,780			23,400			590	437	
Streptococcus pneumoniae	11,600				181	4,070	247		467		1,560				2,110		2,930		
All pathogens	141,000	5,250	2,610	3,820	6,580	22,400	15,500	1,310	31,100	122	7,030	18.3	747	23,400	2,170	49.8	10,700	7,650	132

Counts
- < 5k
- 5k – <10k
- 10k – <25k
- 25k – <50k
- >=100k

***Fig. 2*: Heatmap representing deaths attributable to bacterial antimicrobial resistance by pathogen-drug combination in the WHO Region of the Americas, 2019.** Values are rounded to three significant figures. Results for *Salmonella enterica* serovar Paratyphi excluded from this figure due to no appreciable AMR burden for this pathogen in the Region of the Americas (see Table 2). 3GC = third-generation cephalosporins; 4GC = fourth-generation cephalosporins; Anti-pseudomonal = anti-pseudomonal penicillins with or without β-lactamase inhibitors; BL-BLI = β-lactams with β-lactamase inhibitors; Group A *Streptococcus* = *Streptococcus pyogenes*; Group B *Streptococcus* = *Streptococcus agalactiae*; MDR = multidrug resistance; Mono INH = isoniazid mono-resistance; Mono RIF = rifampicin mono-resistance; Resistance to 1+ = resistance to one or more drugs; S Typhi = *S. enterica* serovar Typhi; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; XDR = extensive drug resistance.

associated with AMR (ranked from lowest to highest) were Canada, the USA, Colombia, Cuba, Panama, Costa Rica, Chile, Venezuela, Uruguay, and Jamaica, all of which had a mortality rate lower than 50 deaths associated with AMR. Rankings of countries by age-standardised attributable mortality rate were generally similar, with the highest observed mortality in Haiti (30.0 attributable deaths per 100,000 [20.0–42.4]) and the lowest observed in Canada (4.1 attributable deaths per 100,000 [2.7–6.0]) (Fig. 3b).

Fig. 4 shows the pattern of AMR death rates by detailed age for all the countries in the Americas. Death rates associated and attributable to AMR followed a generally consistent pattern across countries, with a spike in deaths among neonates followed by near zero rates among 1–4-year-olds that slowly increase until about age 65, after which they begin to increase more dramatically. AMR death rates among neonates were the highest observed of any age group in several countries, namely Dominica, the Dominican Republic, Guyana,

Haiti, Jamaica, Suriname, and Venezuela. The rate of neonatal burden was beneath 1000 associated AMR deaths per 100,000 person-years in eight countries: Antigua and Barbuda, Argentina, Canada, Chile, Costa Rica, Cuba, the USA, and Uruguay.

A comparison between AMR mortality rates and each country's self-reported progress towards developing a National Action Plan (NAP) against AMR is shown in Fig. 5. The ten countries with the highest age-standardised mortality rates associated with AMR all either did not have an AMR NAP or had not published their AMR NAP. Chile, Colombia, Costa Rica, and the USA, were four of the five countries that had both published their AMR NAP and financed the plan in at least one year since 2018, and all had among the lowest AMR mortality rates.[18]

Discussion

To our knowledge, this is the most comprehensive study to date describing the burden of AMR in the WHO
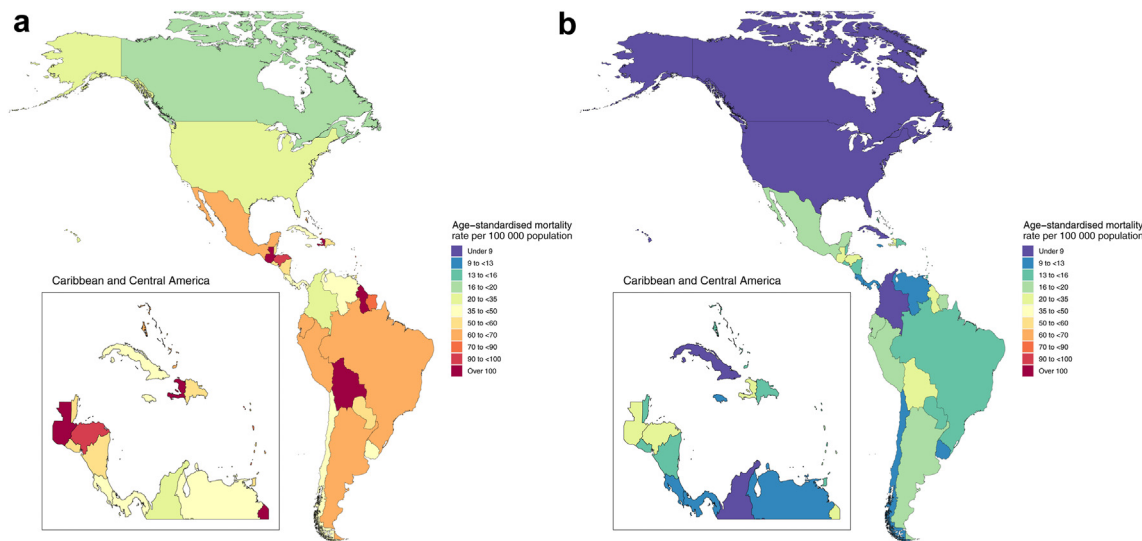
Fig. 3: **Map of age-standardised mortality rates per 100,000 person-years for deaths associated with (A) and attributable to (B) antimicrobial resistance in the WHO Region of the Americas in 2019.** For country-specific results presented in a heatmap, please refer to Appendix 1 Figure S4 (attributable burden) and Appendix 1 Figure S5 (associated burden).

Region of the Americas for an extensive list of pathogens and pathogen–drug combinations. Our analysis reveals that 11.1% (95% UI 9.9–12.1) of the total estimated global deaths attributable to AMR and 11.5% (10.6–12.3) of the global deaths associated with AMR occurred within the Americas (a region with approximately 13% of the world's population) in 2019, based on our published global estimates.[5] In a scenario where all drug-resistant infections were replaced by no infection, 569,000 deaths in the Americas could have been prevented in 2019. Similarly, if all drug-resistant infections were replaced by drug-susceptible infections, 141,000 deaths in the region could have been prevented (Fig. 2).

We identified substantial burden caused by *S. aureus* and *E. coli*, with each responsible for more than 100,000 deaths associated with AMR in the region. These two bacteria also represent a large burden in other regions of the world,[5] and are the first AMR pathogens considered part of the Sustainable Development Goals (indicator 3.d.2),[21] which aims to reduce bloodstream infections related to MRSA and third-generation cephalosporin-resistant *E. coli*. The ranking of these two pathogens as leading AMR pathogens globally should be leveraged by health ministries and organisations to prompt calls for broad international initiatives to address their AMR risk. As the burden for *S. aureus* and *E. coli* combined represents approximately 40% of both the attributable and associated AMR burdens in the Americas, controlling the treatment, spread, and development of resistance of these pathogens will be paramount in minimising the AMR burden in the region.

With respect to *S. aureus*, a recent report underscored that at least 25% of *S. aureus* isolates carry methicillin resistance in Latin America,[22] although it is likely that this percentage is higher as indicated by research showing MRSA prevalence at 48.3%,[23] and a Latin America SENTRY report for the 2011–2014 time period that documented a prevalence of 44.7%.[24] Our estimates for 2019 align with and further reinforce these concerning trends, showing a median MRSA prevalence of 45% in the region, ranging from 18% in Canada to 63% in Trinidad and Tobago. Since the turn of the millennium, community-acquired MRSA infections have grown in scope, expanding from a medical obscurity to a now common cause of skin and soft tissue infections across Latin America,[25] Canada,[26] and the United States.[27] From a health burden perspective, MRSA infections are very onerous: our results suggest that infections with a methicillin-resistant strain of *S. aureus* (as contrasted with a methicillin-susceptible strains) are associated with a 43% increased risk of death (Appendix 1, Table S4 pp 58-59) among infections evaluated from sterile sites.

In high-income North America, the Canadian Antimicrobial Resistance Surveillance System has documented that the rate of MRSA infections has been increasing steadily since 2012, primarily driven by the proliferation of community-acquired strains.[26] Our study confirms that MRSA is the combination with the highest age-standardised mortality rate in Canada, where this pathogen–drug combination was responsible for 490 deaths (95% UI 200–870), an age-standardised mortality rate of 0.69 (0.27–1.24), and 8000 DALYs (3000–15,000) attributable to AMR. Previous studies
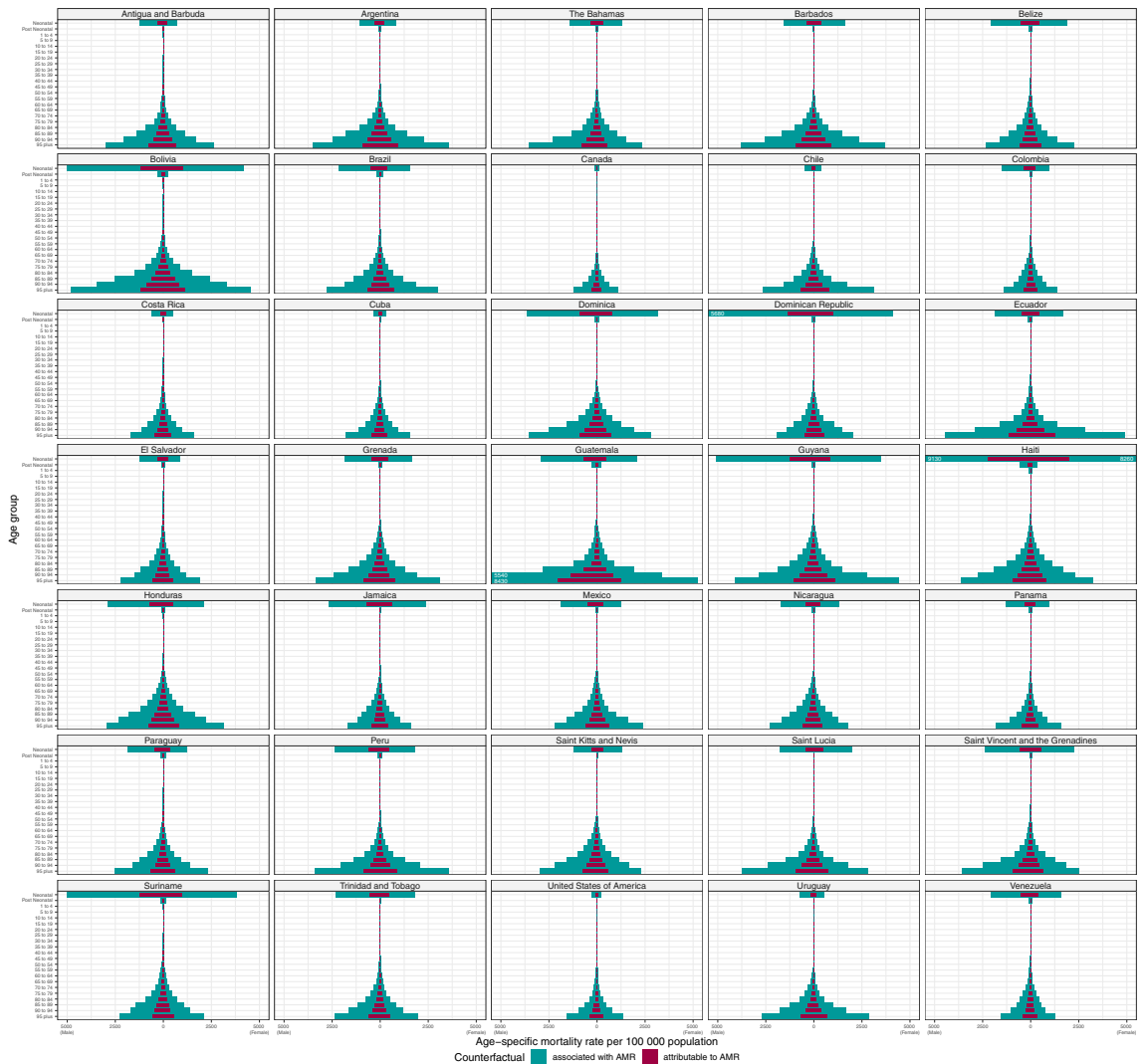
Fig. 4: Age–specific mortality rates for deaths attributable to and deaths associated with AMR per country in the WHO Region of the Americas, 2019. Rates for males are shown on the left-hand side of each plot, while rates for females are shown on the right. To improve within-country rate comparisons for countries with lower rates of burden, the X-axis is truncated at 5250. Rates higher than 5250 are represented by bars that extend to the edge of the plot, with the true rate written in white text. Results for the Region of the Americas as a whole (and the six GBD regions contained within) can be found in Appendix 1 Figure S13.

have shown that lower prevalence of MRSA is observed in the Atlantic Provinces when compared to the national average (0.5% versus 5.6%),[27] and subnational data would facilitate a refined analysis of drug consumption and resistance rates in the country.

The large burden of *E. coli* coincides with high burden of resistant *Enterobacterales* in this region more broadly, and echoes results from Karlowsky and colleagues[28] that showed resistance to third-generation cephalosporins among *E. coli* species increased substantially in Latin America from 2015 to 2019, while *K. pneumoniae* resistant to third-generation cephalosporins increased substantially in Canada, Latin

America, and the USA during the same time period.[28,29] Carbapenem-resistant *E. coli* and *K. pneumoniae* are particularly serious health threats in Latin America and the Caribbean.[29–31] In Barbados, the results of the 2017 prevalence study by Forde and colleagues on carbapenem-resistant *K. pneumoniae* prompted national action and changed screening recommendations to include rectal swabs for all patients hospitalised for a period longer than one month. This subsequently instigated the introduction of several AMR surveillance programmes across the English-speaking Caribbean.[32] The sizable burden of *K. pneumoniae* we identify in Barbados, Dominica,
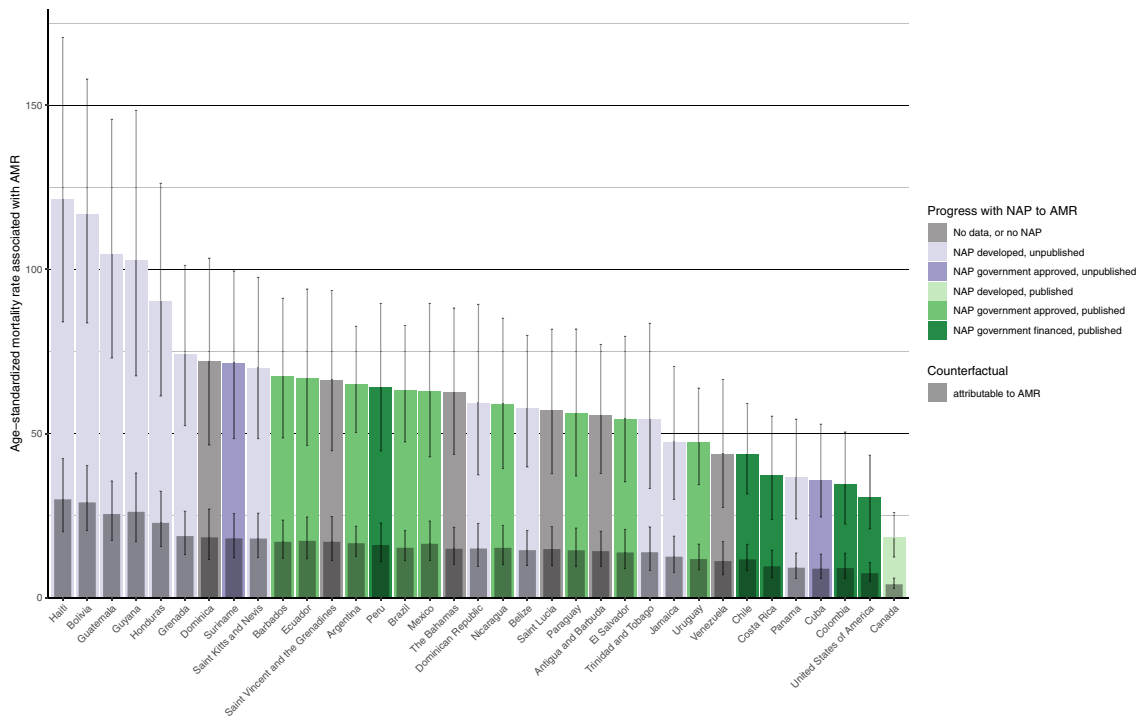
Fig. 5: Age-standardised mortality rate associated with and attributable to AMR in relation to the status of NAPs for the countries in the WHO Region of the Americas. Rates per 100,000 person-years are coloured according to two dimensions NAP status: the highest self-reported government engagement with the NAP between 2018 and 2021 and whether the NAP was published online as reported in surveys or the WHO NAP website. Grey error bars indicate 95% uncertainty intervals. NAP data was acquired from the Global Database for Tracking Antimicrobial Resistance Country Self-Assessment Survey (TrACSS) responses for the years 2018–2021[19] and the WHO library of AMR NAPs.[20] Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Antigua and Barbuda, Dominica, Grenada, Haiti, Saint Kitts and Nevis and Venezuela AMR NAP progress was last reported in the 2018–2019 survey responses. AMR = antimicrobial resistance; NAP = national AMR action plan.

Haiti, and Guyana aligns with the Caribbean Public Health Agency's decision to focus on that pathogen for their Caribbean-wide pilot project to monitor AMR through phenotypic resistance assessment and whole-genome sequencing.[33] Based on our results, we argue that *A. baumannii* and *S. pneumoniae* should be strongly considered as future candidates.[28–32]

It should be noted that rigid comparison of our estimates with previous publications is somewhat complicated due to our novel methodological approach; however, certain parallels can be drawn. For instance, the CDC published a 2019 report on AMR infections and deaths in the USA for 18 AMR threats by using surveillance data, and showed that more than 2.8 million AMR infections occur in the USA every year, resulting in more than 35,000 deaths.[34] Our estimates for the USA indicate that 42,000 deaths (28,000–60,000) are attributable to and 173,000 deaths (120,000–243,000) associated with AMR for the 88 pathogen–drug combinations and 23 bacterial pathogens included in our study. However, the CDC analysis included resistant fungi, and these two analyses differed substantively with respect to the analysed

bacterial pathogens (acknowledging the potential sources of variation and uncertainty in both sets of results). Interestingly, other than as a component of multidrug-resistant *P. aeruginosa*, fluoroquinolone resistance was not identified as a major threat or concern in the CDC report. By contrast, our study finds substantial burden attributable to fluoroquinolone resistance in the USA (with 9400 deaths [6200–13,900]) and fluoroquinolone-resistant *E. coli* is the pathogen–drug combination with the third greatest attributable burden in the country (Appendix 2 p 79). In the three years following a 2016 Food and Drug Administration warning that the risks of adverse effects of fluoroquinolones outweigh the benefits of their use in many types of infections, there was a 42% reduction in outpatient fluoroquinolone prescription fills in the USA, though prescribing patterns were enduring among some physicians, namely otolaryngologists and those 65 or older.[35,36] We argue that given the historical patterns of overprescribing,[37] the impact of fluoroquinolone exposure in selecting for mutations that pave the way for the development of methicillin-resistance and extended-spectrum β-lactamase production in various

pathogens,[38] and the high burden we identify here, there is strong justification to carefully monitor the use of and resistance to fluoroquinolones in the USA.[38]

Strategies to address AMR differ across countries in the Americas given the heterogeneity in wealth in the region. The region is posed in between two distinct challenges: reducing the number of infections and maintaining antibiotic efficacy. In countries where there is low socio-demographic development and deficient access to antibiotics, infection prevention and control measures and vaccination campaigns might have the largest impact on burden, as access to appropriate care once infected would be limited. For example, given low vaccination rates for *S. pneumoniae* in many Caribbean nations, PCV vaccination represents a promising avenue for addressing both resistant and susceptible pneumococcal disease in these countries (Appendix 1 Figure S14 p 52). Expansion of microbiological testing capacity is also vital in lower-income countries, not only to better characterise the problem of AMR in these geographies but also to inform antibiotic treatment regimens for clinicians. In countries with strong health care systems and plentiful stocks of antibiotics, conversely, opportunities for strategic antimicrobial stewardship could have the largest impact in reducing the burden from AMR. Stewardship would benefit from a surveillance monitoring network of public health officials which can provide feedback to medical teams and pharmacists regarding the current state of antibiotic use and resistance.

The fraction of all-cause mortality that involved infection and the proportion of infectious deaths that were associated with resistance are important indicators signalling the strategies that may be most beneficial for a given country. Despite having the lowest proportion of infectious deaths that were associated with resistance, Haiti has the highest age-standardised AMR attributable mortality rate due its high baseline rate of infection-related mortality, which is nearly 50% greater than that of the next highest country in the region. For countries in which infections make up a larger share of all-cause mortality—Haiti and Bolivia lead in this metric in the Americas (Appendix 1 Table S6 pp 61–63 and Appendix 1 Figure S12 p 50)—infection prevention and control could yield the greatest reductions in AMR burden. Conversely, countries in which a larger share of infectious deaths are associated with resistance, such as Chile and Mexico (Appendix 1 Table S6 pp 61–63 and Appendix 1 Figure S12 p 50), could benefit from more stringent antimicrobial stewardship and surveillance. Peru, which ranks third in the Americas for both of these metrics, is uniquely positioned to benefit from both of these strategies.

One method to institutionalise a strong surveillance monitoring network is through the implementation of national action plans (NAP). There are 14 countries in the Americas that have published their NAP online, be it developed, approved, budgeted, financed, or implemented. An additional 15 countries have developed or approved an unpublished NAP, while six countries had not yet developed a NAP or otherwise did not report their progress towards an AMR NAP.[19,20] Only four countries reported sufficient capacity to collect data on AMR across all relevant sectors in 2021, and six countries reported they have weak or no policies to optimise antimicrobial use in humans.[39] It is important that the systems developed are used to inform guidelines and interventions in the region. The Organisation for Economic Co-operation and Development estimated that 75% of the AMR burden could be reduced by investing US$2 per person per year across the member countries, and quantified the cost-effectiveness of policies that tackle the AMR burden on different fronts.[40]

The surveillance of antimicrobial use must be strengthened to monitor trends in resistance and improve future estimates. The contribution of high-income North America and Latin America and the Caribbean to the total antibiotic consumption on a global level is considerable, with 7.7% and 6.2% of global antibiotic consumption occurring in these two regions, respectively.[18] In the USA, as many as 30% of antibiotic prescriptions are deemed medically unnecessary,[41] and over the past two decades there has been an increasing trend in national antibiotic consumption rates for most countries in Latin America.[42] Although data on antimicrobial sales for human health remain scarce in the Americas, several countries (such as Bolivia, Brazil, Costa Rica, Paraguay, and Peru) have already provided valuable data for the 2016–2018 WHO Report on Surveillance of Antibiotic Consumption.[40,43] Based on our estimates, we did not find a significant correlation between overall antibiotic consumption and attributable AMR mortality rates (Appendix 3 p 2), in contrast with Europe, where such a correlation was found.[13] This assessment is complicated by the juxtaposition of low-SDI countries with low antimicrobial use but high rates of infection (elevating the AMR burden, as shown in Appendix 1 Figures S9 and S10 pp 47–48) against some of the wealthiest countries in the world with established resistance monitoring regimes. Despite this heterogeneity, we do find significant correlations between the use of six (of the 13 estimated) antimicrobial classes and their corresponding attributable burden (Appendix 3). Further surveillance efforts are needed to better inform these comparisons and other research on the interaction between prescribing practices and the outbreak of resistance.

Limitations

Our study has several limitations. Notwithstanding the general issue of data scarcity, especially data points that link AMR with mortality and DALYs, there was a notable data paucity for several pathogen–drug combinations, particularly for Cuba, Paraguay, and Uruguay.

Such limited data in some countries was consequential for the prevalence of resistance and relative risk modelling components of our work. Additionally, these two components were not stratified by age and sex groups nor by infectious syndromes; these methodological assumptions are explained in the Appendix of the global burden of AMR study.[5] Still, our estimation process is robust as it is informed by data from all countries in the Americas. When data for a specific country are lacking, our estimates rely on regional patterns, covariates, and out-of-sample predictive validity. Even though we have accounted for various biases, we must be cognisant that selection bias may occur in passive microbial surveillance data, while potential bias and misclassification can arise when combining and standardising data from various providers (ie, different levels of care provision), as well as various domains (eg, the difference between community-acquired and health-care-associated infections). Finally, despite our use of the most recent CLSI breakpoint guidelines whenever possible,[14] there are no universal laboratory standards to distinguish resistance versus susceptibility, and deferring to source laboratory interpretation for classifying the isolates in our study may have resulted in heterogeneous classification.

Conclusion

The WHO Region of the Americas has a long history of surveillance of AMR, but there are still challenges to translate this surveillance into public action. One of these challenges relates to the differentiated nature of the problem for the countries in the region. A few countries face low access to antibiotics and basic health-care services, and some also face the largest age-standardised mortality rates associated with and attributable to AMR in the region. For those, the most cost-effective solutions may lie in policies which prevent infections, especially among the age groups that are most affected by infectious diseases. However, several countries have widespread access to basic health-care services, vaccination, antenatal care, and antibiotic treatment, and may achieve the largest gains by emphasising antimicrobial stewardship. By quantifying the health loss and understanding the groups which experience the greatest burden from AMR, we aim to inform public action to address this growing global health problem.

Editor note

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