Association between particulate matter $(PM)_{2·5}$ air pollution and clinical antibiotic resistance: a global analysis

Zhenchao Zhou, Xinyi Shuai, Zejun Lin, Xi Yu, Xiaoliang Ba, Mark A Holmes, Yonghong Xiao, Baojing Gu, Hong Chen

Summary

Background Antibiotic resistance is an increasing global issue, causing millions of deaths worldwide every year. Particulate matter $(PM)_{2·5}$ has diverse elements of antibiotic resistance that increase its spread after inhalation. However, understanding of the contribution of $PM_{2·5}$ to global antibiotic resistance is poor. Through univariate and multivariable analysis, we aimed to present the first global estimates of antibiotic resistance and burden of premature deaths attributable to antibiotic resistance resulting from $PM_{2·5}$ pollution.

Methods For this global analysis, data on multiple potential predictors (ie, air pollution, antibiotic use, sanitation services, economics, health expenditure, population, education, climate, year, and region) were collected in 116 countries from 2000 to 2018 to estimate the effect of $PM_{2·5}$ on antibiotic resistance via univariate and multivariable analysis. Data were obtained from ResistanceMap, European Centre for Disease Prevention and Control Surveillance Atlas (antimicrobial-resistance sources), and PLISA Health Information Platform for the Americas. Future global aggregate antibiotic resistance and premature mortality trends derived from $PM_{2·5}$ in different scenarios (eg, 50% reduced antibiotic use or $PM_{2·5}$ controlled to 5 μg/m³) were projected until 2050.

Findings The final dataset included more than 11·5 million tested isolates. Raw antibiotic-resistance data included nine pathogens and 43 types of antibiotic agents. Significant correlations between $PM_{2·5}$ and antibiotic resistance were consistent globally in most antibiotic-resistant bacteria (R^2=0·42–0·76, p<0·0001), and correlations have strengthened over time. Antibiotic resistance derived from $PM_{2·5}$ caused an estimated 0·48 (95% CI 0·34–0·60) million premature deaths and 18·2 (13·4–23·0) million years of life lost in 2018 worldwide, corresponding to an annual welfare loss of US$395 (290–500) billion due to premature deaths. The 5 μg/m³ target of concentration of $PM_{2·5}$ in the air quality guidelines set by WHO, if reached in 2050, was estimated to reduce antibiotic resistance by 16·8% (95% CI 15·3–18·3) and avoid 23·4% (21·2–25·6) of premature deaths attributable to antibiotic resistance, equivalent to a saving of $640 (580–671) billion.

Interpretation This analysis is the first to describe the association between $PM_{2·5}$ and clinical antibiotic resistance globally. Results provide new pathways for antibiotic-resistance control from an environmental perspective.

Funding National Natural Science Foundation of China, Fundamental Research Funds for the Central Universities, Zhejiang University Global Partnership Fund, and China Postdoctoral Science Foundation.

Lancet Planet Health 2023; 7: e649–59

College of Environmental and Resource Sciences (Z Zhou PhD, X Shuai BSc, Z Lin BSc, X Yu BSc, Prof B Gu PhD, Prof H Chen PhD), **Ministry of Education Key Laboratory of Environment Remediation and Ecological Health** (Prof H Chen), **State Key Laboratory for Diagnosis and Treatment of Infectious Disease, The First Affiliated Hospital** (Prof Y Xiao PhD), **Zhejiang University, Hangzhou, China; Department of Veterinary Medicine, University of Cambridge, Cambridge, UK** (X Ba PhD, Prof M A Holmes PhD); **Zhejiang International Science and Technology Cooperation Base of Environmental Pollution and Ecological Health, Hangzhou, China** (Prof H Chen)

Correspondence to:
Prof Baojing Gu, College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310058, China
bjgu@zju.edu.cn

or

Prof Hong Chen, College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310058, China
chen_hong@zju.edu.cn

Introduction

Currently, the world is in an era of antibiotic resistance in which antibiotic-treatment failure and mortality caused by bacterial infections are increasing.[1] Antibiotic resistance is a severe global issue, causing approximately 1·27 million premature deaths in 2019 worldwide,[2] substantially exceeding the estimated 0·70 million deaths in 2016.[3] Although the misuse and overuse of antibiotics are the main drivers of antibiotic resistance, the rapid spread of antibiotic-resistant bacteria and antibiotic-resistance genes across global regions and sectors (eg, human beings, animals, and environments) is also important for the transmission and prevalence of antibiotic resistance.[4,5] However, there is little quantitative data on such a pathway, which restricts the full understanding of the effects of antibiotic resistance on human health.

The One Health approach recognises that antibiotic resistance is not just a human health issue, but also affects animals and the environment.[4] Humans are exposed to antibiotic-resistant bacteria and antibiotic-resistance genes via food, the environment (eg, water, soil, and air), or direct contact with infectious sources, such as animals (figure 1). For example, antibiotic-resistant bacteria and antibiotic-resistance genes in hospitals or livestock farming could be transmitted to sewage-treatment facilities or ecosystems, and could even be emitted from these settings into the atmosphere and be exposed to humans through inhalation.[6] Air is recognised as being a direct pathway and key vector for disseminating antibiotic resistance.[6] The major air pollutant, in the form of particulate matter $(PM)_{2·5}$, has been shown to contain diverse antibiotic-resistant bacteria and antibiotic-resistance genes, which are transferred between environments and directly inhaled by

Research in context

Evidence before this study

Antibiotic resistance is increasingly becoming a threat to global health. Particulate matter ($PM_{2·5}$) air pollution contains diverse elements of antibiotic resistance that could exacerbate widespread antibiotic resistance and human exposure via inhalation. However, there is little quantitative data on such a pathway, which restricts the full understanding of the effects of antibiotic resistance on human health. We searched PubMed for studies examining associations between air pollution and antibiotic resistance published from database inception until Dec 11, 2022. We used the keywords ("$PM_{2·5}$" OR "fine particulate matter" OR "fine particles" OR "air pollution") AND ("antibiotic resistance" OR "antimicrobial resistance") AND ("global" OR "worldwide" OR "world" OR "globe") without language restrictions. We identified 12 research studies that estimated the emergence of antibiotic-resistance genes or bacteria in atmospheric environments; three of these 12 estimated the global dispersal of antibiotic-resistance genes via air pollution. However, none evaluated the associations between $PM_{2·5}$ and burden of antibiotic resistance worldwide.

Added value of this study

To our knowledge, this analysis is the first to comprehensively estimate the global associations between $PM_{2·5}$ and clinical antibiotic resistance via univariate and multivariate analysis. We identified that antibiotic resistance increased with increasing $PM_{2·5}$. Through future population and air-quality scenarios, we evaluated the burden of antibiotic resistance associated with $PM_{2·5}$ worldwide for the first time. Our results highlight that controlling air pollution to reduce $PM_{2·5}$ concentrations might lead to substantial health and economic benefits by reducing antibiotic resistance.

Implications of all the available evidence

Insights from understanding factors driving global antibiotic resistance are essential for implementing and monitoring policies to overcome antibiotic resistance. Our analysis adds to emerging evidence that $PM_{2·5}$ air pollution is linked to increased antibiotic resistance. Although measures to regulate antibiotic use and improve basic drinking-water services are still needed, controlling $PM_{2·5}$ might be a promising way to reduce global antibiotic resistance in the future.

humans, causing respiratory-tract injury and infection.[7–9] $PM_{2·5}$ could also increase cell-membrane permeability to enhance the efficiency of horizontal gene transfer, accelerating the evolution and exchange of antibiotic-resistance elements in bacterial pathogens.[10,11] Despite previously reported studies on the widespread distribution of antibiotic-resistant bacteria and antibiotic-resistance genes in $PM_{2·5}$, the quantified consequences of antibiotic resistance caused by $PM_{2·5}$ have not been documented. Empirical evidence of the effects of $PM_{2·5}$ on population-level antibiotic resistance that enable the global impact to be assessed is clearly needed.

In this study, we aimed to collect an extensive database of antibiotic resistance and predictors to explore whether $PM_{2·5}$ is a primary factor driving global antibiotic resistance. Through univariate and multivariable analysis, we aimed to present the first global estimates of antibiotic resistance and burden of premature deaths attributable to antibiotic resistance resulting from $PM_{2·5}$ pollution. Finally, we aimed to estimate the future global aggregate antibiotic resistance and the premature mortality trends under different scenarios for a projection until 2050.

Methods

Data sources

For this global analysis, we created a dataset of antibiotic resistance patterns across 116 countries using data from 2000 to 2018 from the ResistanceMap, European Centre for Disease Prevention and Control Surveillance Atlas (antimicrobial-resistance sources), and PLISA Health Information Platform for the Americas.[12–14] The final dataset included tested isolates (eg, isolates obtained from blood, cerebrospinal fluid, or both) classified as susceptible, intermediate, or resistant to antibiotics according to Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing breakpoints.[15,16] Information on the methods used by the open-source dataset for harmonising data to present similar definitions of antibiotic resistance from several sources is available.[12] Antibiotic resistance was defined as the percentage of tested isolates (only included if there were ≥30 isolates) that were non-susceptible (ie, intermediate or resistant) to an antibiotic. To simplify the visualisation of antibiotic-resistance trends for many different antibiotics, we normalised the data via min–max standardisation and centred it on the mean to show the aggregate resistance.[17–19] The study protocol is available online.[20]

Evaluated predictors

We selected relevant predictors that help to predict antibiotic resistance based on previous literature.[11,21–24] Data on antibiotic use (ie, defined daily doses [DDD] per 1000 people per day) had been collected from 2000 to 2018 for 116 countries in a previous spatial modelling study.[25] Air pollutants (ie, $PM_{2·5}$, PM_{10}, ozone, sulphur dioxide, nitrogen dioxide, and carbon monoxide) were collected from the air-quality databases of WHO, the Health Effects Institute, and the European Environment Agency for 2000–18 for 116 countries.[26–29] Data on people using at least basic drinking-water services (BDWS), governance indicators, people using safely managed drinking water services, people using safely managed sanitation services, gross domestic

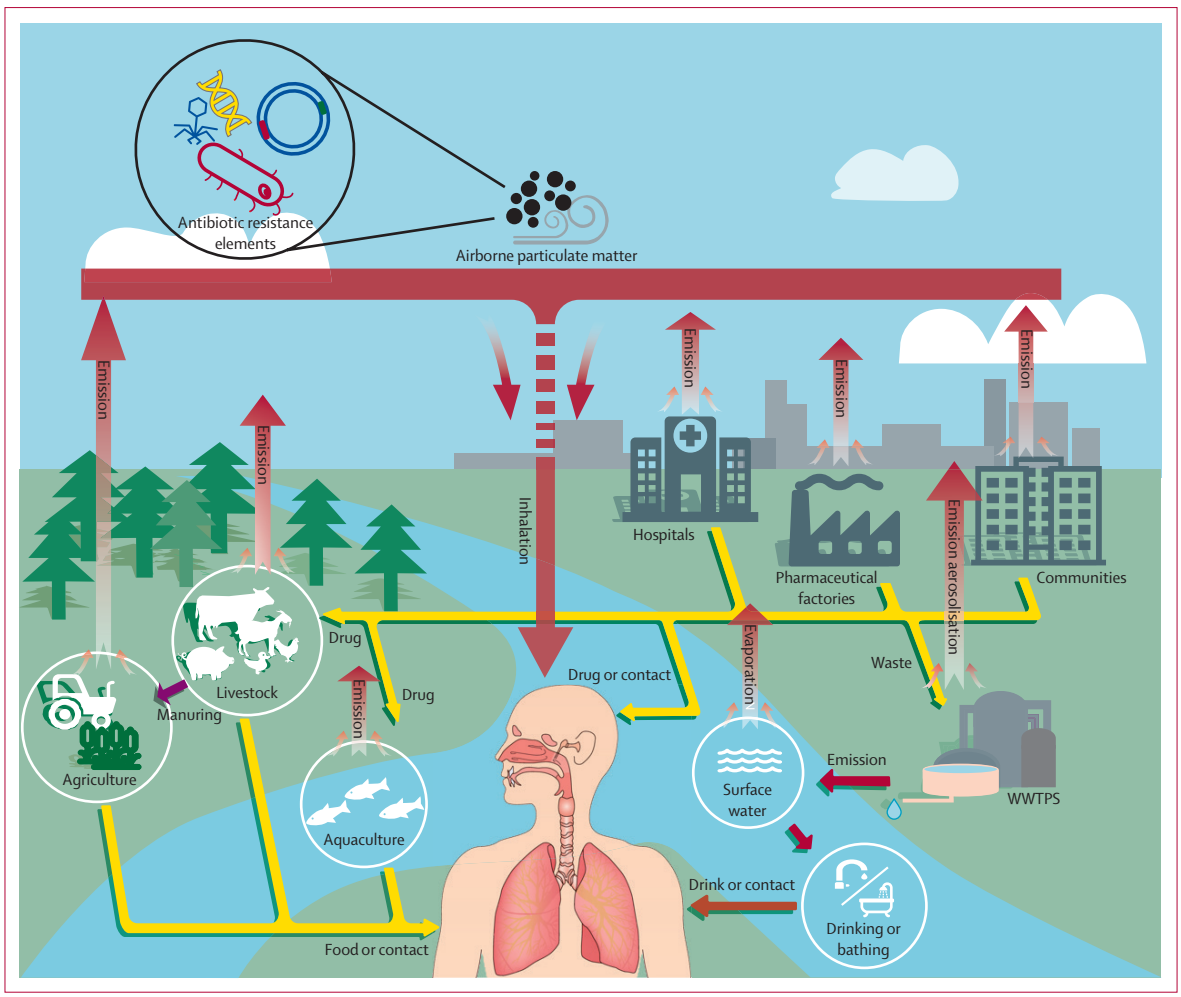

Figure 1: **Pathways of antibiotic-resistance dissemination**
WWTPS=waste water treatment plants.

product (GDP), GDP per capita, current health expenditure (CHE), CHE per capita, population density, population (ie, number of inhabitants), total adult literacy rate, total primary completion rate, annual temperature, and rainfall were obtained from the World Bank's databank for 2000–18 in up to 116 countries.[30] Relevant predictors were antibiotic use, sanitation services, economics, health expenditure, population, education, climate, and air pollution (appendix pp 2, 7).

Scenarios

We analysed a set of scenarios until 2050: one baseline scenario, five shared socioeconomic pathway (SSP) scenarios, four single-factor control scenarios (ie, CHE doubled, 50% reduction in antibiotic use, $PM_{2·5}$ controlled to 5 μg/m³, and 100% BDWS), and three multifactor-control scenarios (ie, multivariate 1, multivariate 2, and multivariate 3). The baseline scenario assumed that global antibiotic resistance continued at current rates, as estimated by ETS models.[31] The SSP scenarios set different air-pollution-control pathways; the concentrations of $PM_{2·5}$ in SSPs from the Intergovernmental Panel on Climate Change were used as prediction references, as described by Rao and colleagues.[17] SSP1 refers to low challenges to mitigation and adaptation, SSP2 refers to medium challenges to mitigation and adaptation, SSP3 refers to high challenges to mitigation and adaptation, SSP4 refers to low challenges to mitigation but high challenges to adaptation, and SSP5 refers to high challenges to mitigation but low challenges to adaptation.[32] The single-factor control scenarios assumed four different control pathways (ie, double the current CHE per capita, reduce antibiotic use by 50%, control $PM_{2·5}$ to 5 μg/m³, and enable 100% of people to access BDWS). Multifactor-control scenarios assumed combined control pathways with four single factors, differing only in $PM_{2·5}$ (ie, 15 μg/m³, 10 μg/m³, or 5 μg/m³). For each of the 13 scenarios, we calculated the trends of antibiotic resistance and the number of premature deaths attributable to antibiotic

See Online for appendix

resistance until 2050. Projections of antibiotic resistance were estimated and conducted with the generalised additive model in R version 4.0.5 using multivariables.

Statistical analysis

The multivariable regression analysis and dominance analysis were conducted in Stata version 16 with a robust fixed-effect regression model to quantify the contributions of antibiotic use, sanitation services, GDP in US$, GDP per capita in US$, health expenditure, population, education, climate, and air pollution factors to antibiotic resistance. A fixed-effect regression model was selected after a Breusch and Pagan Lagrangian multiplier test and a Hausman test (appendix pp 8, 9). All predictors were checked for multicollinearity by calculating their variation inflation factors (VIFs; only regression with VIF <10 was done). Aspects of the region, year, and income were introduced as dummy variables in each model. Multivariable regressions were validated with trimmed (5–95%) multivariate regression analysis, residual analysis, and heteroskedasticity test by White's test. Stepwise regression analysis was used with an F probability of 0·05 for the chosen factor thresholds in the linear regression fitting via SPSS version 25.0 to establish predictive variables for selecting the suitable regression equation automatically. The coefficient of determination (R^2) defined the fit of each multivariable regression model. The multivariate linear regression model evaluated the change in antibiotic resistance related to $PM_{2·5}$ and other predictors. Future population scenario data were obtained from the 2022 Revision of World Population Prospects by the Population Division of the Department of Economic and Social Affairs of the UN Secretariat.[18] We estimated deaths attributable to antibiotic resistance by applying the population-attributable fraction (PAF) to the number of deaths involving infections described by Murray and colleagues.[2] The death counts involving infection were calculated at current rates. All-cause deaths,[19] deaths involving infection, change in PAF, and deaths attributable to bacterial antibiotic resistance[2] were visualised (appendix p 3). The aggregate relative risk (RR) of deaths attributable to antibiotic resistance extracted from previous literature[2] was used for calculating the PAF using the following formula:

$$PAF = p(RR-1)/[1+p(RR-1)]$$

where p is the prevalence of antibiotic resistance among the infection. Years of life lost (YLLs) were used for estimating the welfare loss of premature death, as detailed in our previous study,[33] calculated using the following formula:

$$YLL_{i,j} = YLL_{EU} \times (Y_{i,j}/Y_{EU})e$$

where $YLL_{i,j}$ is the YLL cost of country i in year j, YLL_{EU} is the mean base YLL cost in EU countries, $Y_{i,j}$ is GDP per capita for country i in year j, Y_{EU} is the mean GDP per capita of EU countries, and e is the income elasticity of the YLL. The mean values of YLLs and premature deaths according to the Global Burden of Disease estimation were applied to the countries or regions in the projection. Future GDP per capita was estimated with SSP data.[34,35]

Global distribution maps were visualised on the basis of the mean value of antibiotic resistance, $PM_{2·5}$, and other evaluated predictors. Univariate analyses of the association between antibiotic resistance and evaluated predictors were conducted with Pearson and Spearman tests, with the correlation coefficient R^2. Trend bars represent weighted linear-fitted models via log scales of the values, and regression coefficients represent slopes to evaluate the effects of predictors on specific antibiotic resistance. All map plots, box plots, heatmaps, weighted linear regression plots, and slope circus-bar plots were created with the ggplot2, maptools, and maps packages in R version 4.0.5. Source data and script codes are available elsewhere.[36]

We collected a large amount of data of different predictors and pre-analysed and pre-processed the data at an early stage. The missing values were randomly distributed, with the probability of any particular value being missing from dataset being unrelated to anything else. In our analysis, we left these missing data empty.

Role of the funding source

The funders of the analysis had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The final dataset included more than 11·5 million tested isolates. Raw antibiotic-resistance data included nine pathogens (ie, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes or E cloacae*, *Enterococcus faecalis*, and *Enterococcus faecium*) and 43 types of antibiotic agents.

Using a fixed-effect panel model, we evaluated the correlations between $PM_{2·5}$ and aggregate antibiotic resistance. Significant correlations between $PM_{2·5}$ and antibiotic resistance were consistent globally in most antibiotic-resistant bacteria (R^2=0·42–0·76, p<0·0001), and correlations have strengthened over time (figure 2; appendix pp 4–5). High levels of antibiotic resistance were found in north Africa, the Middle East, and south Asia, whereas Europe and North America had low antibiotic-resistance levels (appendix p 4). The weighted linear regression analysis showed that an increase in concentration of $PM_{2·5}$ globally was associated with an increase in aggregate antibiotic resistance (mean normalised antibiotic resistance; R^2=0·47, p<0·0001; figure 2A).

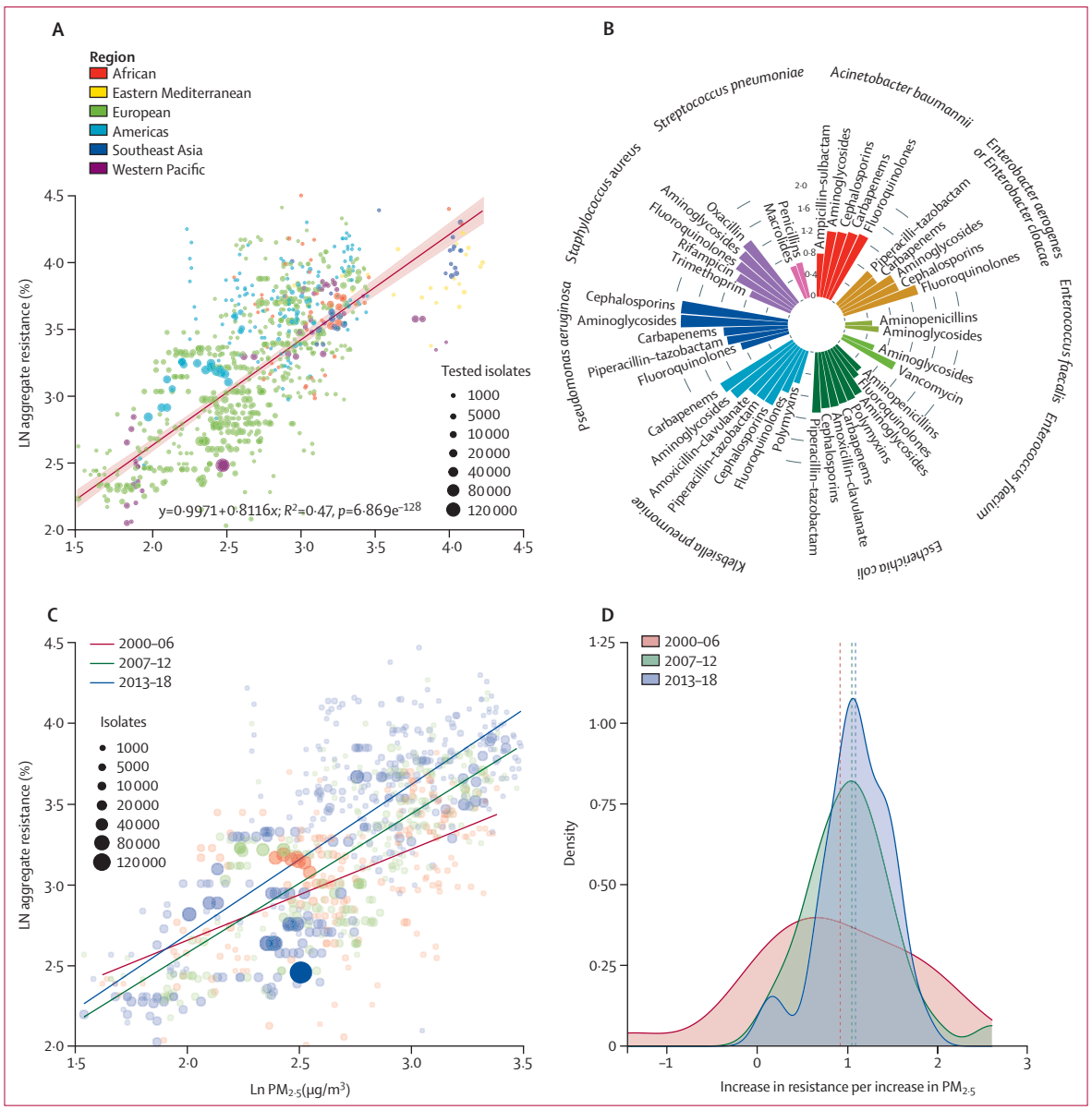

Figure 2: **Aggregate antibiotic resistance increases relevant to concentration of $PM_{2·5}$**

(A) Scatter plot of aggregate resistance *vs* concentration of $PM_{2·5}$. The weighted linear trend line is shown in black; the red shading shows the 95% CI. (B) Slope of relationship (ie, percentage change in resistance per percentage change in $PM_{2·5}$) between concentration of $PM_{2·5}$ and antibiotic resistance. Different colours represent different pathogens. Cephalosporins refer to third-generation cephalosporins. (C) Antibiotic resistance *vs* concentration of $PM_{2·5}$ stratified by year (ie, 2000–06, 2007–12, and 2013–18). Weighted linear trend lines are shown in different colours. (D) Density distributions of slopes stratified by year (ie, 2000–06, 2007–12, and 2013–18). Median densities are shown by vertical dashed lines. Ln=natural logarithm. PM=particulate matter.

The slopes of the relationships between $PM_{2·5}$ and antibiotic resistance for each of the different bacteria ranged from 0·5 to 1·9 (p<0·0001; figure 2B). For example, an increase of 1% in $PM_{2·5}$ across regions was associated with an increase in *Klebsiella pneumoniae* resistance to carbapenems of 1·49% (R^2=0·24), aminoglycosides of 1·41% (0·47), amoxicillin–clavulanate of 1·16% (0·54), piperacillin–tazobactam of 1·15% (0·35), third-generation cephalosporins of 1·14% (0·49), fluoroquinolones of 0·83% (0·31), and polymyxins of 0·61% (0·12; p<0·0001). Moreover, changes in concentration of $PM_{2·5}$ led to larger increases in antibiotic resistance since 2013 (figure 2C, D). The results of the univariate correlation analysis are shown in the appendix (p 6).

In the multivariable analysis, after the predictors with collinearity were excluded, we found that BDWS, health expenditure and rainfall were inversely correlated with aggregate antibiotic resistance, whereas $PM_{2·5}$ and antibiotic use were positively correlated (table).

	Coefficient	Dominance (95% CI)	p value
$PM_{2·5}$	0·433	10·9% (4·3–17·4)	<0·0001
CHE per capita	–0·00209	10·1% (2·8–17·3)	<0·0001
People using at least basic drinking-water services	–0·582	2·7% (0·7–4·7)	<0·0001
Antibiotic use	0·479	2·4% (1·8–2·9)	<0·0001
Rainfall	–0·00272	0·9% (0·7–1·1)	<0·0001
Gross domestic product per capita	–0·0000423	9·5% (2·2–16·8)	0·31
Temperature	–0·0305	4·9% (0·0–9·7)	0·67
Governance	–0·354	4·1% (0·8–7·4)	0·92
Completion of primary education	0·0675	1·2% (0·0–2·4)	0·053
Population density	0·000586	0·2% (0·1–0·3)	0·71
Country income classification	Yes	11·3% (3·7–18·9)	<0·0001
Region	Yes	7·5% (3·5–11·4)	<0·0001
Year	Yes	6·7% (4·6–8·8)	<0·0001
R^2	0·72	..	..
Total number of observations	882	..	..

Income, Region, and Year are dummy predictors. Yes means that predictor has been considered in the analysis. CHE=current health expenditure. PM=particulate matter.

Table: **Fixed-effects panel model of predictors associated with antibiotic resistance**

Generally, antibiotic-resistance levels could increase by 0·43% (0·34–0·52) and 0·48% (0·38–0·57) per unit increase (1 μg/m³ and 1 DDD per 1000 people) in $PM_{2·5}$ and antibiotic use, and antibiotic-resistance levels could decrease by 0·0021% (0·0013–0·0029) for every unit improvement in CHE, 0·0027% (0·0012–0·0042) for every unit improvement in rainfall, and 0·58% (0·41–0·75) for every unit improvement and drinking-water services (table). The residual analysis and trimmed (5–95%) multivariable regression analysis of evaluated predictors of antibiotic resistance also showed that $PM_{2·5}$ and antibiotic use were positively correlated with aggregate antibiotic resistance (R^2=0·72; p<0·0001; appendix p 10). Stepwise regression analysis (0·80; p<0·0001) of antibiotic resistance versus evaluated predictors showed that $PM_{2·5}$ has an important effect on most bacterial antibiotic resistance (appendix p 11).

$PM_{2·5}$ was one of the largest drivers of antibiotic resistance, contributing 10·9% (95% CI 4·3–17·4) of variation in aggregate resistance, followed by CHE (10·1%, 2·8–17·3), drinking-water services (2·7%, 0·7–4·7), and antibiotic use (2·4%, 1·8–2·9). North Africa and west Asia were the regions where $PM_{2·5}$ had the highest contribution (18·9%, 16·2–21·5) to antibiotic resistance (figure 3A; table). In eight (89%) of nine investigated pathogens, $PM_{2·5}$ consistently contributed to the increase of antibiotic resistance, ranging from 4·0% for *E faecium* to 16·0% for *E coli* (figure 3B). $PM_{2·5}$ substantially affected the resistance observed in *A baumannii*, *K pneumoniae*, and *E coli*, with resistance increasing by 0·62% for *A baumannii*, 0·58% for *K pneumoniae*, and 0·52% for *E coli* for every 1 μg/m³ increase in concentration of $PM_{2·5}$ (appendix p 12). Globally, a 10% increase in annual $PM_{2·5}$ could lead to a 1·1% (1·0–1·2) increase in aggregate antibiotic resistance and 43 654 premature deaths attributable to antibiotic resistance. Africa and Asia are the regions where an increase in $PM_{2·5}$ could lead to the largest increase in antibiotic resistance (figure 3C). Saudi Arabia would have a 3·0% increase in antibiotic resistance resulting from a 10% increase in $PM_{2·5}$, Niger a 2·9% increase, United Arab Emirates a 2·6% increase, Pakistan a 2·6% increase, Nigeria a 2·5% increase, India a 2·5% increase, Cameroon a 2·2% increase, Bahrain a 2·2% increase, and China a 2·1% increase (figure 3C). Furthermore, China and India could be the countries where changes in $PM_{2·5}$ have the largest effect on premature deaths attributable to antibiotic resistance due to their large populations (figure 3D). Antibiotic resistance derived from $PM_{2·5}$ caused an estimated 0·48 (95% CI 0·34–0·60) million premature deaths and 18·19 (13·4–23·0) million YLLs worldwide in 2018, corresponding to an annual welfare loss of US$395 (290–500) billion due to premature deaths (figure 4).

To understand how the antibiotic resistance and premature deaths attributable to antibiotic resistance could be derived from $PM_{2·5}$, we projected their changes in the coming decades until 2050 with a set of scenarios. We found that, in the baseline scenario in which no policies were applied, antibiotic resistance increased by 17·0% (95% CI 13·0–21·0) and annual deaths attributable to antibiotic resistance increased by 56·4% (43·6–80·6) by 2050 globally (figure 5). In this baseline scenario, the most substantial increase in premature mortality attributable to antibiotic resistance was observed in sub-Saharan Africa (figure 5), whereas moderate decreases in premature mortality were seen in east Asia and southeast Asia. Our analysis predicted that the number of deaths attributable to antibiotic resistance derived from $PM_{2·5}$ could increase to 0·84 million in 2050 in the baseline scenario. In other scenarios, such as increasing CHE, controlling $PM_{2·5}$, improving drinking-water services, and reducing antibiotic use, antibiotic resistance could be substantially reduced (figure 5A). Compared with the baseline scenario, the welfare policy for controlling $PM_{2·5}$ to 5 μg/m³ could decrease global antibiotic resistance by 16·8% (95% CI 15·3–18·3) and prevent deaths attributable to antibiotic resistance by approximately 23·4% (21·2–25·6); 0·63 (95% CI 0·57–0·66) million by 2050, corresponding to an annual welfare of $640 (580–671) billion, benefited from reduced premature deaths (figure 5). In the multivariate 3 scenario, global antibiotic resistance could be decreased by 50·0% (45·5–55·5) and deaths attributable to antibiotic resistance could be reduced by 54·5% (49·6–60·5; 1·4 [1·3–1·6] million) by 2050 compared with the baseline scenario. These findings substantiate that $PM_{2·5}$ is a primary factor driving global antibiotic resistance, suggesting global health could benefit from mitigating antibiotic resistance with $PM_{2·5}$ controls.

Discussion

This analysis used data collected from worldwide surveillance reports to estimate the effect that $PM_{2·5}$ has on antibiotic resistance. We introduced multiple potential cofounding predictors (eg, antibiotic use, sanitation services, economics, health expenditure, population, education, climate, year, and region) to test the validity of this correlation. We showed that correlations between $PM_{2·5}$ and antibiotic resistance are consistent across the world in most antibiotic-resistant bacteria, and that the correlations have strengthened over time. Together, multivariate and univariate results suggested a positive and robust association between $PM_{2·5}$ and antibiotic resistance. In two scenarios, north African and west Asian regions could benefit the most, as indicated by the reduced deaths attributable to antibiotic resistance (figure 5). These findings substantiate that $PM_{2·5}$ is a primary factor driving global antibiotic resistance, suggesting global health could benefit from mitigating antibiotic resistance with $PM_{2·5}$ controls. Our analysis is the first report on the relationship between $PM_{2·5}$ and clinical antibiotic resistance worldwide.

One Health promotes the concept that humans, animals, and environments are responsible for the emergence, evolution, and dissemination of antibiotic resistance.[4] Our analysis allows the simultaneous effects of multiple predictors on antibiotic resistance to be quantified. Increased health expenditure can improve sanitation facilities, rational use of medicines, and antibiotic-resistance treatment. Increased rainfall would benefit regional drought relief and the quality of the water supplied.[37] Safe and readily available water is crucial for public health, and improved basic drinking-water supply and sanitation can substantially restrict pathogen dissemination.[38] Moreover, rainfall might also benefit the mitigation of $PM_{2·5}$ pollution that reduces the dissemination of antibiotic resistance as precipitation is one of the main mechanisms for removing aerosol particles in the atmosphere.[39] However, overuse of antibiotics in humans and animals exacerbates the emergence of antibiotic-resistance elements, which can be primarily discharged into environments via waste water, agricultural manure application, or evaporation. On many occasions, these antibiotic-resistance elements can be transferred from environmental microorganisms to human pathogens through drinking water, food, and air inhalation.[4] The air environment can cross regional boundaries and spread antibiotic resistance over long distances and on a large scale, which could be a crucial link between the dissemination of environmental and human antibiotic resistance.

Our findings show a consistent association between $PM_{2·5}$ and aggregate resistance across regions and pathogens, indicating that $PM_{2·5}$ is one of the primary factors driving global antibiotic resistance. Furthermore, we found that the magnitude of the contribution of $PM_{2·5}$ to aggregate antibiotic resistance is greater than

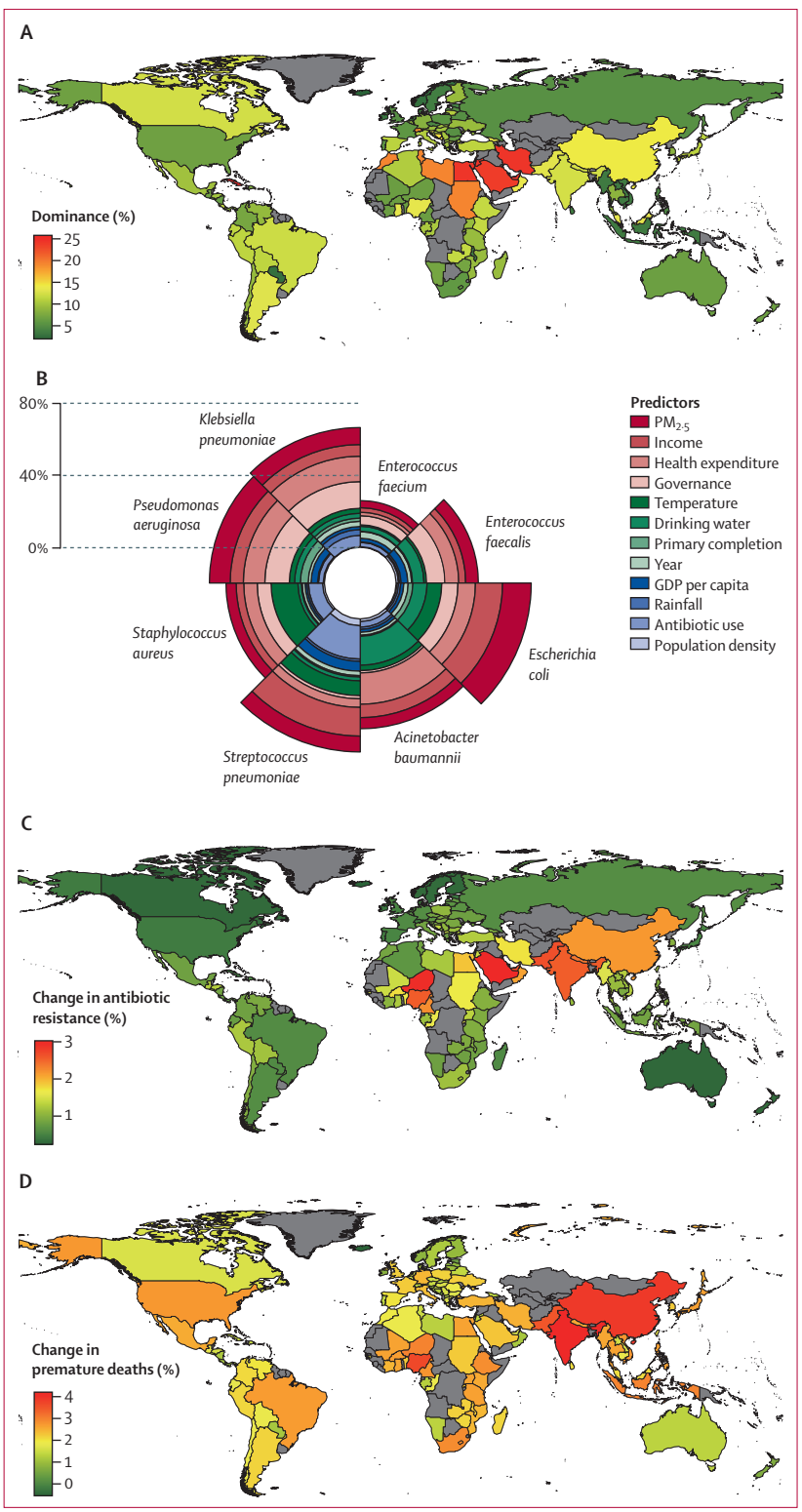

Figure 3: **Contribution of $PM_{2·5}$ to aggregate antibiotic resistance**
(A) Contribution of $PM_{2·5}$ to antibiotic resistance in different countries and regions. (B) Contribution of predictors to antibiotic resistance for each pathogen. (C) Changes in antibiotic resistance per 10% change in concentration of $PM_{2·5}$. (D) Changes in premature death attributed to antibiotic resistance per 10% change in concentration of $PM_{2·5}$. GDP=gross domestic product. PM=particulate matter.

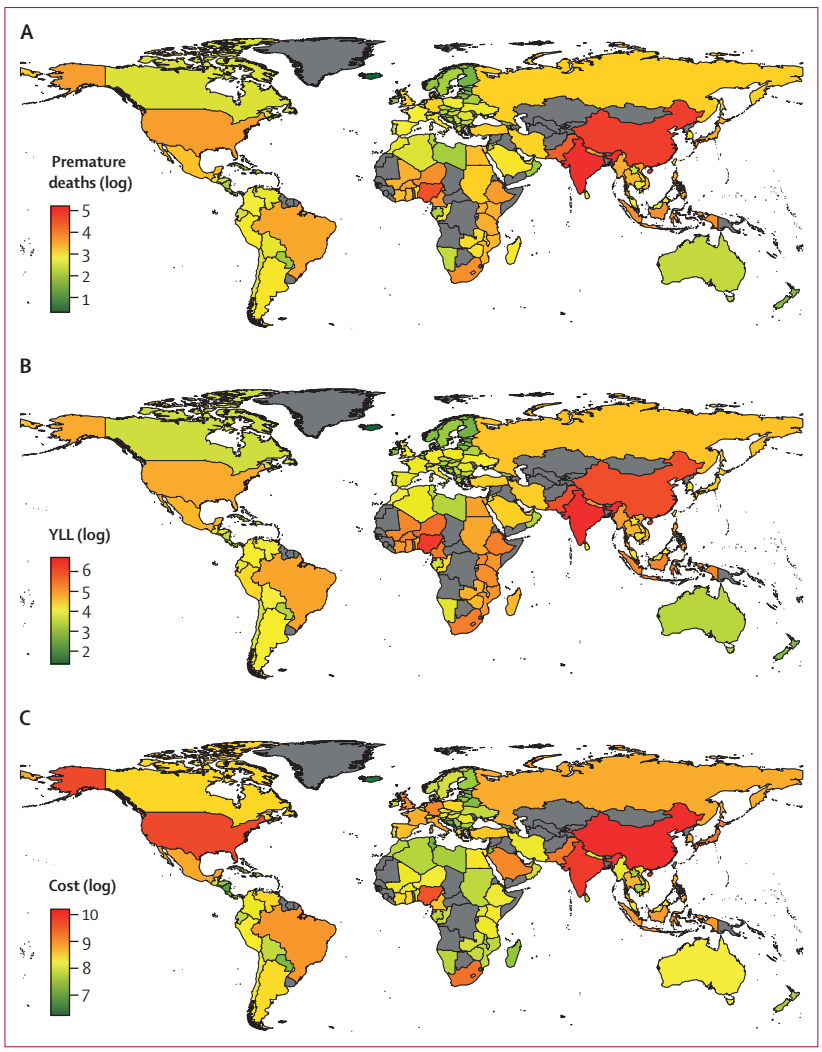

Figure 4: **Mortality cost attributed to aggregate antibiotic resistance derived from $PM_{2·5}$ pollution in 2018**
(A) Premature death attributed to antibiotic resistance derived from $PM_{2·5}$ pollution. (B) YLL for premature death attributed to antibiotic resistance derived from $PM_{2·5}$ pollution. (C) Welfare loss in US$ for premature death attributed to antibiotic resistance derived from $PM_{2·5}$ pollution. PM=particulate matter. YLL=years of life lost.

that of antibiotic use, drinking-water services, and CHE (10·9% *vs* 2·4–10·1%). $PM_{2·5}$ contains a high abundance of antibiotic resistance-determinant genes and the abundance of these genes in urban $PM_{2·5}$ is higher than in sediment, soil, rivers, and some engineering-treatment systems.[7] Antibiotic-resistance elements carried by air pollutants could be directly exposed to humans, which is a substantial risk as the daily intake of antibiotic-resistance genes through inhalation exceeds intake of antibiotic-resistance genes through drinking water.[8,9] Antibiotic-resistance elements in $PM_{2·5}$ can be replenished from the natural environment and anthropogenic settings (eg, hospitals, farms, and sewage-treatment facilities) through wind action, water evaporation, dust transport, and wet or dry settlement spread over long distances and across regions.[24] However, most surface aerosols below the convective boundary layer that can carry antibiotic-resistant bacteria and genes might not reach the high atmospheric altitudes necessary to travel intercontinental distances.[40] Furthermore, $PM_{2·5}$ can facilitate the horizontal gene transfer of antibiotic-resistance genes between bacteria. For example, the conjugative transfer efficiency of antibiotic-resistance genes increases with the $PM_{2·5}$ in a specific concentration, which upregulates expressional levels of genes related to reactive oxygen species, SOS response, cell membranes, pilus generation, and transposition.[10,11] A higher frequency of antibiotic-resistance gene exchanges might lead to a more frequent emergence of antibiotic-resistant bacteria during antibiotic treatment. Taken together, our findings emphasise the importance of air environments as antibiotic-resistance diffusion vectors and reservoirs.

$PM_{2·5}$ positively correlates with bacterial resistance. However, $PM_{2·5}$ contributes with varying degrees to antibiotic resistance in different regions and bacteria. The variation of $PM_{2·5}$ contributions to antibiotic resistance in different regions and bacteria could be explained by the differences in regional air-pollution levels and bacterial niches. Regional airborne antibiotic-resistance elements and microbial richness positively correlate with $PM_{2·5}$ concentration.[8,9] Inhalation exposure to a high abundance of these matters leads to an increased risk of antibiotic-resistance transfer from air to humans, resulting in an increased risk of clinical antibiotic-resistant bacterial infection.[41] *K pneumoniae*, *P aeruginosa*, and *E coli* are the dominant pathogens in air and are likely to cause infections.[42] The effects derived from $PM_{2·5}$ on these bacteria are higher than on other bacteria (eg, *E faecium* and *E faecalis*). The association between $PM_{2·5}$ and antibiotic resistance is increasing at an accelerating rate, which could hasten the beginning of a so-called post-antibiotic era. The harm caused by global air pollution has no borders,[43,44] as shown by the increasing number of premature deaths worldwide during the past decade. Therefore, the comprehensive control of global air pollution requires the coordinated actions of governments of all countries and the joint efforts of all humans.

We estimate that a 10% increase in annual $PM_{2·5}$ could lead to a 1·1% increase in antibiotic resistance and 43 654 premature deaths attributable to antibiotic resistance worldwide (figure 3). If no actions are taken, this negative effect on health caused by increasing air pollution and antibiotic resistance is expected to escalate, especially with the global population approaching 9·7 billion by 2050. North Africa and west Asia are the regions with the most severe $PM_{2·5}$ pollution. Policies in $PM_{2·5}$ control in these regions might lead to substantial changes in antibiotic resistance, as suggested by the finding that deaths attributable to antibiotic resistance could be reduced in 2050 in the scenario in which the 5 μg/m³ $PM_{2·5}$ target set by WHO is met.

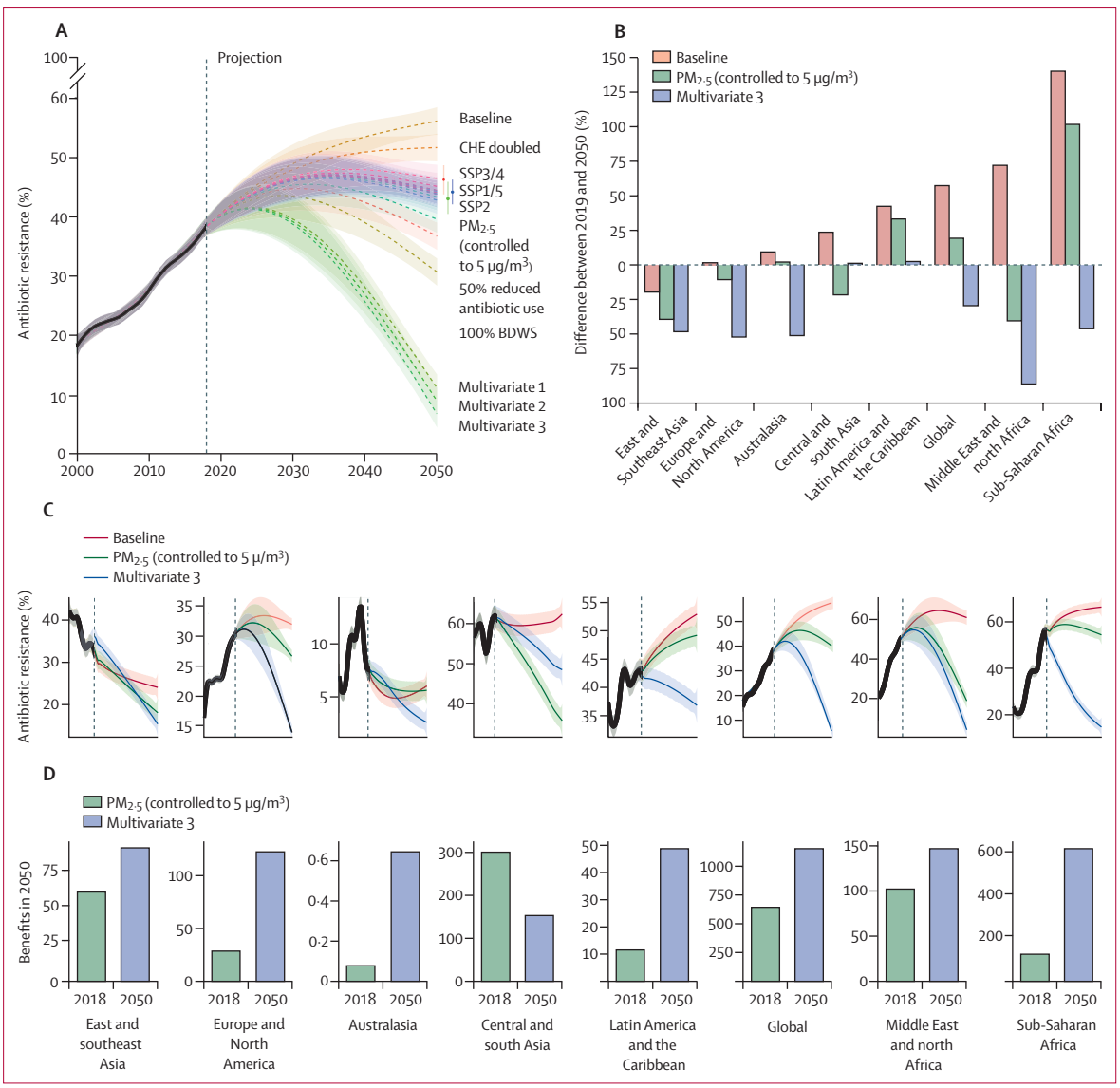

***Figure 5*: Trends in aggregate resistance and mortality from 2018 to 2050**

(A) Global annual aggregate resistance until 2050 for the 11 types of scenarios. Shaded areas around each line show the 95% CI; vertical dotted lines show the year 2018 to distinguish between predicted and actual values. (B) Percentage difference in mortality attributable to antibiotic resistance between 2019 and 2050 for three scenarios. (C) Regional annual aggregate antibiotic resistance until 2050 for three scenarios Shaded areas around each line show the 95% CI; vertical dotted lines show the year 2018 to distinguish between predicted and actual values and solid black lines show the actual values. (D) Benefits of two scenarios in 2050 in billion US$. 100% BDWS=100% of people using at least basic drinking water services. CHE=current health expenditure per capita. Multivariate 1=combined control factors of CHE doubled, 50% reduced antibiotic use, 100% BDWS, and $PM_{2·5}$ (15 µg/m³). Multivariate 2=combined control factors of CHE doubled, 50% reduced antibiotic use, 100% BDWS, and $PM_{2·5}$ (10 µg/m³). Multivariate 3=combined control factors of CHE doubled, 50% reduced antibiotic use, 100% BDWS, and $PM_{2·5}$ (5 µg/m³). PM=particulate matter. SSP=shared socioeconomic pathways. SSP1/5=mean of SSP1 and SSP5. SSP3/4=mean of SSP3 and SSP4.

SSP scenarios provide multiple pathways for global development. $PM_{2·5}$ is projected to be more than 10 µg/m³ in most scenarios and was used to project antibiotic resistance in 2050. SSP3/4 scenarios were less effective in reducing antibiotic resistance than other SSPs, mainly because of a low international priority for addressing environmental concerns in SSP3/4 scenarios.[17] Our results suggest that if the projected increase in mortality attributable to antibiotic resistance derived from $PM_{2·5}$ is to be avoided, intensive air-pollution-control measures will be needed, particularly in regions where the pollution is most severe, such as north Africa, eastern Mediterranean, and southeast Asia. Although reaching the $PM_{2·5}$ concentration target set in the WHO's air quality guidelines (ie, 5 µg/m³) could significantly reduce antibiotic resistance and premature deaths attributable to antibiotic resistance globally in 2050, its effect on different regions varies. North America and Europe are the regions with the smallest change in antibiotic resistance derived from the change in $PM_{2·5}$,

but reaching the 5 μg/m³ target could significantly reduce antibiotic resistance and deaths attributable to antibiotic resistance in North America and Europe. In sub-Saharan Africa, premature deaths attributable to antibiotic resistance continue to increase from 2019 to 2050, even with the same target being met. Population growth is partly responsible for this difference, but antibiotic use could also be responsible as it is expected to increase rapidly in low-income and middle-income regions in the next three decades.[25] Only in east and southeast Asia did premature deaths attributable to antibiotic resistance decline during the next three decades in the baseline scenario. The underlying reason for this finding could be that regional deaths associated with antibiotic resistance are strongly influenced by the proportion of premature deaths in China, where strict air-pollution-control and antibiotic restrictions were implemented during the 2010s, resulting in a decline in $PM_{2·5}$ and antibiotic resistance in recent years, which is predicted to continue.[45,46] Together, these results suggest that, although measures of other drivers of antibiotic resistance are still needed, controlling $PM_{2·5}$ could be a promising way to reduce global antibiotic resistance.

Global antibiotic resistance is caused by multiple factors, especially the effect derived from the environment, which is poorly understood in relation to antibiotic resistance. Our analysis provides further information on the environmental impact on antibiotic resistance within the framework of One Health. Our findings have expanded the understanding of factors influencing antibiotic resistance and promoted the latest research of environmental factors that might substantially contribute to antibiotic resistance. These findings come from worldwide data and have more generalisability than small-scale or short-term cases. We have provided potential measures to control antibiotic resistance, suggesting that improving air quality or blocking airborne transmission of antibiotic resistance might have substantial benefits for public health.

We acknowledge some limitations of our analysis. First, some countries did not provide data for each combination of pathogen and antibiotic and data for all predictors are not uniformly available for all countries, restricting univariate and multivariate analyses. For example, low-income and middle-income countries are the most affected by antibiotic resistance. However, the little data available in these countries might affect overall antibiotic-resistance analysis. Second, comparing results between countries should be done cautiously due to differences in the breadth of testing and RR in regions and years. Third, the underlying mechanism of air pollutants affecting antibiotic resistance is still unclear, and more medical evidence is still needed to verify this occurrence. Finally, due to a part of contributions still being unexplained, some factors could be almost as important as $PM_{2·5}$ in contributing to antibiotic resistance. Additional social, economic, and environmental factors should be introduced to comprehensively assess the association with antibiotic resistance, such as food ingestion, veterinary antibiotic use, exposure to other pollutants, extreme environmental events, habits, and customs. However, the data presented here do not exclude other factors as promoters of the emergence and dissemination of antibiotic resistance. Possible interactions between different factors should be included in future research.

Our analysis presents strong evidence that increasing levels of air pollution are associated with increased risk of antibiotic resistance. This analysis is the first to show how air pollution affects antibiotic resistance globally. The findings have substantial policy and environmental implications by presenting a new pathway to combat clinical antibiotic resistance by controlling environmental pollution.

Contributors

ZZ and HC designed the analysis. BG helped to develop the analysis plan. ZZ, XS, ZL, and XY collected, accessed, verified, and analysed the data. ZZ wrote the manuscript. HC, YX, BG, XB, and MAH gave suggestions for implementation of the research design and reviewed and edited the manuscript. HC, BG, and MAH supervised this work. All authors contributed to the final manuscript, had full access to all the data in the analysis, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Source data for figures 2–5, the table, and the appendix figures and tables (appendix pp 2–12) are available on request to ZZ (zhouzc@zju.edu.cn). The source data and code for all analyses are currently available at https://github.com/zhenchaozhou/PM2.5-AMR.

Acknowledgments

This Article was funded by the National Natural Science Foundation of China (52270201), Fundamental Research Funds for the Central Universities (226-2023-00117), Zhejiang University Global Partnership Fund (100000-11320/198), and China Postdoctoral Science Foundation.

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