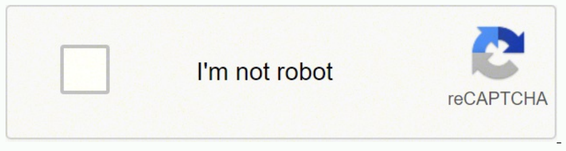

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Location-years of data refer to unique GBD locations and years for which we have records or isolates. A J Stewardson reports grants or contracts from Merck, Sharp, & Dohme paid to Monash University, Melbourne, outside of the study. World Health Organization, Geneva2018View in Article 57.Non-prescription antimicrobial use worldwide: a
systematic review.Lancet Infect Dis. We give thanks to the late Rattanaphone Phetsouvanh, the Lao Ministry of Health, and the Directorate of Mahosot Hospital who enabled the collection and sharing of Lao data, Vientiane, Lao People's Democratic Republic. 2019; 101124View in Article Scopus (248) PubMed Crossref Google Scholar63.Increasing
role of Staphylococcus aureus and community-acquired methicillin-resistant Staphylococcus aureus infections in the United States: a 10-year trend of replacement and expansion.Microb Drug Resist. Error bars show 95% uncertainty intervals. LRI+=lower respiratory infections and all related infections in the thorax. For the second counterfactual
scenario—where all drug-resistant infections are replaced by no infection—we estimated all deaths and DALYs associated with resistant infection. World Health Organization, Geneva2015View in Article 9.Estimating the burden of antimicrobial resistance: a systematic literature review.Antimicrob Resist Infect Control. Despite scarcity, our estimates
are informed by data from all regions (figure 7, table 1). When two or more antibiotics were resistant in a single profile, we used the relative risk for the antibiotic class that was the largest as the relative risk for calculating the PAF:Where R is prevalence of resistance, RR is relative risk, K is a pathogen with d=1, ..., n resistance profiles with
resistance to at least one antibiotic class, and D is the antibiotic class in profile d with the highest relative risk (appendix pp 56–60).We computed two counterfactuals to estimate the drug-resistant burden: the burden attributable to bacterial AMR based on the counterfactual of drug-sensitive infection and the burden associated with bacterial AMR
based on the counterfactual of no infection (appendix pp 56–60). Although sub-Saharan Africa had the highest all-age death rate attributable to and associated with AMR, the percentage of all infectious deaths attributable to AMR was lowest in this super-region (appendix p 97).Figure 2All-age rate of deaths attributable to and associated with
bacterial antimicrobial resistance by GBD region, 2019Show full captionEstimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. 2013; 8e75392View in Article Scopus (99) PubMed Crossref Google Scholar51.Distinguishable epidemics of multidrug-resistant Salmonella Typhimurium DT104 in different
hosts.Science. We produced estimates for 11 of these 16 combinations; we did not estimate colistin resistance in E coli, P aeruginosa, or A baumannii because of the paucity of data on colistin resistance in LMICs, or multidrug resistance in P aeruginosa or A baumannii because of our approach to MDR infections. 2015; 109: 309-318View in Article
Scopus (705) PubMed Crossref Google Scholar8.Global action plan on antimicrobial resistance. 2013; 13: 1057-109859.Substandard/counterfeit antimicrobial drugs.Clin Microbiol Rev. The non-susceptible group includes isolates reported as “non-susceptible”, “intermediate”, and “resistant”. BSI=bloodstream infections. 2011; 17: 321-328View in
Article Scopus (79) PubMed Crossref Google Scholar64.A longitudinal analysis of methicillin-resistant and sensitive Staphylococcus aureus incidence in respect to specimen source, patient location, and temperature variation.Int J Infect Dis. Error bars show 95% uncertainty intervals.The share of AMR burden caused by each of the six leading
pathogens differed substantially across GBD super-regions. Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. We used this fraction to subdivide sepsis deaths with non-infectious underlying causes into specific infectious syndromes. 4GC=fourth-generation cephalosporins. CNS=meningitis and
other bacterial CNS infections. World Health Organization, Geneva2019View in Article 56.WHO sepsis technical expert meeting—meeting report. MDR=multidrug resistance. Estimates of AMR burden based on each counterfactual are useful in different ways for informing the development of potential intervention strategies to control AMR., , We
used several data collection strategies. Vaccination programmes are an important strategy for preventing S pneumoniae, and vaccine development is crucial for pathogens that currently have no vaccine. We estimated both measures of burden because there is insufficient evidence to determine the extent to which drug-resistant infections would be
replaced by no infection or susceptible infection if drug resistance was eliminated. Two of five components included data from every GBD region and two of five included data from 19 of 21 GBD regions. However, our framework for estimating the total envelope of infectious syndrome mortality used GBD cause-specific mortality estimates to minimise
reliance on these sparse data.Figure 1Data inputs by source typeShow full captionTotal sample size for each source type, regardless of specific inclusion criteria for a given estimation step. Although the intention of this list was to set new antibiotic research and development priorities rather than identify the most burdensome pathogen–drug
combinations, its utility in dictating priorities has still been limited by the absence of a global assessment of the burden of bacterial AMR. WHO and numerous other groups and researchers agree that the spread of AMR is an urgent issue requiring a global, coordinated action plan to address.5WHOAntimicrobial resistance., 6US Centers for Disease
Control and PreventionAntibiotic resistance threats in the United States, 2019., , 8WHOGlobal action plan on antimicrobial resistance. To show where data are available and how the modelled estimates differ from the input data, figure 7 also shows the raw, unadjusted prevalence of resistance for each of the seven leading pathogen–drug
combinations.Figure 7Raw data and modelled estimates for the percentage of pathogen isolates that are resistant by country and territory, 2019Show full captionMeticillin-resistant Staphylococcus aureus (A), isoniazid and rifampicin co-resistant (excluding XDR) Mycobacterium tuberculosis (B), third-generation cephalosporin-resistant Escherichia
coli (C), carbapenem-resistant Acinetobacter baumannii (D), fluoroquinolone-resistant E coli (E), carbapenem-resistant Klebsiella pneumoniae (F), and third-generation cephalosporin-resistant K pneumoniae (G). We used predictive statistical modelling to produce estimates of AMR burden for all locations, including for locations with no data. The
Medical Research Council Unit—The Gambia at the LSHTM acknowledges all the staff in the microbiology clinical laboratory for their support. For underlying causes of death that are themselves infectious, all deaths were assigned to their single corresponding infectious syndrome (eg, the GBD cause “lower respiratory infections” was assigned to the
infectious syndrome “lower respiratory infections and all related infections in the thorax”; appendix pp 21–23).Due to the pathogen distributions varying substantially for hospital-acquired and community-acquired infections in two infectious syndromes—lower respiratory and thorax infections and urinary tract infections—we further estimated the
subdivision of these syndromes into community-acquired and hospital-acquired infections (appendix pp 17–30; table with community-acquired and hospital-acquired subdivisions presented on pp 24–25).For the nine infectious syndromes in this study that were estimated as one or more causes of death and disability in GBD 2019 (lower respiratory and
thorax infections; CNS infections; typhoid, paratyphoid, and invasive non-typhoidal Salmonella spp; urinary tract infections; diarrhoea; tuberculosis; bacterial skin infections; cardiac infections; and gonorrhoea and chlamydia), we used GBD 2019 incidence estimates as a baseline for infectious syndrome incidence (appendix p 16). Improvements to the
input data and models compared with previous publications make our AMR estimates the most robust of any to date. 2020; 1013767View in Article Scopus (9) PubMed Crossref Google Scholar62.Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage.Nat Commun. Intra-abdominal=peritoneal and intra-
abdominal infections. the UN Interagency Coordination Group, the One Health Global Leaders Group,36WHOGlobal Leaders Group on antimicrobial resistance. If left unchecked, the spread of AMR could make many bacterial pathogens much more lethal in the future than they are today.One major challenge to tackling AMR is understanding the true
burden of resistance, particularly in locations where surveillance is minimal and data are sparse. In the future, these estimates could be used to better inform treatment guidelines. Information about the current magnitude of the burden of bacterial AMR, trends in different parts of the world, and the leading pathogen–drug combinations contributing
to bacterial AMR burden is crucial. The dominant bacterial pathogens for a given infectious syndrome and the antibiotics that would offer effective treatment could be identified using the data for this study, which, along with estimates of pathogen–drug burden, could be used to inform empirical syndromic treatment guidelines tailored to a specific
location.Our analysis clearly shows that bacterial AMR is a major global health problem. We thank the Kenya Medical Research Institute, United States Army Medical Research Directorate-Africa, Kenya, Nairobi, Kenya; we acknowledge the International Nosocomial Infection Control Consortium, Buenos Aires, Argentina; we would like to thank the
CHILDS Trust Medical Research Foundation, Chennai, India; we acknowledge the Childhood Acute Illness & Nutrition Network investigators; we thank Institut Pasteur and Laboratoire National de Biologie Clinique et de Santé Publique in Bangui, Central African Republic; we would like to acknowledge the Global Tuberculosis Programme of WHO,
Geneva, Switzerland; we thank the SENTRY Antimicrobial Surveillance Program, JMI Laboratories, North Liberty, Iowa, USA; we acknowledge the Sihanouk Hospital Center of Hope, Phnom Penh, Cambodia.Editorial note: the Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional
affiliations.1.Tackling drug-resistant infections globally: final report and recommendations. S Dunachie acknowledges funding from NIHR Global Research Professorship (NIHR300791). We modelled all-age and age-specific deaths and disability-adjusted life-years (DALYs) for 204 countries and territories, and we present aggregated estimates for 21
GBD regions, seven GBD super-regions, and globally in 2019 (a full list of GBD locations by region is available in the appendix pp 100–05).For the first counterfactual scenario—where all drug-resistant infections are replaced by susceptible infections—we estimated only deaths and DALYs directly attributable to resistance. A full list of data sources
included in this study, organised by data type, is included in the appendix (pp 8–15).All data inputs for the models were empirical data, not modelled estimates, except for a custom meta-analysis of vaccine probe data that we did to estimate the fraction of pneumonia caused by Streptococcus pneumoniae (appendix pp 37–38). The list was intended to
inform research and development priorities related to new antibiotics and put the most emphasis on pathogens with multidrug resistance that cause severe and often deadly infections in health-care and nursing home settings. 2018; 7: 58View in Article Scopus (185) PubMed Crossref Google Scholar10.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. H van Doorn reports grants or contracts from the University of Oxford and is the principal investigator for the Fleming Fund pilot grant; and he is a board member of Wellcome Trust's
Surveillance and Epidemiology of Drug Resistant Infections. This comparison is not perfect because there is not complete overlap in the locations included in western and central Europe and EU member countries (ie, Switzerland is included in our estimate and not in the EU designation, whereas Estonia is in the EU but is part of our eastern Europe
region; appendix pp 100–05), but it offers some idea of how our estimates compare with those of previous publications.Some of our estimates might be unexpected and deserve special attention, particularly the high burden in sub-Saharan Africa and the burden of carbapenem-resistant A baumannii. These CFRs allowed us to integrate sources that
reported pathogen distribution only for deaths and those that reported only incidence by mapping the reported deaths by pathogen into implied cases by pathogen. T Walsh reports financial support from the Bill & Melinda Gates Foundation for the BARNARDS (neonatal sepsis and mortality) study for the present manuscript. With these Pearson
correlations and our prevalence of resistance estimates, we used an optimisation-based approach to solve for multivariate binomial distributions that define the prevalence of resistance of every combination of resistance to the antibiotics analysed. To model the infectious syndrome pathogen distribution comprehensively, we estimated, where
applicable, the incidence and death proportions attributable to viral, fungal, parasitic, and bacterial pathogens; however, AMR burden was calculated only for selected bacteria for which resistance is clinically relevant and sufficient data are available. Published by Elsevier Ltd. We thank Sabrina Bacci, Liselotte Diaz Högberg, Marlena Kaczmarek,
Maria Keramarou, Favelle Lamb, Dominique L Monnet, Gianfranco Spiteri, Carl Suetens, Therese Westrell and Klaus Weist at the ECDC, Solna, Sweden, for providing information on databases and discussions on data interpretation. Finally, we calculated DALYs by summing YLLs and YLDs. To estimate the overall AMR burden of this counterfactual,
we repeated the described calculations with the prevalence of resistance to one or more antibiotics estimated and summed across all pathogens.Following previously described GBD methods, 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. We acknowledge the Department of Pathology and Laboratory Medicine, and Department of Paediatrics and Child Health, Aga Khan University, Karachi, Pakistan. Our models of sepsis and infectious syndrome were the most geographically sparse,
covering 16 countries from ten regions; the input data for these models were highly detailed microdata that are only sparsely available. 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. Review on
Antimicrobial Resistance, London2016View in Article 2.Antimicrobial resistance: tackling a crisis for the health and wealth of nations. N Feasey acknowledges that the Malawi Liverpool Wellcome Trust Clinical Research Programme diagnostic microbiology service is funded by a Wellcome Asia and Africa Programme grant. In the past few decades,
investments have been small compared with those in other public health issues with similar or less impact.55WHO2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. It must fix it. For deaths attributable to AMR, E coli was responsible for the most deaths in 2019, followed by K pneumoniae,
S aureus, A baumannii, S pneumoniae, and M tuberculosis.Figure 4Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019Show full captionEstimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Six pathogens accounted for 73·4% (95%
uncertainty interval 66·9–78·8) of deaths attributable to bacterial AMR. The observed prevalence of each drug overall and Pearson correlations between drugs provided noisy partial observations of combinations of these entries. BL-BLI=β-lactam or β-lactamase inhibitors. The number of positive isolates identified for each pathogen–drug combination
is shown in the appendix (pp 90–91). Likewise, Lim and colleagues estimated the burden of multidrug resistance in six bacterial pathogens in Thailand in 2010, and Temkin and colleagues estimated the incidence of Escherichia coli and Klebsiella pneumoniae resistant to third-generation cephalosporins and carbapenems in 193 countries in
2014.Although these publications are important contributions to the body of work on AMR, they are insufficient to understand the global burden of AMR and identify and target the highest priority pathogens in different locations. To calculate DALYs, we took the sum of YLLs and YLDs. To estimate the overall AMR burden of the drug-sensitive
counterfactual, we added the burden estimates of all the pathogen–drug combinations.The approach for calculating the fatal burden associated with AMR was identical to that for fatal burden attributable to AMR, except we replaced the mortality PAF for each resistance profile with the prevalence of resistance in deaths. Table 1 shows the number of
individual records or isolates used and number of countries covered in each of the five broad modelling components separately by GBD region. On the basis of a counterfactual scenario of no infection, we estimated that 4·95 million deaths (3·62–6·57) were associated with bacterial AMR globally in 2019 (including those directly attributable to AMR).
Through our large collaborator networks, we obtained datasets not previously available for AMR research, including hospital and laboratory data, as well as datasets published previously and those outlined in research articles.19Ashley EA Recht J Chua A et al.An inventory of supranational antimicrobial resistance surveillance networks involving low-
and middle-income countries since 2000.Crossref PubMed Scopus (28) Google Scholar Each component of the estimation process had different data requirements and, as such, the input data used for each modelling component differed. Both preventing bacterial AMR and increasing microbiological laboratory and data collection capacity to improve
scientific understanding of this health threat should be a very high priority for global health policy makers.Bacterial antimicrobial resistance (AMR)—which occurs when changes in bacteria cause the drugs used to treat infections to become less effective—has emerged as one of the leading public health threats of the 21st century. There is widespread
agreement that AMR poses a serious potential threat to human health around the world. NA=not applicable. F Krapp was supported by Framework Agreement Belgian Directorate of Development Cooperation-Institute of Tropical Medicine in Antwerp. 2017; 5: 25243.The WHO made a big mistake on tuberculosis. GBD=Global Burden of Diseases,
Injuries, and Risk Factors Study.In 2019, meticillin-resistant S aureus was the one pathogen–drug combination in our analysis with more than 100 000 deaths and 3·5 million DALYs attributable to resistance (figure 6; appendix pp 121–22, 129). Western sub-Saharan Africa had the highest burden, with 27·3 deaths per 100 000 (20·9–35·3) attributable
to AMR and 114·8 deaths per 100 000 (90·4–145·3) associated with AMR. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.We estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204
countries and territories in 2019. 2018; 73: 1737-1749View in Article Scopus (28) PubMed Crossref Google Scholar20.Global Burden of Disease Study 2019 (GBD 2019) data input sources tool.View in Article 21.Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a
systematic analysis from the Global Burden of Disease Study 2016.Lancet. Combined, these three syndromes accounted for 78·8% (95% UI 70·8–85·2) of deaths attributable to AMR in 2019; lower respiratory infections alone accounted for more than 400 000 attributable deaths and 1·5 million associated deaths (figure 3).Figure 3Global deaths
(counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019Show full captionEstimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Our findings, which—to our knowledge—are the most comprehensive estimates of the burden of bacterial AMR to date,
clearly show that drug resistance in each of these leading pathogens is a major global health threat that warrants more attention, funding, capacity building, research and development, and pathogen-specific priority setting from the broader global health community.Resistance to fluoroquinolones and β-lactam antibiotics (ie, carbapenems,
cephalosporins, and penicillins)—antibiotics often considered first line for empirical therapy of severe infections41WHOThe selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children).—accounted for
more than 70% of deaths attributable to AMR across pathogens. Extensive literature exists estimating incidence, deaths, hospital length of stay, and health-care costs associated with AMR from a small number of drug-resistant infections in select locations. 2020; 57: 95-101View in Article Scopus (9) PubMed Crossref Google Scholar18.Improving the
estimation of the global burden of antimicrobial resistant infections.Lancet Infect Dis. while Cassini and colleagues estimated the burden of eight bacterial pathogens and 16 pathogen–drug combinations in the EU and European Economic Area for 2007–15. A Stewardson is supported by an Australian National Health and Medical Research Council
Early Career Fellowship (GNT1141398). We searched the evidence available in PubMed for published works that evaluate exposure to antimicrobial resistant organisms (bacteria only) and evaluated all human-focused publications with more than ten cases, all genders, and all age groups. Using these components, we estimated disease burden based
on two counterfactuals: deaths attributable to AMR (based on an alternative scenario in which all drug-resistant infections were replaced by drug-susceptible infections), and deaths associated with AMR (based on an alternative scenario in which all drug-resistant infections were replaced by no infection). By contrast, in sub-Saharan Africa, the
leading pathogens were distinct from those of the high-income super-region, and each represented a smaller share of the AMR burden; S pneumoniae contributed to 15·9% (11·4–21·0) of the deaths attributable to AMR and 19·0% (17·1–21·1) of the deaths associated with AMR, whereas K pneumoniae contributed to 19·9% (15·1–25·4) of the deaths
attributable to AMR and 17·5% (16·3–18·7) of the deaths associated with AMR.Figure 5Pathogen-attributable fraction of deaths attributable to (A) and associated with (B) bacterial AMR for the six leading pathogens by GBD super-region, 2019Show full captionError bars show 95% uncertainty intervals. In 2017, WHO published a priority list for
developing new and effective antibiotic treatments. Only five of the seven pathogen–drug combinations that we estimated to have caused the most deaths attributable to bacterial AMR in 2019 are currently on the list; MDR tuberculosis and fluoroquinolone-resistant E coli are not included.34WHOGlobal priority list of antibiotic-resistant bacteria to
guide research, discovery, and development of new antibiotics. We acknowledge The Australian Group for Antimicrobial Resistance, and The Australian Commission on Safety and Quality in Healthcare, Sydney, Australia. Data input citations are available online.First, to define the number of deaths where infection plays a role, we used GBD 2019
cause of death estimates to determine the number of deaths by age, sex, and location for which either the underlying cause of death was infectious or—for non-communicable, maternal, neonatal, nutritional, and injury deaths—for which the pathway to death was through sepsis. 2019; 365eaaw1944View in Article Scopus (283) PubMed Crossref
Google Scholar49.The risk of low concentrations of antibiotics in agriculture for resistance in human health care.FEMS Microbiol Lett. We used the same modelling framework for excess length of stay as we used for relative risk of death. Individual isolates that were tested multiple times for resistance to different antibiotics are listed only once here
whenever isolates were identified uniquely in the data. Due to data sparsity on the excess risk of death associated with drug-resistant N gonorrhoeae, we did not produce a fatal estimate for this pathogen.To produce burden estimates of multiple pathogen–drug combinations that were mutually exclusive within a given pathogen (and thus could be
added), we produced a population-attributable fraction (PAF) for each resistance profile with resistance to at least one drug (appendix pp 56–60). To this baseline, we added the number of incident cases of each infectious syndrome that co-occurred with underlying non-communicable diseases (NCDs); maternal, neonatal, and nutritional diseases
(MNNDs); and injuries, which we calculated by dividing the number of infectious syndrome deaths that occurred with underlying NCDs, MNNDs, and injuries (by age, sex, location, and GBD cause) by syndrome-specific and pathogen-specific case-fatality ratios (CFRs; estimation described in the following subsection). Furthermore, in LMICs, hospital
microbial data might skew towards more urban populations or more severe disease, which might not be representative of the broader population. Because we do not know the extent to which drug-resistant infections would be replaced by susceptible infections or by no infection in a scenario in which all drug resistance was eliminated, it is important
to quantify the burden on the basis of both these counterfactual scenarios.In this study, we present the first global estimates of the burden of bacterial AMR covering an extensive set of pathogens and pathogen–drug combinations using consistent methods for both counterfactual scenarios.We developed an approach for estimating the burden of AMR
that makes use of all available data and builds on death and incidence estimates for different underlying conditions from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, which provides age-specific and sex-specific estimates of disease burden for 369 diseases and injuries in 204 countries and territories in 1990–2019.
2018; 6: e969-e97913.Burden of antimicrobial resistance: compared to what?.Epidemiol Rev. World Health Organization, Geneva2020View in Article 26.Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care.Crit Care Med. and AMR has been highlighted in the political arena through the Global
Action Plan on AMR,8WHOGlobal action plan on antimicrobial resistance. We used two categories of susceptibility: susceptible and non-susceptible. Together, these six pathogens were responsible for 929 000 (95% UI 660 000–1 270 000) of 1·27 million deaths (0·911–1·71) attributable to AMR and 3·57 million (2·62–4·78) of 4·95 million deaths (3·62–
6·57) associated with AMR globally in 2019. US Department of Health and Human Services, Atlanta, GA2019View in Article 7.Antimicrobial resistance: a global multifaceted phenomenon.Pathog Glob Health. We acknowledge Tien Viet Dung Vu and Nguyen Minh Trang Nghiem, Oxford University Clinical Research Unit, Wellcome Africa Asia
Programme, National Hospital for Tropical Diseases, Hanoi, Vietnam; and the VINARES Consortium. Every such distribution was characterised by a contingency table specifying probabilities of all combinations of resistance and susceptibility among the antibiotics analysed. as well as our collaborators' process of data collation and cleaning, we were
unable to collect more contemporary data; we assumed no change in prevalence of resistance for 2019. It might be that, in certain locations, cultures are drawn only if a patient does not respond to initial antibiotic therapy, which might lead to an overestimate of the prevalence of resistance. 2021; 10: 60View in Article Scopus (2) PubMed Crossref
Google Scholar55.2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Because of data sparsity, we assumed the relative risk was the same for every syndrome, location, and age group; the assumptions on location and age group risk are consistent with those in the estimation process
previously used by Cassini and colleagues. This approach could lead to misclassification, since the criteria used in this coding are not strictly related to community versus hospital acquisition. Mono INH=isoniazid mono-resistance. Using the counterfactual of susceptible infection, AMR would have been the 12th leading GBD Level 3 cause of death
globally, ahead of both HIV and malaria (more information on GBD causes by level presented in the appendix pp 18, 67–75). Although we estimated sub-Saharan Africa to be the super-region with the lowest percentage of infectious deaths attributable to AMR (appendix p 97), the rate of deaths in which infection plays a role was so much greater in
sub-Saharan Africa than in other super-regions that it overcame a relatively low prevalence of resistance and was the super-region with the highest estimated AMR burden in 2019.Regarding carbapenem-resistant A baumannii, we estimated that it was the fourth leading pathogen–drug combination globally for 2019, responsible for slightly fewer
deaths than third-generation cephalosporin-resistant E coli. The Review on Antimicrobial Resistance estimated 700 000 deaths in 2014 attributable to resistance to six pathogens: HIV, tuberculosis, malaria, S aureus, E coli, and K pneumoniae. We chose these 88 combinations by first creating an exhaustive list of all clinically relevant combinations for
which we had any data and then eliminating combinations that did not meet minimum data availability and computational feasibility requirements for accurate statistical modelling (appendix pp 59–60).For the pathogen–drug combinations in the 2014 WHO AMR global report on surveillance, as well as fluoroquinolone and multidrug resistance in
Salmonella enterica serotypes Typhi and Paratyphi, we supplemented microbial datasets from collaborators and surveillance networks with aggregate microbiology data from systematic reviews and published surveillance reports. Expanding our resistance analysis to more pathogen–drug combinations—particularly adding viruses, parasites, and fungi
—would increase our estimate of the burden and could alter some of the results reported, depending on the correlation structure of resistance between the newly added and original 88 pathogen–drug combinations. When only a phenotypic disk interpretation was available, we used the interpretation as provided. TMP-SMX=trimethoprim-
sulfamethoxazole. T Wangrangsimakul acknowledges funding from the Wellcome Trust, as part of the MORU Tropical Health Network institutional funding support. We acknowledge John Murray, Becton, Dickinson and Company. When thinking about the role of vaccination to combat AMR, the no-infection counterfactual is more appropriate because
infections would be eliminated, whereas interventions based on antimicrobial stewardship might be better informed by the susceptible infection counterfactual because some resistant bacteria might be replaced by susceptible bacteria.22Browne A Chipeta M Haines-Woodhouse G et al.Global antibiotic consumption in humans, 2000 to 2018: a spatial
modelling study. S Dunachie reports financial support for the present manuscript from UL Flemming Fund at the Department of Health and Social Care, the Bill & Melinda Gates Foundation, and the Wellcome Trust; a paid membership role for the Wellcome Trust Vaccines Advisory Selection Panel Vaccines and AMR in November, 2019; and an
unpaid role as an expert adviser to WHO's Global Antimicrobial Resistance Surveillance System, from November, 2018 onwards, outside the submitted work. Out-of-sample validity estimates are provided in the appendix for our models of sepsis (pp 25–30), infectious syndrome distribution (pp 25–30), pathogen distribution (pp 43–44), prevalence of
resistance (pp 51–53), and relative risk (pp 55–56).The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.We estimated that, in 2019, 1·27 million deaths (95% uncertainty interval [UI] 0·911–1·71) were directly attributable to resistance (ie, based on the counterfactual
scenario that drug-resistant infections were instead drug susceptible) in the 88 pathogen–drug combinations evaluated in this study. We analysed data from 65 Demographic and Health Surveys and 138 Multiple Indicator Cluster Surveys using model-based geostatistics to quantify antibiotic usage in LMICs. These LMIC-specific estimates of antibiotic
usage were combined with pharmaceutical sales data from IQVIA, WHO, and the European Centre for Disease Prevention and Control (ECDC) by use of an ensemble spatiotemporal Gaussian process regression model to produce a location-year covariate on antibiotic consumption for all 204 countries and territories included in this study.22Browne A
Chipeta M Haines-Woodhouse G et al.Global antibiotic consumption in humans, 2000 to 2018: a spatial modelling study. Briefly, to estimate the burden attributable to AMR, we first calculated the deaths attributable to resistance by taking the product of deaths for each underlying cause, the proportion of these deaths in which infection played a role,
the proportion of infectious deaths attributable to each infectious syndrome, the proportion of infectious syndrome deaths attributable to each pathogen, and the mortality PAF for each resistance profile. The notion of antibiotic stewardship remains a core strategy in most national and international AMR management plans, although barriers to
implementing stewardship programmes in LMICs should be addressed., 54Rolfe Jr, R Kwobah C Muro F et al.Barriers to implementing antimicrobial stewardship programs in three low- and middle-income country tertiary care settings: findings from a multi-site qualitative study.Crossref PubMed Scopus (2) Google ScholarFifth, maintaining
investment in the development pipeline for new antibiotics—and access to second-line antibiotics in locations without widespread access—is essential. AMR is a leading cause of death around the world, with the highest burdens in low-resource settings. We acknowledge Jephté Kaleb and Giscard Wilfried Koyaweda, National Laboratory of Clinical
Biology and Public Health, Bangui, Central African Republic. 2019; 19: e392-e39819.An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000.J Antimicrob Chemother. Community-based programmes are particularly important in LMICs where the AMR burden is highest and
clean water and sanitation infrastructure is weak; sustained support for these programmes is an essential element of combating AMR.Second, preventing infections through vaccinations is paramount for reducing the need for antibiotics. To our knowledge, our study is the first to report burden both attributable to and associated with AMR for an
extensive list of pathogens and pathogen–drug combinations, with global and regional findings based on estimates for 204 countries and territories. These figures, and the appendix (pp 26–30, 43–44, 52–53, and 56, which provides out-of-sample model validation), suggest that our modelled estimates fit the data, where available.Our analysis echoes
that of another paper in highlighting critical AMR data gaps in several regions.65Oldenkamp R Schultsz C Mancini E Cappuccio A Filling the gaps in the global prevalence map of clinical antimicrobial resistance.Crossref PubMed Google Scholar There are many well described barriers to good-quality clinical bacteriology in LMICs, and proper quality
assurance and quality-control measures are crucial for quality care and accurate laboratory-based surveillance. These regressions predicted the proportion of sepsis-related deaths that were caused by a given infectious syndrome separately for each communicable, maternal, neonatal, and nutritional underlying cause of death; non-communicable
underlying cause of death; and injury underlying cause of death. P Turner acknowledges that the Cambodia Oxford Medical Research Unit is part of the Mahidol-Oxford Tropical Medicine Research Unit Tropical Health Network and is core funded by Wellcome (220211/Z/20/Z). At the global level, the difference is nearly four-times that attributable to
AMR. 2021; 0: 1-13View in Article Scopus (12) Crossref Google Scholar30.Antimicrobial resistance global report on surveillance 2014. Yellow boxes indicate that the source type was used in that estimation step. TF–PF–iNTS= typhoid fever, paratyphoid fever, and invasive non-typhoidal Salmonella spp. J Sifuentes-Osornio reports financial support
from Oxford University for the present manuscript; research grants from Oxford, CONACYT, Sanofi, and Novartis, outside of the study; consulting fees from Senosiain and speaker fees from Merck, outside of the study; and membership of the Sanofi advisory board of COVID-19 Vaccine Development, which is currently in progress, outside of the study.
We used previously described GBD methods to convert age-specific deaths into years of life lost (YLLs) using the standard counterfactual life expectancy at each age.34WHOGlobal priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. However, only one of these pathogens has been the focus of a
major global health intervention programme—S pneumoniae, primarily through pneumococcal vaccination.37WHOPneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper—February 2019. 2016; 5e18082View in Article Scopus (128) PubMed Crossref Google Scholar12.Estimating the number of infections
caused by antibiotic-resistant Escherichia coli and Klebsiella pneumoniae in 2014: a modelling study.Lancet Glob Health. We present final estimates aggregated to the global and regional level.On the basis of our predictive statistical models, there were an estimated 4·95 million (3·62–6·57) deaths associated with bacterial AMR in 2019, including 1·27
million (95% UI 0·911–1·71) deaths attributable to bacterial AMR. Given the many challenges to data collection and reporting caused by the COVID-19 pandemic,32New York Department of HealthHospital associated infection reporting persuant to Public Health Law section 2819., 33Centers for Medicare and Medicaid ServicesCOVID-19 emergency
declaration blanket waivers for health care providers. S Paratyphi=Salmonella enterica serotype Paratyphi. Our mortality envelope consisted of all deaths in which infection played a role, which included all sepsis deaths with non-infectious underlying causes, plus all deaths with an infectious underlying cause in GBD 2019 (appendix pp 21–23).In
estimation step two, we used details on the pathways of disease provided in multiple causes of death and hospital discharge data in a second stage of random effects logistic regression models to further subdivide deaths in which infection played a role into 12 major infectious syndromes and one residual category. Given the global importance of
bacterial AMR, more assessment of which policies have worked, and where, is urgently needed.Many might expect that with higher antibiotic consumption in high-resource settings, the burden of bacterial AMR would be correspondingly higher in those settings. Mono RIF=rifampicin mono-resistance. In light of data sparsity, we made several
additional methodological assumptions (appendix pp 17–60). indicator for antimicrobial resistance was only proposed in 2019, and this indicator (3.d.2) is very limited in scope.39WHOIndicator 3.d.2: percentage of bloodstream infections due to selected antimicrobial-resistant organisms., 40UNReport of the Inter-Agency and Expert Group on
Sustainable Development Goal indicators. Additionally, existing studies have generally considered only one measure of AMR burden. P Turner reports grants, consulting fees, and support for attending meetings or travel from Wellcome Trust, outside the study. M Mussi-Pinhata reports support for the present manuscript from research from grant
funding from Fondazione PENTA—Onlus and the Clinical Trial Manager Global Antibiotic R&D Partnership (GARDP). National Office for Animal Health, Middlesex2016View in Article 5.Antimicrobial resistance.View in Article 6.Antibiotic resistance threats in the United States, 2019. The only global burden estimates for AMR are from the Review on
Antimicrobial Resistance,1Tackling drug-resistant infections globally: final report and recommendations. We converted incidence into YLDs using a YLDs per incident case ratio for each infectious syndrome based on a proxy GBD cause (a simplified YLD calculation compared with the standard sequelae-based method; appendix pp 56–60). Further
limitations specific to each modelling component can be found in the appendix (pp 119–20).Despite these limitations, this study is the most comprehensive analysis of bacterial AMR burden to date, reflecting the best and widest range of available data and the use of models that have been tested and iterated over years of GBD analysis to incorporate
disparate data sources. Clinical and Laboratory Standard Institute (CLSI) guidelines were used to define minimum inhibitory concentration breakpoints when these minimums were provided. To this end, building infrastructure that allows clinicians to diagnose infection accurately and rapidly is crucial so that antimicrobial use can be narrowed or
stopped when appropriate. This study uses major methodological innovations to provide important new insights into the AMR burden. 2016; 315: 801-810View in Article Scopus (9696) PubMed Crossref Google Scholar24.Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study.Lancet.
2015; 28: 443-464View in Article Scopus (99) PubMed Crossref Google Scholar60.Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis.Lancet Planet Health. By any metric, bacterial AMR is a leading global health issue. Seven pathogen–drug combinations each caused more
than 50 000 deaths, highlighting the importance of developing policies that specifically target the deadliest pathogen–drug combinations, particularly through expansion of infection prevention and control programmes, improving access to essential second-line antibiotics where needed, and through vaccine and antibiotic development. Enhanced
infrastructure would also expand AMR research in the future to evaluate the indirect effects of AMR, such as the effect of AMR on perioperative prophylaxis or prophylaxis of infections in transplant recipients, the effects of AMR on transmission, the impact and prevalence of specific variants evaluated through genotypic epidemiology, and more.
Members of the core research team for this topic area had full access to the underlying data used to generate estimates presented in this paper. World Health Organization, Geneva2017View in Article 42.Tuberculosis missing from WHO bacteria list.Lancet Respir Med. We optimised over the space of such contingency tables to find the nearest
feasible distribution given the data, producing, for each pathogen, a set of resistance profiles: the proportions of bacteria with each combination of resistance and susceptibility among all the antibiotics analysed (appendix pp 48–49).Using data from 164 sources representing 511 870 patients with known outcome and resistance information, we
estimated the relative risk of death for each pathogen–drug combination for a resistant infection compared with that of a drug-sensitive infection using MR-BRT. The toll taken by AMR on patients and their families is largely invisible but is reflected in prolonged bacterial infections that extend hospital stays and cause needless deaths.1 Moreover,
AMR disproportionately affects poor individuals who have little access to second-line, more expensive antibiotics that could work when first-line drugs fail. For isoniazid and rifampicin co-resistant (MDR excluding XDR) M tuberculosis, isolate resistance was highest (primarily 10% to less than 30%) in eastern Europe and under 5% in many countries
around the world (figure 7B). Some evidence from the spread of meticillin-resistant S aureus and meticillin-susceptible S aureus suggests that drug-resistant infections do not simply replace drug-susceptible infections,63Mera RM Suaya JA Amrine-Madsen H et al.Increasing role of Staphylococcus aureus and community-acquired methicillin-resistant
Staphylococcus aureus infections in the United States: a 10-year trend of replacement and expansion.Crossref PubMed Scopus (79) Google Scholar, but this finding might not generalise to all other pathogens and other mechanisms of resistance.Both measures are informative in different ways. 2001; 29: 1303-1310View in Article Scopus (6413)
PubMed Crossref Google Scholar27.The epidemiology of sepsis in the United States from 1979 through 2000.N Engl J Med. Efforts to build laboratory infrastructure are paramount to addressing the large and universal burden of AMR, by improving the management of individual patients and the quality of data in local and global AMR surveillance and
bolstering national AMR plans of action. We would like to acknowledge Tomislav Mestrovic for his significant contributions to this manuscript and the overall research enterprise. 2021; () 21)00280-1View in Article 23.The third international consensus definitions for sepsis and septic shock (sepsis-3).JAMA. We acknowledge scientific contributions to
this work from the Pan American Health Organization. For these same 11 pathogen–drug combinations, we estimated 23 100 deaths (95% UI 14 600–34 600) and 393 000 DALYs (246 000–595 000) attributable to bacterial AMR for western and central Europe combined. Our approach can be divided into ten estimation steps that occur within five broad
modelling components (a flowchart of the estimation steps is given in the appendix p 123). It would provide a more thorough account of the threat of AMR and improve the accuracy of our estimates for the combinations reported here that share a high degree of co-resistance with combinations not yet analysed.This study has several limitations, the
most important being the sparsity of data from many LMICs on the distribution of pathogens by infectious syndrome, the prevalence of resistance for key pathogen–drug combinations, and the number of deaths involving infection; and the severe scarcity of data linking laboratory results to outcomes such as death. Briefing note for EU/EEA countries.
Although antibiotic stewardship is a foundational aspect for preventing the spread of AMR, limiting access to antibiotics is not a suitable response to AMR in all settings. In future iterations of the project, we hope to improve on the identification of community-acquired and hospital-acquired infections.Additionally, no universal laboratory standard
exists to demarcate resistance versus susceptibility, and we often had to defer to laboratory interpretation to classify the isolates in our data, resulting in heterogeneous classification. From these findings, we extracted study type, pathogen–drug combinations, counterfactuals, locations, methods, outcomes, and population. 2020; 396: 1204-
122215.Measuring and mapping the global burden of antimicrobial resistance.BMC Med. At the regional level, we estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27·3 deaths per 100 000 (20·9–35·3), and lowest in Australasia, at 6·5 deaths (4·3–9·4) per 100 000. The six leading pathogens for
deaths associated with resistance (Escherichia coli, followed by Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa) were responsible for 929 000 (660 000–1 270 000) deaths attributable to AMR and 3·57 million (2·62–4·78) deaths associated with AMR in 2019. For
estimation step three, we took data that linked pathogen-specific disease incidence to deaths to develop models for pathogen-specific CFRs that varied by age, location, and syndrome. We used a two-stage nested mixed effects meta-regression model to estimate relative risk of death for each pathogen–drug combination that was adjusted for age,
admission diagnosis, hospital-acquired versus community-acquired infection, and site of infection (appendix pp 54–56). High bacterial AMR burdens are a function of both the prevalence of resistance and the underlying frequency of critical infections such as lower respiratory infections, bloodstream infections, and intra-abdominal infections, which
are higher in these regions. There are serious data gaps in many low-income settings, emphasising the need to expand microbiology laboratory capacity and data collection systems to improve our understanding of this important human health threat.Bill & Melinda Gates Foundation, Wellcome Trust, and Department of Health and Social Care using
UK aid funding managed by the Fleming Fund.Research in contextEvidence before this studyTo identify previous estimates of antimicrobial resistance (AMR) burden before this study, we did a systematic review and consulted with content experts. Bacterial AMR is a problem in all regions; we estimated that, in 2019, the highest rates of AMR burden
were in sub-Saharan Africa. We produced estimates for four of those pathogens—tuberculosis, S aureus, E coli, and K pneumoniae—and estimated 670 000 deaths attributable to resistance to those pathogens in 2019.Cassini and colleagues produced an estimate for the EU of 16 pathogen–antibiotic combinations in 2015. 2020; 396: 1223-
124932.Hospital associated infection reporting persuant to Public Health Law section 2819.View in Article 33.COVID-19 emergency declaration blanket waivers for health care providers. Cassini and colleagues used a mix of both counterfactuals to inform their estimates, so it is expected that their EU estimate is somewhat higher than ours for the
susceptible counterfactual. Other vaccines, such as the influenza or rotavirus vaccines, also play a role in preventing febrile illness, which can lead to a reduction in antibiotic prescribing and can reduce AMR emergence even for pathogens without vaccines.Third, reducing exposure to antibiotics unrelated to treating human disease is an important
potential way to reduce risk. Extensive literature exists estimating the effects of AMR on incidence, deaths, hospital length of stay, and health-care costs for select pathogen–drug combinations in specific locations,1Tackling drug-resistant infections globally: final report and recommendations., 2Antimicrobial resistance: tackling a crisis for the health
and wealth of nations., 6US Centers for Disease Control and PreventionAntibiotic resistance threats in the United States, 2019., , , , but, to our knowledge, no comprehensive estimates covering all locations and a broad range of pathogens and pathogen–drug combinations have ever been published. which did not provide death estimates by
pathogen–drug combination, making direct comparison challenging. C Carvalheiro reports financial support for the present manuscript from the Global Antibiotic Research and Development Partnership, who provided payments to Fundação de Apoio ao Ensino, Pesquisa e Assistência of the Clinical Hospital of the Faculty of Medicine of Ribeirão Preto,
University of São Paulo, Brazil. YLDs=years lived with disability. WHO has explained that the absence of MDR tuberculosis from its priority list is because it has already been established globally as a top priority for innovative treatments, but this exclusion remains a source of considerable debate., 43The WHO made a big mistake on tuberculosis.
Additional details on our estimation method for prevalence of resistance are available in the appendix (pp 44–53).To account for multidrug resistance, we used line-level microbiology data that tested multiple antibiotics for the same isolate to produce Pearson correlation coefficients of the co-occurrence of resistance to different antibiotics. 2018; 18:
e248-e25867.Understanding and addressing CLSI breakpoint revisions: a primer for clinical laboratories.J Clin Microbiol. XDR=extensive drug resistance.In the appendix, we present the equivalent AMR findings for DALYs instead of deaths (pp 124–29), as well as the burden attributable to and associated with specific pathogen–drug combinations by
age group (neonatal, post-neonatal, age 1–4 years, and age 5 years or older) and super-region (pp 106–18).Among the seven leading pathogen–drug combinations for deaths attributable to resistance, the proportion of isolates estimated to be resistant varied substantially by country and territory (figure 7A–G). We acknowledge Jennifer R Verani and
team, CDC, Nairobi, Kenya; Allan Audi and team, Centre for Global Health Research, KEMRI, Kisumu, Kenya. P Newton reports support for the present manuscript from research grant funding from the Wellcome Trust. 2018; 16: 78View in Article Scopus (67) PubMed Crossref Google Scholar16.GBD 2010: design, definitions, and metrics.Lancet. Data
on length of stay were available from 59 sources representing 455 906 admissions. In the next tier of pathogen–drug combinations, ten combinations each caused between 25 000 and 50 000 deaths attributable to AMR. Five regions had all-age death rates associated with bacterial AMR higher than 75 per 100 000: all four regions of sub-Saharan Africa
and south Asia. We describe data inputs for each of ten estimation steps in greater detail in the following subsections and in the appendix (pp 17–18, 31, 34–35, 44, 54). First, the principles of infection prevention and control remain a foundation for preventing infections broadly and a cornerstone in combating the spread of AMR.44Organisation for
Economic Co-operation and DevelopmentEuropean Centre for Disease Prevention and ControlAntimicrobial resistance: tackling the burden in the European Union. Additionally, meticillin-resistant S aureus—the leading pathogen–drug combination in our analysis for attributable deaths in 2019—is listed as “high” but not “critical”
priority.34WHOGlobal priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. World Health Organization, Geneva2019View in Article 38.SDG Indicators—global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development.View in Article
39.Indicator 3.d.2: percentage of bloodstream infections due to selected antimicrobial-resistant organisms. We found, however, that the highest rates of death were in sub-Saharan Africa and south Asia. STAT. OECD Publications, Paris2019View in Article 45.The role of vaccines in preventing bacterial antimicrobial resistance.Nat Med. UTI=urinary
tract infections and pyelonephritis.In 2019, six pathogens were each responsible for more than 250 000 deaths associated with AMR (figure 4): E coli, Staphylococcus aureus, K pneumoniae, S pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa, by order of number of deaths. Although these forecasts have been criticised by some,,
4National Office for Animal HealthNOAH response to final O'Neill AMR review report July 2016. All study-level covariates for models, such as age and sex, were extracted from empirical data. the inappropriate use of antibiotics driven by insufficient regulations and ease of acquisition, inadequate access to second-line and third-line antibiotics,
counterfeit or substandard antibiotics that can drive resistance,, , and poor sanitation and hygiene., 61Ramay BM Caudell MA Cordón-Rosales C et al.Antibiotic use and hygiene interact to influence the distribution of antimicrobial-resistant bacteria in low-income communities in Guatemala.Crossref PubMed Scopus (9) Google Scholar, The higher
burden in low-resource health systems highlights the importance—both for the management of individual patients and for the surveillance of AMR—of well developed national action plans and laboratory infrastructure in all regions and countries. A Haselbeck reports support for the present manuscript from the Bill & Melinda Gates Foundation
(OPP1205877). We would like to acknowledge the scientific contributions made from the GRAM advisory committee, specifically Neil Ferguson and Sharon Peacock. We used the Bayesian meta-regression tool MR-BRT to estimate CFRs as a function of the Healthcare Access and Quality Index and various bias covariates (appendix pp 31–34). 2018; 24:
10-19View in Article Scopus (128) PubMed Crossref Google Scholar46.Impact of existing vaccines in reducing antibiotic resistance: primary and secondary effects.Proc Natl Acad Sci USA. 2003; 348: 1546-1554View in Article Scopus (4670) PubMed Crossref Google Scholar28.Incidence and trends of sepsis in US hospitals using clinical vs claims data,
2009–2014.JAMA. For resistance profiles that had resistance to more than one antibiotic class, we redistributed burden to the individual antibiotic classes proportionally on the basis of excess risk, providing a mutually exclusive burden for each pathogen–drug combination (appendix pp 56–60). Our approach can be divided into five broad components:
number of deaths where infection played a role, proportion of infectious deaths attributable to a given infectious syndrome, proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antibiotic of interest, and the excess risk of death or duration of an infection associated with this
resistance. The PAF represents the proportional reduction in deaths or years lived with disability (YLDs) that would occur if all infections with the resistance profile of interest were instead susceptible to all antibiotics included in the analysis. Review on Antimicrobial Resistance, London2014View in Article 3.Will 10 million people die a year due to
antimicrobial resistance by 2050?.PLoS Med. For instance, the US Centers for Disease Control and Prevention (CDC) published a 2019 report on AMR infections and deaths in the USA for 18 AMR threats using surveillance data,6US Centers for Disease Control and PreventionAntibiotic resistance threats in the United States, 2019. Additionally, our
analysis showed that AMR all-age death rates were highest in some LMICs, making AMR not only a major health problem globally but a particularly serious problem for some of the poorest countries in the world.All six of the leading pathogens contributing to the burden of AMR in 2019 (E coli, S aureus, K pneumoniae, S pneumoniae, A baumannii,
and P aeruginosa) have been identified as priority pathogens by WHO34WHOGlobal priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. The Review on Antimicrobial Resistance, published in 2016, estimated that as many as 10 million people could die annually from AMR by 2050. 2018; 391:
2236-227122.Global antibiotic consumption in humans, 2000 to 2018: a spatial modelling study.Lancet Planet Health. Six more pathogen–drug combinations each caused between 50 000 and 100 000 resistance-attributable deaths in 2019: MDR excluding XDR tuberculosis, third-generation cephalosporin-resistant E coli, carbapenem-resistant A
baumannii, fluoroquinolone-resistant E coli, carbapenem-resistant K pneumoniae, and third-generation cephalosporin-resistant K pneumoniae (figure 6). The pattern of AMR varies geographically, with different pathogens and pathogen–drug combinations dominating in different locations. The methods used to estimate infectious underlying causes of
death and sepsis deaths have been published previously, and are summarised in the appendix (pp 17–18).In estimation step one, we used data for multiple causes of death covering 121 million deaths, 5·54 million hospital discharges with discharge status of death, and 264 000 records of multiple causes of death linked to hospital records from ten
countries and territories, as well as 870 deaths from Child Health and Mortality Prevention Surveillance (CHAMPS) sites across six countries (appendix pp 17–18), to develop random effects logistic regression models to predict the fraction of sepsis occurring in each communicable, maternal, neonatal, and nutritional underlying cause of death; non-
communicable underlying cause of death; and injury underlying cause of death. The Review on Antimicrobial Resistance, commissioned by the UK Government, argued that AMR could kill 10 million people per year by 2050.1Tackling drug-resistant infections globally: final report and recommendations., 2Antimicrobial resistance: tackling a crisis for
the health and wealth of nations. Selection bias in how samples get incorporated into surveillance systems; scarcity of laboratory facilities to test for AMR and other challenges in identifying AMR; insufficient data linking prevalence of resistance to infectious syndrome, underlying cause, and outcome; barriers to sharing data that have been collected;
and other data-linking and data optimisation issues continue to complicate the assessment and interpretation of the results in many cases.A second limitation of our study was the several potential sources of bias we noted when combining and standardising data from a wide variety of providers. Finally, this study is the first to quantify the burden of
AMR using two different AMR counterfactual scenarios.Implications of all the available evidenceOur estimates indicate that bacterial AMR is a health problem whose magnitude is at least as large as major diseases such as HIV and malaria, and potentially much larger. 19 of 204 countries and territories had no data available for any of our modelling
components. One pathogen–drug combination, meticillin-resistant S aureus, caused more than 100 000 deaths attributable to AMR in 2019, while six more each caused 50 000–100 000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant E coli, carbapenem-resistant A baumannii,
fluoroquinolone-resistant E coli, carbapenem-resistant K pneumoniae, and third-generation cephalosporin-resistant K pneumoniae.To our knowledge, this study provides the first comprehensive assessment of the global burden of AMR, as well as an evaluation of the availability of data. United Nations Economic and Social Council, New York,
NY2020View in Article 41.The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Skin=bacterial infections of the skin and subcutaneous systems. Lower respiratory infections accounted for
more than 1·5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. Recent estimates of the burden of drug-resistant infections covering several pathogens have also been published for the USA, Thailand, the EU and European Economic Area, and several other locations, as well as estimates for
several pathogen–drug combinations for a wider range of locations. Another substantial assumption we made due to insufficient linked data was that the relative risk of death or length of stay for infection from an MDR organism was assumed to be equal to the highest individual relative risk among the drugs assessed. To account for bias in resistance
data provided by tertiary care facilities, we adjusted tertiary rates of resistance by crosswalking them to data from non-tertiary and mixed facilities using MR-BRT as described in the appendix (pp 45–48).We used a two-stage spatiotemporal modelling framework to estimate the prevalence of resistance in each pathogen–drug combination by location
for 2018. Although many factors were considered in producing the WHO priority list, these new estimates of the global burden of specific pathogen–drug combinations can inform future work on WHO priority pathogen–drug combinations.Intervention strategies for addressing the challenge of bacterial AMR fall into five main categories. Anti-
pseudomonal=anti-pseudomonal penicillin or beta-lactamase inhibitors. Full-Text PDF Bloodstream infections, bone and joint infections, and intra-abdominal infections are not estimated in GBD, so for these infectious syndromes, we exclusively used the number of incident cases of each infectious syndrome that co-occurred with underlying NCDs,
MNNDs, and injuries to estimate incidence (appendix pp 56–60).To estimate the pathogen distribution of each infectious syndrome separately for deaths and incident cases for each age, sex, and location, we made use of multiple data sources. World Health Organization, Geneva2020View in Article 40.Report of the Inter-Agency and Expert Group on

Sustainable Development Goal indicators. Four of these ten combinations included fluoroquinolone resistance, three included carbapenem resistance, and two had trimethoprim-sulfamethoxazole resistance.Figure 6Global deaths (counts) attributable to bacterial antimicrobial resistance by pathogen–drug combination, 2019Show full captionFor this figure, only deaths attributable to resistance, not deaths associated with resistance, are shown due to the very high levels of correlation for resistance patterns between some drugs. United Nations, 2017View in Article 36.Global Leaders Group on antimicrobial resistance.View in Article 37.Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper—February 2019. Furthermore, the first Sustainable Development Goal38UNSDG Indicators—global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development. Cardiac=endocarditis and other cardiac infections. For the 11 pathogen–drug combinations that overlap, Cassini and colleagues estimated approximately 30 000 deaths and 796 000 DALYs caused by resistance in the EU in 2015. 2021; () in Article Scopus (3) PubMed Crossref Google Scholar14.Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.Lancet. These include both hospital-based infection prevention and control programmes focused on preventing health-care-acquired infections, and community-based programmes focused on water, sanitation, and hygiene. All other authors declare no competing interests.AcknowledgmentsFunding was provided by the Bill & Melinda Gates Foundation (OPP1176062), the Wellcome Trust (A126042), and the UK Department of Health and Social Care using UK aid funding managed by the Fleming Fund (R52354 CN001). S Typhi=S enterica serotype Typhi. The diverse data sought included the following sources: pharmaceutical companies that run surveillance networks, diagnostic laboratories, and clinical trial data; high-quality data from researchers including large multisite research collaborations, smaller studies, clinical trials, and well established research institutes based in low-income and middle-income countries (LMICs); data from public and private hospitals and public health institutes providing diagnostic testing; global surveillance networks; enhanced surveillance systems; national surveillance systems; and surveillance systems for specific organisms such as Mycobacterium tuberculosis and Neisseria gonorrhoeae (all sources are listed by data type in the appendix pp 8–15).Figure 1 shows a summary of the distinct data types gathered and for which estimation step each data type was used. XDR=extensively drug resistant.The global burden associated with drug-resistant infections assessed across 88 pathogen–drug combinations in 2019 was an estimated 4·95 million (95% UI 3·62–6·57) deaths, of which 1·27 million (0·911–1·71) deaths were directly attributable to drug resistance. XDR=extensively drug resistant.Figure 7Raw data and modelled estimates for the percentage of pathogen isolates that are resistant by country and territory, 2019Show full captionMeticillin-resistant Staphylococcus aureus (A), isoniazid and rifampicin co-resistant (excluding XDR) Mycobacterium tuberculosis (B), third-generation cephalosporin-resistant Escherichia coli (C), carbapenem-resistant Acinetobacter baumannii (D), fluoroquinolone-resistant E coli (E), carbapenem-resistant Klebsiella pneumoniae (F), and third-generation cephalosporin-resistant K pneumoniae (G). Increased use of antibiotics in farming has been identified as a potential contributor to AMR in humans,2Antimicrobial resistance: tackling a crisis for the health and wealth of nations., , , although the direct causal link remains controversial., Fourth, minimising the use of antibiotics when they are not necessary to improve human health—such as treating viral infections—should be prioritised. At first glance, this finding seems to contrast with other estimates such as those from Cassini and colleagues or the CDC, who have estimated the burden of carbapenem-resistant A baumannii to be substantially lower than that of third-generation cephalosporin-resistant E coli.6US Centers for Disease Control and PreventionAntibiotic resistance threats in the United States, 2019., When assessed by super-region, however, our results are much more consistent with the published literature: similar to the CDC and ECDC, we found the burden of third-generation cephalosporin-resistant E coli to exceed that of carbapenem-resistant A baumannii in high-income settings, whereas the inverse pattern was found in south Asia, where a higher relative burden of carbapenem-resistant A baumannii than that in high-income regions has been documented. Does not include gonorrhoea and chlamydia because we did not estimate the fatal burden of this infectious syndrome. M Khorana and S Boonkasidecha would like to acknowledge GARDP. Bone+=infections of bones, joints, and related organs. C Lim was supported by the Wellcome Trust Training Fellowship between September, 2017 and March 2020 (206736/Z/17/Z), outside the submitted work. We also received various data from tertiary care facilities; although we adjusted for bias in the prevalence of resistance data collected from these sources, much of our data came from mixed-classification or unclassifiable facilities, so it is possible that we did not fully adjust for all potential tertiary bias. Table 2 provides estimates of deaths, YLLs, and DALYs from AMR for each counterfactual.Table 2Deaths, YLLs, YLDs, and DALYs (in counts and all-age rates) associated with and attributable to bacterial antimicrobial resistance, globally and by GBD super-region, 2019DALYs=disability-adjusted life-years. and several others. 2019; 57: e00203-e00219View in Article Scopus (54) PubMed Crossref Google ScholarPublished: January 19, 2022DOI: 21)02724-0© 2021 The Author(s). 2018; 2: e398-e40561.Antibiotic use and hygiene interact to influence the distribution of antimicrobial-resistant bacteria in low-income communities in Guatemala.Sci Rep. A Peleg acknowledges the support from an Australian National Health and Medical Research Council Practitioner Fellowship. Creative Commons Attribution (CC BY 4.0) | Access this article on ScienceDirect The overlooked pandemic of antimicrobial resistanceAs COVID-19 rages on, the pandemic of antimicrobial resistance (AMR) continues in the shadows. 2019; 19: 56-6611.Epidemiology and burden of multidrug-resistant bacterial infection in a developing country.eLife. YLLs=years of life lost.We estimated that among the 21 GBD regions, Australasia had the lowest AMR burden in 2019, with 6·5 deaths per 100 000 (95% UI 4·3–9·4) attributable to AMR and 28·0 deaths per 100 000 (18·8–39·9) associated with AMR in 2019 (figure 2). Identifying strategies that can work to reduce the burden of bacterial AMR—either across a wide range of settings or those that are specifically tailored to the resources available and leading pathogen–drug combinations in a particular setting—is an urgent priority.Antimicrobial Resistance CollaboratorsChristopher J L Murray, Kevin Shunji Ikuta, Fablina Sharara, Lucien Swetschinski, Gisela Robles Aguilar, Authia Gray, Chieh Han, Catherine Bisignano, Puja Rao, Eve Wool, Sarah C Johnson, Annie J Browne, Michael Give Chipeta, Frederick Fell, Sean Hackett, Georgina Haines-Woodhouse, Bahar H Kashef Hamadani, Emmanuelle A P Kumaran, Barney McManigal, Ramesh Agarwal, Samuel Akech, Samuel Albertson, John Amuasi, Jason Andrews, Aleskandr Aravkin, Elizabeth Ashley, Freddie Bailey, Stephen Baker, Buddha Basnyat, Adrie Bekker, Rose Bender, Adhisivam Bethou, Julia Bielicki, Suppawat Boonkasidecha, James Bukosia, Cristina Carvalheiro, Carlos Castañeda-Orjuela, Vilada Chansamouth, Suman Chaurasia, Sara Chiurchiù, Fazle Chowdhury, Aislinn J Cook, Ben Cooper, Tim R Cressey, Elia Criollo-Mora, Matthew Cunningham, Saffiatou Darboe, Nicholas P J Day, Maia De Luca, Klara Dokova, Angela Dramowski, Susanna J Dunachie, Tim Eckmanns, Daniel Eibach, Amir Emami, Nicholas Feasey, Natasha Fisher-Pearson, Karen Forrest, Denise Garrett, Petra Gastmeier, Ababi Zergaw Giref, Rachel Claire Greer, Vikas Gupta, Sebastian Haller, Andrea Haselbeck, Simon I Hay, Marianne Holm, Susan Hopkins, Kenneth C Iregbu, Jan Jacobs, Daniel Jarovsky, Fatemeh Javanmardi, Meera Khorana, Niranjan Kissoon, Elsa Kobeissi, Tomislav Kostyanev, Fiorella Krapp, Ralf Krumkamp, Ajay Kumar, Hmwe H Kyu, Cherry Lim, Direk Limmathurotsakul, Michael James Loftus, Miles Lunn, Jianing Ma, Neema Mturi, Tatiana Munera-Huertas, Patrick Musicha, Marisa Marcia Mussi-Pinhata, Tomoka Nakamura, Ruchi Nanavati, Sushma Nangia, Paul Newton, Chanpheaktra Ngoun, Amanda Novotney, Davis Nwakanma, Christina W Obiero, Antonio Olivas-Martinez, Piero Olliaro, Ednah Ooko, Edgar Ortiz-Brizuela, Anton Yariv Peleg, Carlo Perrone, Nishad Plakkal, Alfredo Ponce-de-Leon, Mathieu Raad, Tanusha Ramdin, Amy Riddell, Tamalee Roberts, Julie Victoria Robotham, Anna Roca, Kristina E Rudd, Neal Russell, Jesse Schnall, John Anthony Gerard Scott, Madhusudhan Shivamallappa, Jose Sifuentes-Osornio, Nicolas Steenkeste, Andrew James Stewardson, Temenuga Stoeva, Nidanuch Tasak, Areerat Thaiprakong, Guy Thwaites, Claudia Turner, Paul Turner, H Rogier van Doorn, Sithembiso Velaphi, Avina Vongpradith, Huong Vu, Timothy Walsh, Seymour Waner, Tri Wangrangsimakul, Teresa Wozniak, Peng Zheng, Benn Sartorius, Alan D Lopez, Andy Stergachis, Catrin Moore*, Christiane Dolecek*, Mohsen Naghavi.*Contributed equally.AffiliationsInstitute for Health Metrics and Evaluation (Prof C J L Murray DPhil, K S Ikuta MD, F Sharara MS, L Swetschinski MSc, A Gray BS, C Han BA, C Bisignano MPH, P Rao MPH, E Wool MPH, S C Johnson MSc, S Albertson BS, A Aravkin PhD, R Bender BS, M Cunningham MSc, Prof S I Hay FMedSci, H H Kyu PhD, J Ma MS, A Novotney MPH, A Vongpradith BA, P Zheng PhD, A Stergachis PhD), Department of Health Metrics Sciences, School of Medicine (Prof C J L Murray, A Aravkin, Prof S I Hay, B Sartorius PhD, Prof M Naghavi PhD), Department of Applied Mathematics (A Aravkin), Department of Global Health (A Stergachis, Prof M Naghavi), Department of Pharmacy, School of Pharmacy (A Stergachis), University of Washington, Seattle, WA, USA; Department of Infectious Diseases (K S Ikuta), Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA; Department of Infectious Diseases (K S Ikuta), University of California, Los Angeles, Los Angeles, CA, USA; Nuffield Department of Medicine, Big Data Institute (F Bailey MBChB, A Browne MPH, M Chipeta PhD, F Fell MSc, N Fisher-Pearson BA, S Hackett PhD, G Haines-Woodhouse MRes, E Kobeissi MPH, E Kumaran MSc, M Lunn BSc, B McManigal PhD, C E Moore DPhil, P Olliaro PhD, G Robles Aguilar DPhil), Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health (E Ashley FRCPath, V Chansamouth MSc, B Cooper PhD, Prof C Dolecek FRCP, S Dunachie PhD, B Kashef Hamadani MPH, C Lim MSc, Prof D Limmathurotsakul PhD, P Newton FRCP, C Perrone MD, G Thwaites FMedSci, P Turner FRCPath, B Sartorius PhD, N Day DM, R Greer MRCGP, H van Doorn PhD, T Wangrangsimakul FRCPath), Ineos Oxford Institute of Antimicrobial Research (Prof T Walsh DSc), University of Oxford, Oxford, UK; Department of Pediatrics (R Agarwal DM), All India Institute of Medical Sciences, New Delhi, India; Health Services Research Unit (S Akech PhD), Nairobi Programme (J Bukosia MSc), Kenya Medical Research Institute (KEMRI)—Wellcome Trust Research Programme, Nairobi, Kenya; Department of Global Health (J Amuasi PhD), Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; Global Health and Infectious Diseases (J Amuasi), Kumasi Centre for Collaborative Research in Tropical Medicine, Kumasi, Ghana; Department of Medicine (J Andrews MD), Stanford University, Stanford, CA, USA; Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (E Ashley, V Chansamouth, P Newton, T Roberts PhD), Mahosot Hospital, Vientiane, Laos; Department of Medicine (S Baker PhD), University of Cambridge, Cambridge, UK; Oxford University Clinical Research Unit-Nepal (B Basnyat FRCPE), Oxford University, Kathmandu, Nepal; Department of Paediatrics and Child Health (A Bekker PhD, A Dramowski PhD), Stellenbosch University, Cape Town, South Africa; Department of Neonatology (A Bethou PhD, N Plakkal MD), Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India; Paediatric Infectious Disease Department (J Bielicki PhD), University of Basel Children's Hospital, Basel, Switzerland; Paediatric Infectious Diseases Research Group (J Bielicki, A J Cook MSc, A Riddell PhD, N Russell MBBS), Institute for Infection and Immunity (T Munera-Huertas PhD), St George's University of London, London, UK; Department of Pediatrics (S Boonkasidecha MD, M Khorana MD), Queen Sirikit National Institute of Child Health, Bangkok, Thailand; Department of Pediatrics (C Carvalheiro PhD), University of Sao Paulo, Ribeirao Preto, Brazil; Colombian National Health Observatory (C Castañeda-Orjuela MD), Instituto Nacional de Salud, Bogota, Colombia; Epidemiology and Public Health Evaluation Group (C Castañeda-Orjuela), Universidad Nacional de Colombia, Bogota, Colombia; Department of Neonatology (S Chaurasia PhD), All India Institute of Medical Sciences, Rishikesh, India; Immunology and Infectious Disease Unit Academic Department of Pediatrics (S Chiurchiù MD), Academic Hospital Pediatric Department (M De Luca MD), Bambino Gesù Children's Hospital, Rome, Italy; Internal Medicine (F Chowdhury PhD), Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Mahidol-Oxford Tropical Medicine Research Unit (F Chowdhury, Prof C Dolecek), Faculty of Tropical Medicine (N P J Day, C Perrone), Mahidol University, Bangkok, Thailand; Nuffield Department of Medicine (B Cooper PhD), University of Oxford, Oxford, UK; PHPT-AMS Research Unit (T R Cressey PhD), Chiang Mai University, Chiang Mai, Thailand; Department of Molecular & Clinical Pharmacology (T R Cressey), University of Liverpool, Liverpool, UK; Department of Pharmacy (E Criollo-Mora BSc), Department of Medicine (A Olivas-Martinez MD, E Ortiz-Brizuela MSc), Department of Infectious Diseases (A Ponce-de-Leon MD), Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; Disease Control and Elimination Department (S Darboe MSc, A Roca PhD), Clinical Services Department (K Forrest FRCP), Laboratory Services Department (D Nwakanma PhD), Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Banjul, The Gambia; Department of Social Medicine and Health Care Organization (K Dokova PhD), Department of Microbiology and Virology (T Stoeva PhD), Medical University of Varna, Varna, Bulgaria; Infectious Disease Epidemiology (T Eckmanns PhD, S Haller MPH), Robert Koch Institute, Berlin, Germany; Infectious Disease Epidemiology (D Eibach MD, R Krumkamp DrPH), Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; Microbiology Department (A Emami PhD), Shiraz University of Medical Sciences, Shiraz, Iran; Clinical Sciences (N Feasey PhD), Liverpool School of Tropical Medicine, Liverpool, UK; Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi (N Feasey); Applied Epidemiology Programs (D Garrett MD), Sabin Vaccine Institute, Washington, DC, USA; Institute of Hygiene (Prof P Gastmeier MD), Charité University Medicine Berlin, Berlin, Germany; Department of Health Policy and Management (A Z Giref PhD), Addis Ababa University, Addis Ababa, Ethiopia; National Data Management Center (A Z Giref), Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Chiangrai Clinical Research Unit (R C Greer, T Wangrangsimakul), Department of Microbiology (S Dunachie, C Lim, Prof D Limmathurotsakul, N Tasak BNS, A Thaiprakong BS), Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand; MMS Medical Affairs (V Gupta PharmD), Becton, Dickinson and Company, Franklin Lakes, NJ, USA; Epidemiology & Public Health Research Department (A Haselbeck Dr rer medic, M Holm PhD), International Vaccine Institute, Seoul, South Korea; National Infection Service (S Hopkins FRCP), Antimicrobial Resistance Division (J V Robotham PhD), Public Health England, London, UK; Department of Medical Microbiology (K C Iregbu MD), National Hospital, Abuja, Nigeria; Department of Medical Microbiology (K C Iregbu), University of Abuja, Abuja, Nigeria; Department of Clinical Sciences (Prof J Jacobs PhD), Institute of Tropical Medicine, Antwerp, Belgium; Department of Microbiology, Immunology, and Transplantation (Prof J Jacobs), KU Leuven, Leuven, Belgium; Pediatric Infectious Disease Department (D Jarovsky MD), Santa Casa de São Paulo, São Paulo, Brazil; Microbiology Department (F Javanmardi PhDc), Shiraz University of Medical sciences, Shiraz, Iran; Department of Pediatrics (N Kissoon MBBS), University of British Columbia, Vancouver, BC, Canada; Laboratory of Medical Microbiology (T Kostyanev MD), University of Antwerp, Antwerp, Belgium; Instituto de Medicina Tropical Alexander von Humboldt (F Krapp MSc), Universidad Peruana Cayetano Heredia, Lima, Peru; Department of Neonatology (A Kumar MD, S Nangia MD), Lady Hardinge Medical College & Kalawati Saran's Children's Hospital, New Delhi, India; Department of Infectious Diseases (M J Loftus MBBS, A Y Peleg PhD, A J Stewardson PhD), Monash University, Melbourne, VIC, Australia; Clinical Research Department (N Mturi MRCPCH, C W Obiero MPH), KEMRI—Wellcome Trust Research Programme, Kilifi, Kenya (E Ooko PhD); Parasites and Microbes Programme (P Musicha PhD), Wellcome Sanger Institute, Cambridge, UK; Department of Pediatrics (M M Mussi-Pinhata MD), University of São Paulo, Ribeirão Preto, Brazil; Department of Immunization, Vaccines, and Biologicals (T Nakamura MSPH), World Health Organization, Geneva, Switzerland; Department of Infectious Disease Epidemiology (T Nakamura), London School of Hygiene and Tropical Medicine, London, UK; Department of Neonatology (R Nanavati MD), Seth GSMC & KEM Hospital, Mumbai, India; Medical Department (C Ngoun MD), Executive Office (C Turner FRCPCH), Cambodia Oxford Medical Research Unit (P Turner), Angkor Hospital for Children, Siem Reap, Cambodia; Department of Global Health (C W Obiero), University of Amsterdam, Amsterdam, Netherlands; Infectious Disease Department (A Y Peleg, A J Stewardson), The Alfred Hospital, Melbourne, VIC, Australia; Department of Medicine (A Ponce-de-Leon), Universidad Panamericana, Mexico City, Mexico; International Operations Department (M Raad MD), International Operations Direction (N Steenkeste PhD), Fondation Mérieux, Lyon, France; Department of Paediatric and Child Health (T Ramdin MBBCh), The Alfred Hospital, Melbourne, VIC, Australia; Department of Medicine (A Ponce-de-Leon), Universidad Panamericana, Mexico City, Mexico; International Operations Department (M Raad MD), International Operations Direction (N Steenkeste PhD), Fondation Mérieux, Lyon, France; Department of Paediatric and Child Health (T Ramdin MBBCh), University of Witwatersrand, Parktown, South Africa; Department of Critical Care Medicine (K E Rudd MD), University of Pittsburgh, Pittsburgh, PA, USA; Doctors in Training (J Schnall MBBS), Austin Health, Heidelberg, VIC, Australia; Department of Infectious Disease Epidemiology (Prof J A G Scott FMedSci), London School of Hygiene & Tropical Medicine, London, UK; Department of Epidemiology & Demography (Prof J A G Scott), KEMRI—Wellcome Trust Research Programme, Kilifi, Kenya; Department of Neonatology (M Shivamallappa DM), King Edward Memorial Hospital Mumbai, Mumbai, India; Department of Medicine (J Sifuentes-Osornio MD), Instituto Nactional de Ciencias Medicas, Mexico City, Mexico; Microbiology Laboratory (T Stoeva), Varna University Hospital, Varna, Bulgaria; Oxford University Clinical Research Unit Viet Nam (G Thwaites, H Vu PhD), University of Oxford, Ho Chi Minh City, Vietnam; Cambodia Oxford Medical Research Unit, Siem Reap, Cambodia (C Turner); Oxford University Clinical Research Unit, Hanoi, Vietnam (H R van Doorn); School of Clinical Medicine, Faculty of Health Sciences (S Velaphi PhD), University of the Witwatersrand, Johannesburg, South Africa; Department of Paediatrics (S Velaphi), Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; Department of Microbiology (S Waner MMed), Lancet Laboratories, Johannesburg, South Africa; Department of Global Tropical Health (T Wozniak PhD), Menzies School of Health Research, Brisbane, QLD, Australia.ContributorsDetailed information about individual author contributions to the research are available in the appendix (pp 65–66). Resistance to 1+=resistance to one or more drug. Antimicrobial resistance (AMR) poses a major threat to human health around the world. To calculate attributable YLDs, we took the product of the infectious syndrome incidence, the proportion of infectious syndrome incident cases attributable to each pathogen, YLDs per incident case, and the non-fatal PAF. AMR=antimicrobial resistance. Our global burden was strongly influenced by this higher relative burden of carbapenem-resistant A baumannii in south Asia and other LMICs.Our estimate for the burden of resistance is confined to the 88 pathogen–drug combinations we analysed. This might underestimate the AMR burden for LMICs, since the relative risk might be higher in locations where fewer second-line and third-line antibiotics are available. 2011; 11: 692-70158.Antibiotic resistance—the need for global solutions.Lancet Infect Dis. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. 2016; 387: 176-18753.Antibiotic stewardship in low- and middle-income countries: the same but different?.Clin Microbiol Infect. A diverse set of pathogens are involved, and resistance is high for multiple classes of essential agents, including beta-lactams and fluoroquinolones. 2016; 363fnw210View in Article Scopus (27) PubMed Crossref Google Scholar50.Comparative analysis of ESBL-positive Escherichia coli isolates from animals and humans from the UK, the Netherlands and Germany.PLoS One. J Bielicki reports grants from the European and Developing Countries Clinical Trials Partnership, Horizon 2020, and Swiss National Science Foundation, and a contract from the National Institute for Health Research (NIHR), outside of the submitted work; and consulting fees from Shionogi and Sandoz and speaking fees from Pfizer and Sandoz, outside the submitted work. This approach follows the methods validated by many researchers in sepsis epidemiology25WHOGlobal report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions., 26Angus DC Linde-Zwirble WT Lidicker J Clermont G Carcillo J Pinsky MR Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care.Crossref PubMed Scopus (6413) Google Scholar, , and used by Rudd and colleagues.We then multiplied the fraction of sepsis predicted from the logistic regression models onto GBD cause-specific mortality estimates to determine the mortality envelope for our analysis. First, we fitted a stacked ensemble model between the input data and selected covariates from the list of plausible and health-related covariates available in GBD 2019 (appendix pp 48–49, 92–93); the estimates from the stacked ensemble model were then inputted into a spatiotemporal Gaussian process regression model to smooth the estimates in space and time. We calculated YLLs using the same methods used to calculate YLLs attributable to AMR. This modelling environment allows for the inclusion of covariates in the network analysis and for Bayesian prior probability distributions to be incorporated. Other drivers of the observed higher burden in LMICs include the scarcity of laboratory infrastructure making microbiological testing unavailable to inform treatment to stop or narrow antibiotics,56WHOWHO sepsis technical expert meeting—meeting report. Centers for Medicare and Medicaid Services, Baltimore, MD2021View in Article 34.Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.View in Article 35.Interagency Coordination Group on Antimicrobial Resistance. Our regional estimates could prove useful for tailoring local responses as a one size fits all approach might be inappropriate. Assuming a single relative risk for all infectious syndromes is a potentially strong assumption; it is not immediately clear what direction this biases results, but it might lead to overestimation. 2017; 318: 1241-1249View in Article Scopus (676) PubMed Crossref Google Scholar29.Trimmed constrained mixed effects models: formulations and algorithms.J Comput Graph Stat. For meticillin-resistant S aureus, resistance was generally highest (60% to less than 80%) in countries in north Africa and the Middle East (eg, Iraq and Kuwait) and lowest (less than 5%) in several countries in Europe and sub-Saharan Africa (figure 7A). Individually, these sources do not fully address the burden of AMR but, when used collectively, they provide a more complete estimate with robust geographical coverage. We acknowledge Samuel Akech, Ednah Ooko, James Bukosia, Neema Mturi, J Anthony G Scott, Philip Bejon, Lynette Isabella Oyier, Salim Mwarumba, Esther Muthumbi, Christina Obiero, Robert Musyimi, Shebe Mohammed, Caroline Ogwang, Christopher Maronga, Ambrose Agweyu, KEMRI Wellcome Trust Research Programme, Kilifi, Kenya. In other words, if all drug-resistant infections were replaced by no infection, 4·95 million deaths could have been prevented in 2019, whereas if all drug-resistant infections were replaced by drug-susceptible infections, 1·27 million deaths could have been prevented. Our estimates of the proportion of infections that were community acquired versus hospital acquired for lower respiratory and thorax infections and urinary tract infections were based on the coding of data from multiple causes of death and hospital discharge data. J Robotham is a member of the UK Government Advisory Committee on Antimicrobial Prescribing Resistance and Healthcare Associated Infections, outside the submitted work. Compared with all underlying causes of death in GBD 2019, AMR would have been the third leading GBD Level 3 cause of death in 2019, on the basis of the counterfactual of no infection; only ischaemic heart disease and stroke accounted for more deaths that year. STAT.View in Article 44.Antimicrobial resistance: tackling the burden in the European Union. Understanding the burden of AMR and the leading pathogen–drug combinations contributing to it is crucial to making informed and location-specific policy decisions, particularly about infection prevention and control programmes, access to essential antibiotics, and research and development of new vaccines and antibiotics. 2016; 13e1002184View in Article Scopus (471) PubMed Crossref Google Scholar4.NOAH response to final O'Neill AMR review report July 2016. On the basis of these death and incidence estimates, we then computed YLLs, YLDs, and DALYs associated with drug-resistant infections. Locations with no data or modelled estimates are presented in white. Additionally, our comprehensive data collection effort shows that high-quality data on infectious disease, pathogens, and AMR are only sparsely available in many low-income settings. 2020; 395: 200-21125.Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. In either case, the magnitude of the global bacterial AMR problem is very large and likely bounded by the two measures.Our ability to compare our estimates with previous estimates is somewhat limited. 2018; 115: 12896-12901View in Article Scopus (74) PubMed Crossref Google Scholar47.Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis.Lancet Planet Health. AMR is a global problem and one that requires both global action and nationally tailored responses.This study evaluated both the burden of bacterial infections associated with drug resistance and the burden directly attributable to drug resistance. Vaccines are available for only one of the six leading pathogens (S pneumoniae), although new vaccine programmes are underway for S aureus, E coli, and others. Whenever possible, we classified resistance using the most recent CLSI guidelines based on the minimum inhibitory concentrations provided in the data; however, CLSI breakpoints have changed over time, and many datasets did not provide sufficient detail to allow for retrospective reanalysis of the data.Finally, there is a possibility of selection bias in passive microbial surveillance data, particularly if cultures are not routinely drawn. First, we obtained data from multiple data sources, including from published studies (eg, microbiology data, inpatient data, data on multiple causes of death, and pharmaceutical sales data) and directly from collaborators on the Global Research on Antimicrobial Resistance project, members of the GBD Collaborator Network, and other data providers.We estimated the disease burdens associated with and attributable to AMR for 12 major infectious syndromes (lower respiratory infections and all related infections in the thorax; bloodstream infections; peritoneal and intra-abdominal infections; meningitis and other bacterial CNS infections; typhoid, paratyphoid, and invasive non-typhoidal Salmonella spp; urinary tract infections and pyelonephritis; diarrhoea; tuberculosis [not including tuberculosis associated with HIV]; bacterial infections of the skin and subcutaneous systems; endocarditis and other cardiac infections; infections of bones, joints, and related organs; and gonorrhoea and chlamydia) and one residual category, 23 bacterial pathogens, 18 drug categories or combinations of drugs for which there is resistance, and 88 pathogen–drug combinations (appendix pp 45–46). World Health Organization, Geneva2014View in Article 31.Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.Lancet. In the high-income super-region, approximately half of the fatal AMR burden was linked to two pathogens: S aureus (constituting 26·1% [95% UI 17·4–34·1] of deaths attributable to AMR and 25·4% [24·1–27·0] of deaths associated with AMR) and E coli (constituting 23·4% [19·5–28·2] of deaths attributable to AMR and 24·3% [22·9–25·8] of deaths associated with AMR; figure 5). Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen–drug combinations in select locations. Many lab-based surveillance systems are not linked to patient diagnoses or outcomes, limiting the inferences that are possible to obtain from such data. Six more pathogens were each responsible for between 100 000 and 250 000 deaths associated with AMR: M tuberculosis, Enterococcus faecium, Enterobacter spp, Streptococcus agalactiae (group B Streptococcus), S Typhi, and Enterococcus faecalis. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.Three infectious syndromes dominated the global burdens attributable to and associated with AMR in 2019: lower respiratory and thorax infections, bloodstream infections, and intra-abdominal infections (figure 3). After mapping, we had 157 million isolates and cases from 118 countries and territories to estimate the pathogen distribution of each infectious syndrome (estimation step four), with each dataset including a unique spectrum of pathogens and groups of pathogens. In fact, it could be argued that an increase in access to antibiotics would decrease the AMR burden in some locations where second-line antibiotics are unavailable and would be lifesaving; this might well be the case in western sub-Saharan Africa. We obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. For instance, when considering the specific burden of each pathogen–drug combination, we believe that the burden attributable to resistance is more appropriate because very high levels of co-resistance among some drugs lead to many deaths being duplicated across drugs when considering burden associated with resistance. For datasets where isolates could not be uniquely identified across pathogen–drug combinations, such as some antimicrobial resistance surveillance systems, some isolates might be double counted. 2013; 341: 1514-1517View in Article Scopus (222) PubMed Crossref Google Scholar52.Understanding the mechanisms and drivers of antimicrobial resistance.Lancet. Also shown in figure 1 is the number of unique study-location-years and individual records or isolates available for each data type. J Scott reports that the London School of Hygiene & Tropical Medicine (LSHTM) received financial support from Emory University to support CHAMPS projects in Ethiopia for the present manuscript; reports a paid fellowship from the Wellcome Trust, research grants from Gavi, the Vaccine Alliance, and NIHR paid to LSHTM, and an African research leader fellowship paid to LSHTM by the Medical Research Council, outside the submitted work; and reports being a member of the data safety and monitoring board for PATH Vaccines Solutions for SII PCV10 in The Gambia. Access to the data are also provided as data use agreements permit.E Ashley reports that Lao-Oxford-Mahosot Hospital—Wellcome Trust Research Unit received financial support from the Global Research on Antimicrobial Resistance Project (GRAM) to extract and prepare data for the present manuscript. In total, 471 million individual records or isolates covering 7585 study-location-years were used as input data to the estimation process. 2021; 118e2013515118View in Article PubMed Crossref Google Scholar66.Clinical bacteriology in low-resource settings: today's solutions.Lancet Infect Dis. By contrast, limiting access to antibiotics in south Asia through stewardship programmes might be the appropriate response for that region because antibiotic overuse or misuse is believed to be a major driver of AMR there. 2012; 380: 2063-206617.The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria.Curr Opin Microbiol. Limited availability of data in some parts of the world was particularly consequential for the prevalence of resistance and relative risk modelling components; we assumed that the relative risk for each pathogen–drug combination, as well as the correlation structure of resistance between drugs, was the same in every location, age, and infectious syndrome. For the number of incident infections associated with resistance, we took the product of infectious syndrome incidence, the proportion of infectious incident cases attributable to each pathogen, and the prevalence of resistance in incident cases. The exceptions to this modelling approach were multidrug-resistant (MDR) excluding extensively drug-resistant (XDR) tuberculosis and XDR tuberculosis, for which published GBD 2019 estimates were already available.Given the strong relationship between antibiotic consumption levels and the proliferation of resistance, we modelled antibiotic consumption at the national level to use as a covariate in the stacked ensemble model of prevalence of resistance. Additionally, since this analysis builds on estimates of disease incidence, prevalence, and mortality from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, our findings on the burden of bacterial AMR can be compared with other causes of death, offering crucial context on the magnitude of the burden of this important health issue. All other authors had access to, and reviewed, estimates as part of the research evaluation process, which includes additional stages of formal review.Citations for the data used in the study can be accessed from the Global Health Data Exchange AMR website. 2017; 54: 50-5765.Filling the gaps in the global prevalence map of clinical antimicrobial resistance.Proc Natl Acad Sci USA. 2017; 23: 812-81854.Barriers to implementing antimicrobial stewardship programs in three low- and middle-income country tertiary care settings: findings from a multi-site qualitative study.Antimicrob Resist Infect Control. To incorporate all these heterogeneous data, we used a new modelling environment, termed multinomial estimation with partial and composite observations. For the non-fatal excess risk, we estimated the relative increase in length of stay associated with a resistant infection compared with that of a drug-sensitive infection, adjusted for length of stay prior to culture being drawn. 2017; 1: e316-e32748.Global trends in antimicrobial resistance in animals in low- and middle-income countries.Science. All country-level covariates were modelled estimates that were produced previously for GBD 2019,20Institute for Health Metrics and EvaluationGlobal Burden of Disease Study 2019 (GBD 2019) data input sources tool., or those that were modelled by Browne and colleagues.22Browne A Chipeta M Haines-Woodhouse G et al.Global antibiotic consumption in humans, 2000 to 2018: a spatial modelling study. This mostly likely underestimates the relative risk of MDR infections because fewer effective antibiotic options remain as resistance accumulates. It poses the largest threat to human health in sub-Saharan Africa and south Asia, but it is important in all regions. 3GC=third-generation cephalosporins. E Ashley acknowledges that Lao-Oxford-Mahosot Hospital–Wellcome Trust Research Unit receives core funding from Wellcome (20211/Z/20/Z). More details on this approach are provided in the appendix (pp 34–44).We used data from 52·8 million isolates to analyse the proportion of phenotypic AMR for each pathogen—the proportion of infections that were drug resistant, hereafter referred to as prevalence of resistance—for 88 pathogen–drug combinations. To our knowledge, however, there have been no comprehensive estimates covering all locations and a broad range of pathogens and pathogen–drug combinations.Added value of this studyThis study is the most comprehensive analysis of the burden of AMR to date, producing estimates for 204 countries and territories, 23 bacterial pathogens, and 88 pathogen–drug combinations, in 2019.

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