World Organisation for Animal Health | AID Animal Industry Data | CGD Center for Global Development | Institute for Health Metrics and Evaluation | RAND Europe | The World Bank IBRD • IDA | World Bank Group

Forecasting the Fallout from AMR: Human Health Impacts of Antimicrobial Resistance

A report from the EcoAMR series

The EcoAMR series (Health and Economic Impacts of AMR in Humans and Food-Producing Animals) is funded by the UK Department of Health and Social Care's Fleming Fund using UK aid. The views expressed in this publication are those of the authors and not necessarily those of the UK Department of Health and Social Care.

Required citation: Vollset SE, Altay U, Bhattacharjee NV, Chalek J, Giannakis K, Gray A, Han C, Lindstedt PA, Naghavi M, Raggi C, Smith AE, Smith G, Swetschinski L, Wool E, Yuan CW, Murray CJL. (2024). – *Forecasting the Fallout from AMR: Human Health Impacts of Antimicrobial Resistance – A report from the EcoAMR series*. Paris (France) and Washington, DC (United States of America): World Organisation for Animal Health and World Bank, pp. 30. https://doi.org/10.20506/ecoAMR.3540. Licence: CC BY-SA 3.0 IGO.

PUBLICATION PHOTO CREDITS:
Cover image: AdobeStock_135936265, ironstealth

Forecasting the Fallout from AMR: Human Health Impacts of Antimicrobial Resistance

A report from the EcoAMR series

Stein Emil Vollset[1,2], Umut Altay[2], Natalia V Bhattacharjee[3], Julian Chalek[3], Konstantinos Giannakis[2], Authia Gray[3], Chieh Han[3], Paulina A Lindstedt[3], Mohsen Naghavi[3], Cat Raggi[3], Amanda E Smith[3], Georgia Smith[3], Lucien Swetschinski[3], Eve Wool[3], Chun-wei Yuan[3], Christopher J L Murray[3]

[1]Department of Health Metrics Sciences, University of Washington; [2]GBD Collaborating Unit, Norwegian Institute of Public Health, Bergen, Norway; [3]Institute for Health Metrics and Evaluation

World Organisation for Animal Health · AID Animal Industry Data · CGD Center for Global Development · Institute for Health Metrics and Evaluation · RAND Europe · The World Bank IBRD • IDA | World Bank Group

Contents

Figures

Tables

Foreword

Antimicrobial resistance (AMR) is a major global health threat. Understanding the global health burden of AMR, including the temporal trends in resistance and which populations are most at risk is important for developing policies and action plans to address the challenge that AMR poses. Further, forecasts and alternative scenarios can help us understand the potential gains if policies and investments are targeted appropriately.

Making an economic case for investment in the fight against AMR has been a challenge across the world, partly due to competing priorities at all levels. Paramount to establishing the required business case for sustainable investment to tackle AMR is cooperation – both within and across human and animal sectors – as well as collaboration with national and global stakeholders, and engagement of private partnerships. Thus, the World Organisation for Animal Health (WOAH) is collaborating with the United Kingdom Department of Health and Social Care (UK DHSC) to pool a consortium of international partners across the human and animal health sectors, who can implement this groundbreaking EcoAMR Series on health and economic consequences of AMR. The project aims to generate the necessary evidence that will inform bold and concrete commitments to mitigate AMR by member states at the United Nations General Assembly (UNGA) High Level Meeting (HLM) on AMR in 2024 and future actions by governments and policy-makers. Among this team are global experts from the Centre for Global Development and the Institute for Health Metrics and Evaluation, utilizing estimates from the Global Research on Antimicrobial Resistance (GRAM) Project to develop the human health component. Meanwhile, RAND Europe, Animal Industry Data and WOAH have addressed the animal health component of this cross-sector initiative. The World Bank has provided quality assurance via a team of global experts serving as peer reviewers of this study's methodologies and outputs. The results from this study will guide action-oriented declarations at the UNGA HLM on AMR, inform governments and policy-makers on effective interventions and policy-making, and facilitate sustainable financing.

In this report, *Forecasting the fallout from AMR: Human health impacts of antimicrobial resistance*, IHME presents forecasts of global and regional health burden due to AMR using historical estimates from the GRAM Project. This analysis also quantifies the health gains possible from key interventions, such as developing new antimicrobials that targets resistant bacteria, or improved healthcare for treating severe infections and better access to existing antimicrobials.

Christopher J.L. Murray
Director, Institute for Health Metrics and Evaluation

Executive summary

INTRODUCTION

Antimicrobial resistance (AMR) is an important future health threat. A recent report concluded that bacterial AMR caused 1.27 million deaths in 2019 and was associated with 4.95 million deaths, emphasising that AMR is an important health concern for the global community [1]. Building on a past time series with extended methodology and data, we utilised the forecasting framework that has been established for the Global Burden of Disease Study (GBD) to provide a reference forecast (the most likely future) and alternative scenarios for the disease burden of AMR for the years 2022–2050.

RESULTS

While the past time series showed relatively stable death numbers due to AMR from 1990 to 2021, the global number of deaths attributable (due) to AMR were forecast to increase by 60.00% (95% UI: 42.62–80.00) from 2022 to 2050, from 1.15 million (0.98–1.33) deaths in 2022 to 1.84 million (1.50–2.20) deaths in 2050. Cumulatively, the reference scenario forecast 38.52 million (32.02–45.04) global deaths due to AMR from 2025 to 2050. The number of deaths associated with AMR was 4.90 million (4.30–5.45) in 2022, and the forecast to 2050 is for 7.73 million (6.45–8.97). While the number of AMR attributable deaths and all-age (crude) death rates are forecast to increase globally and across GBD super-regions, age-standardised rates are forecast to decrease, pointing to population ageing and population growth as the key drivers of the increase in AMR burden. The future AMR burden is forecast to be highest in South Asia; Southeast Asia, East Asia and Oceania; and Sub-Saharan Africa. These overall death numbers conceal opposite trends by age. Globally and in every super-region, AMR deaths under 5 years of age are decreasing, most pronounced in absolute numbers in Sub-Saharan Africa and South Asia. For deaths of people 70 years and older, we forecast substantial increases from 2022 to 2050 in every super-region. The all-cause disability-adjusted life year (DALY) burden of AMR showed different patterns over time compared to deaths. Global DALY counts due to AMR decreased from 1990 to 2021, but flattened out in the future and only showed a moderate increase of around 5% from 2022 to 2050. This moderate increase in the future relative to the increase in deaths is driven by the DALY measure, which is weighted toward premature mortality and disability at younger ages, where we forecast declines in AMR burden in the future.

We assessed the impact of four alternative scenarios on the future AMR burden. A Gram-Negative Drug scenario explored the potential impact of establishing a pipeline for innovation of new drugs that are effective on gram-negative bacteria. Assuming that the pipeline would be fully effective by 2036 with a reduction of the gram-negative burden by 50%, we estimated that a total of 10.23 million (95% UI: 8.46–12.31) cumulative deaths between 2025 and 2050 could be averted. A Better Care scenario explored the impact of health system strengthening to treat infectious diseases by 2030 and was forecast to avert 89.84 million (80.79–99.51) deaths, with the largest impacts in Sub-Saharan Africa; South Asia; and Southeast Asia, East Asia and Oceania between 2025 and 2050. A Combined scenario assessed the impact that could be achieved by combining the Better Care and Gram-Negative Drug scenarios plus the gradual elimination of WASH (water, sanitation and hygiene) risk factors plus 100% vaccine coverage by 2050 for the modelled vaccines. The combined effects

of these scenarios were forecast to amount to averting 110.02 million (44.07–153.19) deaths cumulatively from 2025 to 2050. A pessimistic scenario on past rates of change in the inputs to the forecasting models indicated an excess of cumulative deaths from 2025 to 2050 of 6.69 million (6.05–7.33).

CONCLUSION

Antimicrobial resistance is a growing public health threat, and our forecasts suggest that deaths attributable to AMR will increase by 60.00% (95% UI: 42.62–80.00) between 2022 and 2050. Deaths under the age of 5 years are forecast to decrease globally and in all GBD super-regions, whereas we forecast more than a doubling in AMR deaths among persons 70 years and older. More than half of these deaths by 2050 will be in this oldest age group. In contrast to global deaths, DALY counts due to AMR only showed a moderate increase of around 5% from 2022 to 2050. Our alternative scenarios demonstrate the opportunity to drastically reduce the threat that AMR poses by strengthening health systems including access to antibiotics, scaling up the development of a robust drug pipeline, and continuing to reduce infections through vaccination campaigns and improvements to water, sanitation and hygiene. Particularly in Sub-Saharan Africa, these interventions would lead to substantial decreases in under-5 mortality, where burden among children is still relatively high.

Introduction

Antimicrobial resistance (AMR) is a major health problem and future health threat. With the UK Review on Antimicrobial Resistance initial report in 2014 [2] and final report in 2016 [3], AMR was solidly placed on the international agenda. With forecasts by 2050 of 10 million annual deaths due to AMR and a potential global economic loss of US$ 100 trillion, these reports led to broad concern of the social, economic and health consequences of not tackling further increases in drug resistance. A recent *Lancet* series on sustainable access to effective antibiotics provides a useful summary of the current status in this area [4].

The first detailed global and country-level report on AMR by drug and bacterial species concluded that bacterial AMR caused 1.27 million deaths in 2019 and was associated with 4.7 million deaths, emphasising that AMR is an important health concern for the global community [1].

Understanding the future disease burden due to AMR is important for policy-makers to design programmes and policies tailored to the communities likely to face the greatest burden, and develop strategies that improve access to effective, safe treatment. Further, alternative future scenarios are useful to understand the relative impact that can be achieved through various interventions across countries. Building on the GBD forecasting framework [5-7], combined with a new times series of bacterial AMR from 1990 to 2021 that extended the approach behind the estimates for the year 2019, this work forecast the bacterial AMR disease burden to 2050. We also included alternative future scenarios and the disease burden averted or in excess when compared with our reference forecast projections.

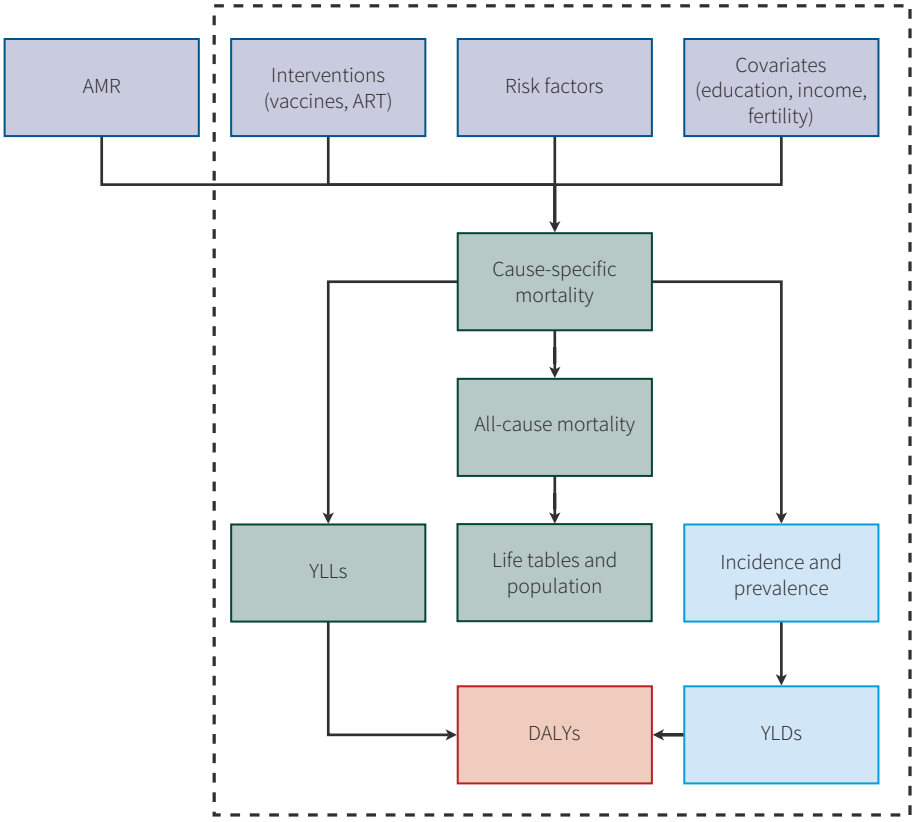
Methodology

The Institute for Health Metrics and Evaluation (IHME) future health scenarios framework uses estimates of disease burden, drivers of disease burden (such as risk exposure) and demographic indicators from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD).

FUTURE HEALTH SCENARIOS PLATFORM OVERVIEW

IHME's Future Health Scenarios Team generates forecast estimates based on GBD past estimates of 359 causes for 21 regions, seven super-regions, and at the global level, across five-year age groups and sex [5-7]. A description of the GBD framework as well as retrospective AMR estimates can be found in the GBD 2021 *Lancet* series and multiple AMR-specific publications [1,8-12]. Figure 1 illustrates an overview of the multi-staged forecasting modelling process. Our previous publications on forecasting provide detailed descriptions of the methods used to forecast the independent drivers, risk factors, mortality, demography indicators and disability-adjusted life years (DALYs) [5-7,13]. We use the reference forecasts (the most likely future) of cause-specific disease burden to estimate both deaths and DALYs *associated* with AMR

FIGURE 1 Schematic representation of antimicrobial resistance (AMR) forecasting modelling framework



Note: AMR = antimicrobial resistance; ART = antiretroviral therapy; YLLs = years of life lost; YLDs = years lived with disability; DALYs = disability-adjusted life years. Purple shading indicates drivers of health burden, green indicates measures of fatal disease burden and demography, blue indicates non-fatal disease burden and red indicates the total disease burden.

(number of deaths and DALYs among people who have a resistant infection) and mortality and DALYs *attributable* to AMR (number of deaths and DALYs due to AMR). Additionally, we produce three policy-based scenarios of *averted* mortality burden (number of deaths and DALYs that can be potentially avoided if a particular policy is implemented), and one pessimistic alternative scenario of excess burden. All modelling is done by age, sex, location and year such that aggregate results (e.g. all-age, global or regional findings) capture trends at the most granular level of detail possible.

FORECASTING AMR POPULATION ATTRIBUTABLE FRACTIONS

To incorporate AMR into the forecasting framework, we used historical estimates of deaths due to AMR (attributable deaths) by GBD cause [12] and computed 19 population attributable fractions (PAFs) for GBD Level 2 causes with AMR attributable death counts.

We forecast the fraction of cause-specific deaths due to AMR using a Generalized Ensemble Model (GenEM). GenEM utilises 12 different sub-models (or child models) where we employ two main modelling approaches: the weighted annualised rate of change (ARC) and a two-stage spline model based on the meta-regression – Bayesian, regularised, trimmed tool (MR-BRT) [14]. Each of these models had six different recency-weighting parameters ranging from 0 to 2.5 (the higher the weight, the more weight given to recent years).

For the ARC child models, we calculated the age-standardised, sex-specific and location-specific annual change of the logit-transformed AMR PAF values. To account for the effect of noisy data, we replaced annual changes outside the 2.5th and 97.5th percentiles with those corresponding percentile-values. The two-stage MR-BRT child models used the first stage to fit age-standardised, sex-specific logit of the AMR PAF on SDI:

$$logit(AMR\ PAF_{c,s,t}) = \beta_0 + \beta_1 spline(SDI_{c,t}) + \varepsilon_{c,s,t}, \quad (1)$$

where $logit(AMR\ PAF_{c,s,t})$ is the logit of the age-standardised AMR PAF in country c, sex s and year t, β_0 is an intercept, β_1 is a coefficient matrix, spline is the spline with five knots placed evenly across the distribution of SDI data and assumes both right and left linear tails, and $\varepsilon_{c,s,t}$ is the residual. This was then followed by the second stage, where the logit of the residuals from the first stage was modelled linearly on time (year):

$$logit(\varepsilon_{c,s,t}) = year_t + \lambda + \Psi_{c,s,t}, \quad (2)$$

where λ is a fixed intercept value and $\psi_{c,s,t}$ is an error term. This model was chosen based on the predictive strength of SDI as a covariate and to capture additional temporal trends in the residual that were not fully captured by SDI.

The weight of each sub-model was defined by running out-of-sample predictive validity experiments. We trained each sub-model based on data from 1990–2011 and validated each sub-model based on 2012–2021 data. We measured each child model's performance using root mean square error (RMSE), based on which we determined sampling weights of each child model.

We then produced the sub-model forecasts based on the 1990–2021 training dataset. For each ARC child model, we used the calculated annual change with the corresponding recency-weighting parameter to produce 2022–2050 AMR PAF forecasts. For the MR-BRT child models, we used forecast SDI values in addition to the recency weights to obtain forecasting values of AMR PAFs based on the model fit.

We then obtained the final AMR PAFs ensemble forecasts by taking a mean over the child models using the sampling weights from the out-of-sample experiments.

COMPUTING FUTURE ATTRIBUTABLE AND ASSOCIATED AMR BURDEN

To compute the attributable AMR burden, we first multiplied our reference mortality and years of life lost (YLL) forecasts for 22 cause groups at the age–sex–location level by the forecast AMR PAFs described in the above section. We then applied a scalar to the attributable YLLs using the global ratio of YLL:YLD

AMR deaths in 2019 [1] to compute AMR-attributable YLDs. Finally, we summed AMR-attributable YLL and YLD results to compute AMR-attributable DALYs.

To compute the associated AMR burden, first, we computed the ratio of AMR-associated deaths to AMR-attributable deaths for 22 cause groups by age–sex–location in the year 2021. We then used this ratio to multiply our AMR PAFs and calculate associated burden forecasts for each measure the same way we computed attributable burden as described above. All modelling computations were done on 500 draws to propagate uncertainty from all sources, and estimates provided represent the mean and 95% uncertainty interval across 500 draws for all measures.

DEVELOPING AMR ALTERNATIVE SCENARIOS

In addition to a reference forecast, our framework allows us to produce four AMR alternative scenarios of disease burden. These scenarios were applied to all locations. In instances where the reference forecast for a given location was more optimistic than the defined alternative scenario, the reference forecast was used.

Gram-Negative Drug scenario

Gram-Negative Drug scenario is defined as a regular release of new drugs targeting gram-negative bacteria. For this scenario, we first calculated the fraction of AMR-attributable deaths due to gram-negative infections in the year 2021 ($fraction_{AMR\_deaths}$). We then multiplied the future reference scenario AMR PAFs by $fraction_{AMR\_deaths}$ and (1 – $fraction_{AMR\_deaths}$) to obtain future *gram-negative PAFs* and future *non gram-negative PAFs*, respectively.

Afterwards, for the future *gram-negative PAFs*, we decreased the gram-negative PAFs linearly from 2021 to 2036 until the PAFs value in 2036 was 50% of the PAFs value in 2021, and then held them constant from 2037 to 2050. Then, we added the *non-gram-negative PAFs* to *scenario gram-negative PAFs* to determine the total PAFs based on the Gram-Negative Drug scenario. Finally, we calculated the fraction of the resulting total PAFs ($fraction_{AMR\_PAFs}$) and then multiplied this fraction by the mortality to obtain the number of deaths *attributable* to AMR for the Gram-Negative Drug scenario.

Better Care scenario

The Better Care scenario is associated with improved case-fatality rates for 11 infectious syndromes, leveraging retrospective estimates reflective of varying health system strength. To calculate the death rates for this scenario ($m_{c\_scenario,t}$) for a cause c at time t, we used case-fatality ratios (CFRs) that varied by age, location and infectious syndrome; fraction of cause due to infectious syndrome:

$$m_{c\_scenario,t} = m_{c,t}\left(1-\sum_{i=1}^{n_s} F_{cs}(1-CFR\_ratio_s)\right)_t$$

where $m_{c,t}$ is the total death rate for a cause c at time t, n_s is the number of infectious syndromes, CFR_ratio_s is a required relative reduction in CFR for an infectious syndrome, and F_{cs} is the fraction of a cause due to an infectious syndrome. The fraction of a cause due to sepsis is accounted for in F_{cs}. The detailed description of sepsis and infectious syndromes definitions can be found in the appendix of the GBD 2021 AMR publication [12].

CFR_ratio_s for infectious syndrome was calculated as $CFR_{s,HAQ\,=\,84.16}/CFR_{ls,2021}$ where $CFR_{s,HAQ\,=\,84.16}$ is CFR value for an infectious syndrome that corresponds to the 85th percentile of Healthcare Access and Quality (HAQ) Index [15] in 2021 (HAQ Index = 84.16) by location and age group; $CFR_{ls,2021}$ is the CFR value in 2021 by location and age group. We chose the 85th percentile of HAQ Index to capture the progress required by 2030 in a country where access to and quality of health care needs improvement (HAQ Index in the majority of high-income countries is already above 84.16 in 2021). To obtain the value of $CFR_{s,HAQ\,=\,84.16}$, we used the age-specific relationship of HAQ Index and CFR across 204 countries for 11 major infectious syndromes. The relationship curves can be found in the GBD 2021 AMR publication [12].

Combined scenario

The combined scenario includes scenarios (1) and (2) plus improved vaccination and improved water/sanitation/hygiene (WASH). For improved vaccination, we applied a linear increase in vaccine coverage from 2023 to 100% by 2050 in all locations for all six modelled vaccines: third-dose diphtheria, tetanus and pertussis (DTP3) vaccine; measles conjugate vaccine doses 1 and 2 (MCV1 and MCV2); *Hemophilus influenzae* type B (HiB) vaccine; pneumococcal conjugate (PCV3) vaccine; and rotavirus vaccine (Rota). For improved WASH, we applied a linear reduction in summary exposure values (SEVs) to unsafe water, unsafe sanitation and hygiene to zero from 2023 to 2050, i.e. full elimination of exposure to unsafe WASH by 2050.

Pessimistic scenario

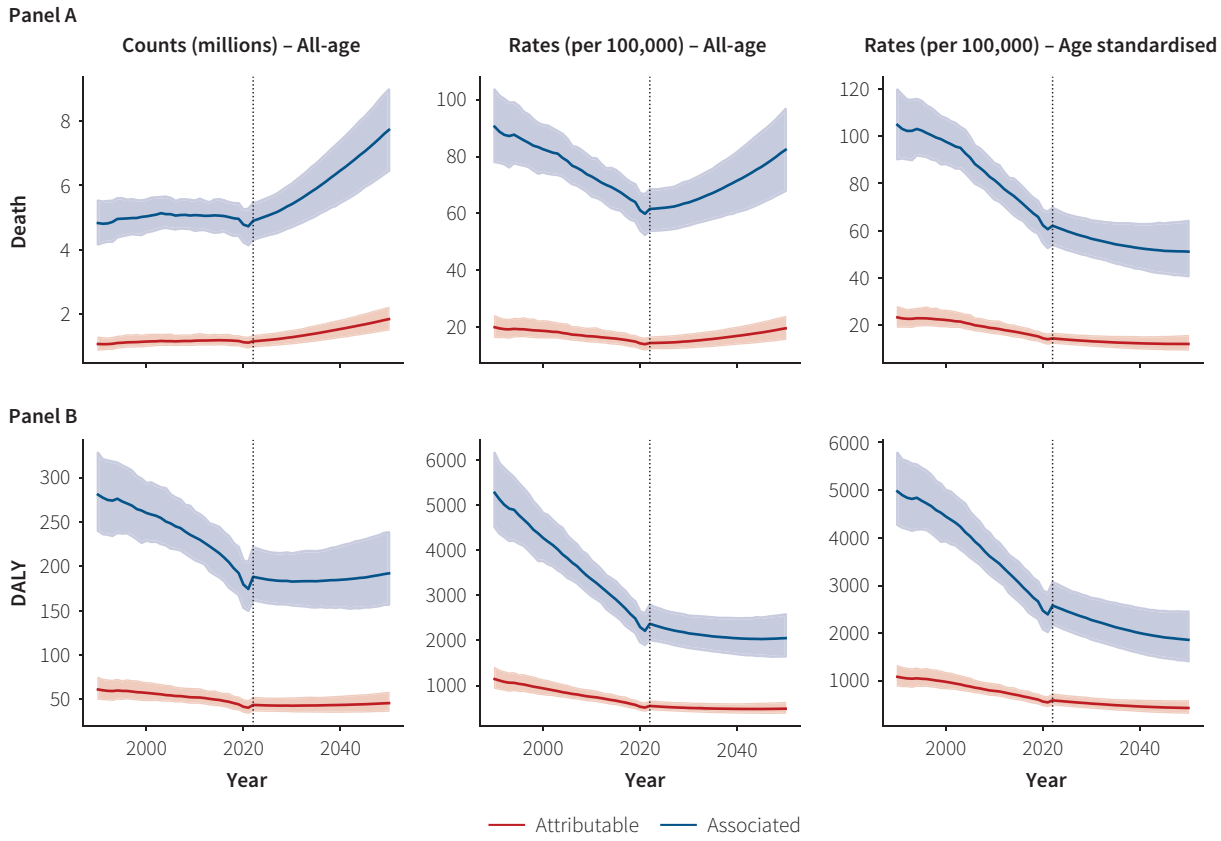
For the pessimistic scenario, we projected the future AMR burden based on the 15th percentile of past rates of change across locations and years. This was done using the Generalized Ensemble Model, where the six annualised rate of change (ARC) sub-models calculated the 15th percentile ARC across location-years in the past and applied these to future projections, and the six MR-BRT sub-models used the 15th percentile rate of change in Socio-demographic Index (SDI). The 15th percentile was chosen as a plausibly pessimistic observed rate of change from the past.

Results

GLOBAL AND REGIONAL BURDEN OF AMR IN 2050 IN THE REFERENCE SCENARIO

The global number of deaths attributable to and associated with AMR changed very little from 1990 to the present but showed a substantial increase to 2050 (Figure 2). The number of deaths attributable to AMR in 2022 (the first year of forecasts) was 1.15 million (95% UI: 0.98–1.33), and the forecast to 2050 was 1.84 million (1.50–2.20) deaths, an increase of 60.0% (Table 1). Cumulatively, the reference scenario forecast 38.52 (32.02–45.04) global deaths due to AMR from 2025 to 2050. The number of deaths associated with AMR was 4.90 million (4.30–5.45) in 2022, and the forecast to 2050 was 7.73 million (6.45–8.97). Figure 2 further shows a decreasing trend from 1990 to the present for all-age (crude) and age-standardised death rates. The forecasts show an increasing global trend for all-age but a decreasing trend in age-standardised AMR attributable death rates, suggesting that ageing and population growth drive the forecast increases in death counts. Figure 3 shows the trends in death counts and all-age and age-standardised

FIGURE 2 Global attributable and associated AMR burden (A) deaths and (B) DALYs in the reference scenario, 2022–2050



Note: shading represents the 95% uncertainty interval. The vertical line is placed at the year 2021 to distinguish estimates from forecasts.

TABLE 1 AMR associated and attributable death and DALY counts in millions, globally and by super-region in the reference scenario, 2022 and 2050

	Attributable deaths in 2022	Associated deaths in 2022	Attributable deaths in 2050	Associated deaths in 2050	Attributable DALYs in 2022	Associated DALYs in 2022	Attributable DALYs in 2050	Associated DALYs in 2050
Global	1.15 (0.98, 1.33)	4.90 (4.30, 5.45)	1.84 (1.50, 2.20)	7.73 (6.45, 8.97)	42.37 (35.81, 50.68)	183.18 (157.16, 215.39)	44.35 (35.59, 56.14)	186.99 (152.68, 231.92)
Central Europe, Eastern Europe and Central Asia	0.06 (0.05, 0.07)	0.27 (0.23, 0.30)	0.08 (0.06, 0.09)	0.33 (0.28, 0.38)	1.69 (1.42, 2.00)	7.15 (6.27, 8.00)	1.54 (1.26, 1.85)	6.60 (5.66, 7.73)
Southeast Asia, East Asia and Oceania	0.26 (0.21, 0.31)	1.16 (0.97, 1.36)	0.39 (0.31, 0.45)	1.71 (1.37, 1.99)	6.86 (5.73, 8.14)	30.39 (25.72, 35.34)	7.01 (5.75, 8.31)	30.75 (25.60, 35.81)
High-income	0.12 (0.09, 0.13)	0.56 (0.44, 0.62)	0.16 (0.12, 0.18)	0.74 (0.56, 0.85)	2.12 (1.81, 2.35)	9.81 (8.51, 10.65)	2.28 (1.82, 2.58)	10.52 (8.66, 11.75)
Latin America and Caribbean	0.08 (0.07, 0.09)	0.34 (0.29, 0.38)	0.13 (0.11, 0.16)	0.59 (0.48, 0.70)	2.22 (1.88, 2.63)	9.62 (8.32, 11.12)	2.57 (2.09, 3.16)	11.22 (9.35, 13.68)
North Africa and Middle East	0.06 (0.05, 0.07)	0.24 (0.20, 0.28)	0.13 (0.10, 0.16)	0.53 (0.43, 0.65)	2.25 (1.81, 2.78)	9.13 (7.43, 11.06)	3.29 (2.54, 4.28)	13.26 (10.30, 16.97)
South Asia	0.35 (0.27, 0.46)	1.34 (1.11, 1.57)	0.63 (0.47, 0.86)	2.39 (1.87, 2.99)	13.68 (10.38, 17.67)	54.6 (44.61, 65.54)	14.50 (10.59, 20.34)	55.41 (42.52, 72.08)
Sub-Saharan Africa	0.22 (0.17, 0.29)	1.00 (0.78, 1.25)	0.32 (0.25, 0.41)	1.43 (1.15, 1.78)	13.53 (9.86, 17.84)	62.47 (45.41, 81.13)	13.15 (9.50, 17.66)	59.24 (43.04, 81.62)

FIGURE 3 Attributable and associated AMR burden (A) deaths and (B) DALYs in the reference scenario by GBD super-region, 2022–2050

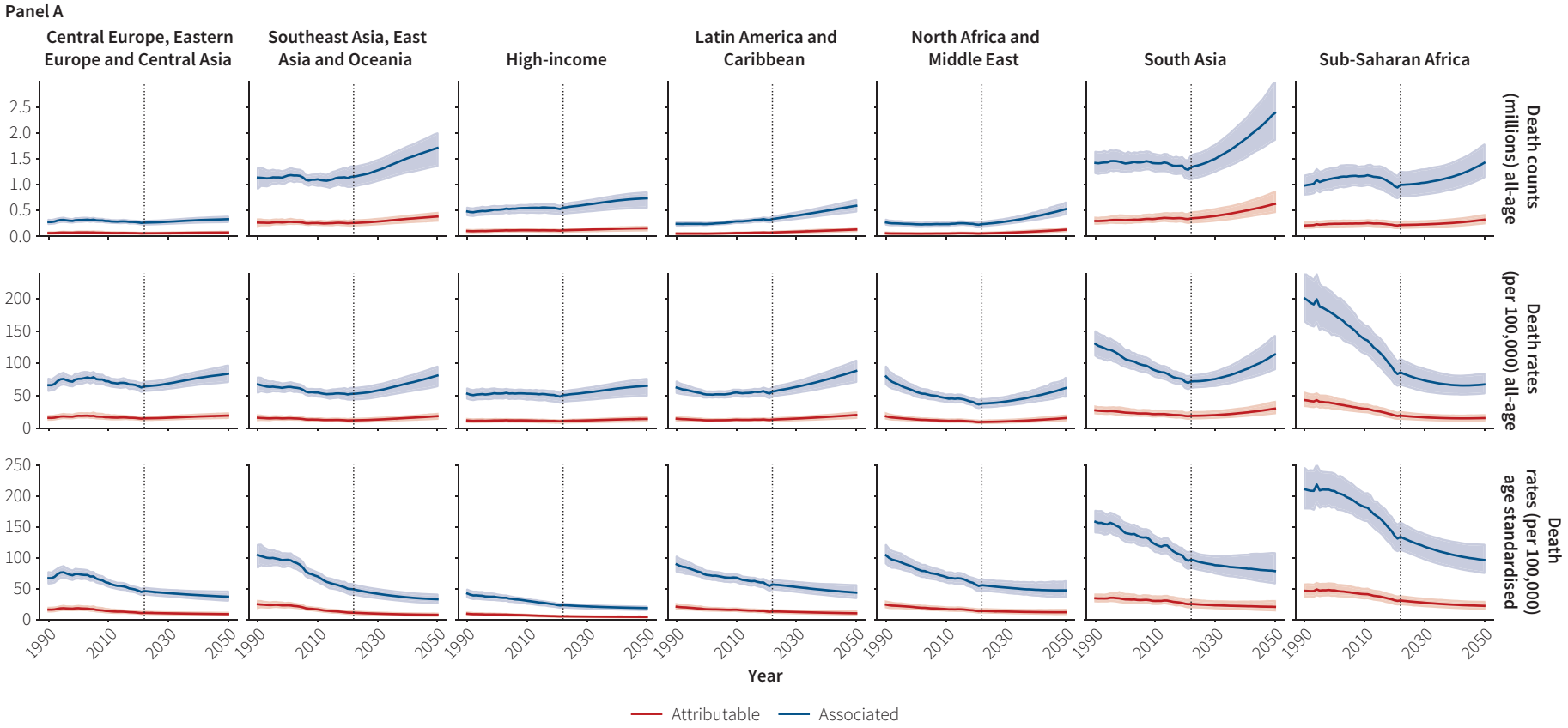
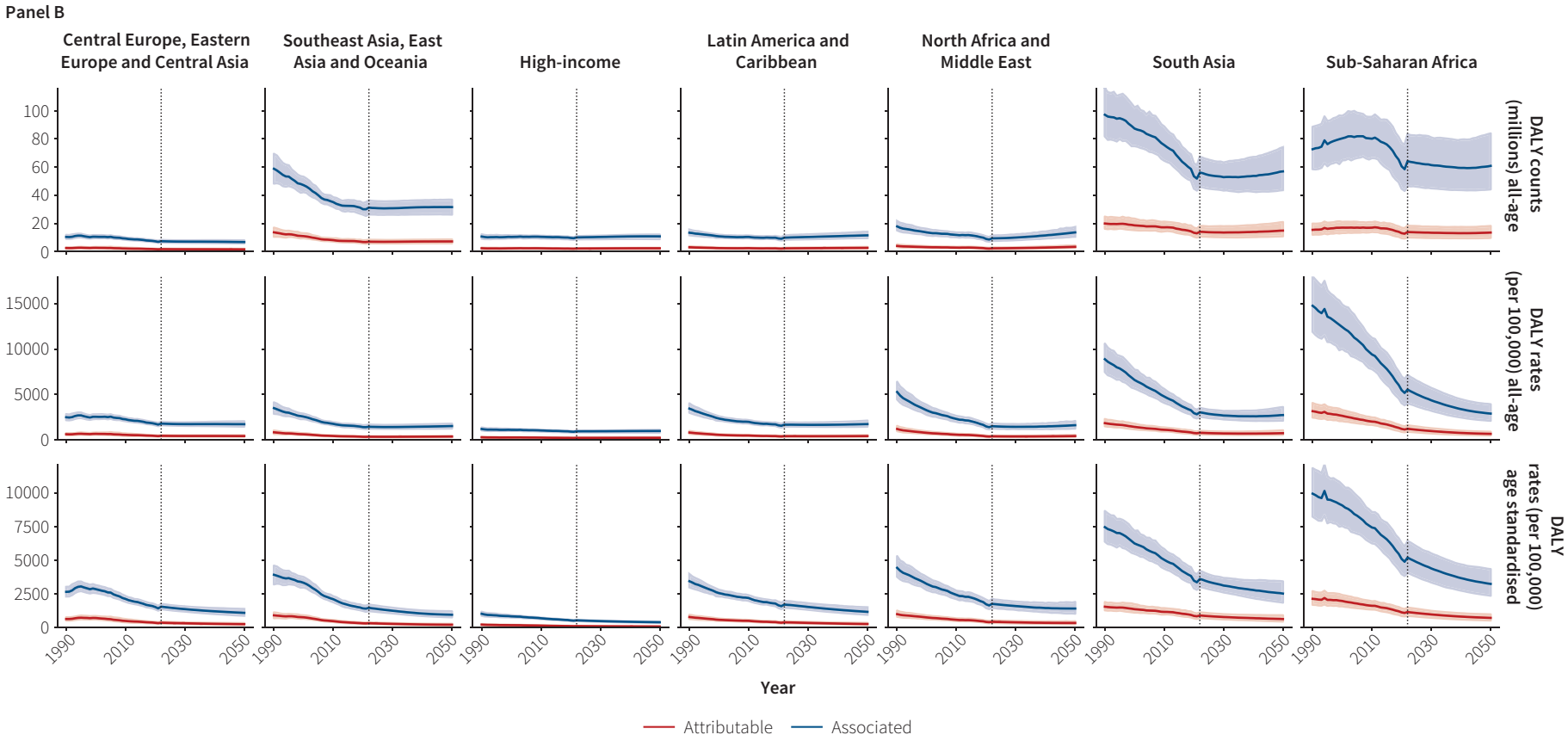


FIGURE 3 *(Continued)*



Note: shading represents the 95% uncertainty interval. The vertical line is placed at the year 2021 to distinguish estimates from forecasts.

death rates by GBD super-region. For deaths associated with and attributable to AMR, the general pattern for number of deaths and all-age rates is an increasing trend, except in Sub-Saharan Africa, where the all-age trend is decreasing and levelling off toward 2050. Both for deaths attributable to and associated with AMR, age-standardised trends are decreasing in every super-region. The future AMR burden is highest in South Asia; Southeast Asia, East Asia and Oceania; and Sub-Saharan Africa, with the forecast cumulative AMR death burden from 2025 to 2050 at 12.42 million (9.51–16.53), 8.50 million (6.90–9.93), and 6.81 million (5.27–8.59), respectively (Table 2).

In contrast to the time trends for deaths, the global counts of AMR-attributable DALYs in the reference scenario showed a decreasing trend from 1990 to the present, and only a moderate increase of 4.7% from 42.37 million (35.81–50.68) in 2022 to 44.35 million (35.59–56.14) DALYs in 2050 (Table 1 and Figure 2). Global all-age (crude) DALY rates showed a steeper decreasing trend from 1990 to the present and a flat future trend. As for age-standardised global death rates, the age-standardised DALY rates showed a decreasing trend in the past that continued into the future with a moderately diminished downward slope. The cumulative (2025–2050) DALY burden of AMR attributable DALYs was forecast to be highest in the South Asia super-region with 353.65 million (262.87–475.78) DALYs followed by Sub-Saharan Africa (336.13 [243.50–445.76]) and Southeast Asia, East Asia and Oceania (179.70 million DALYs [148.87–211.73]).

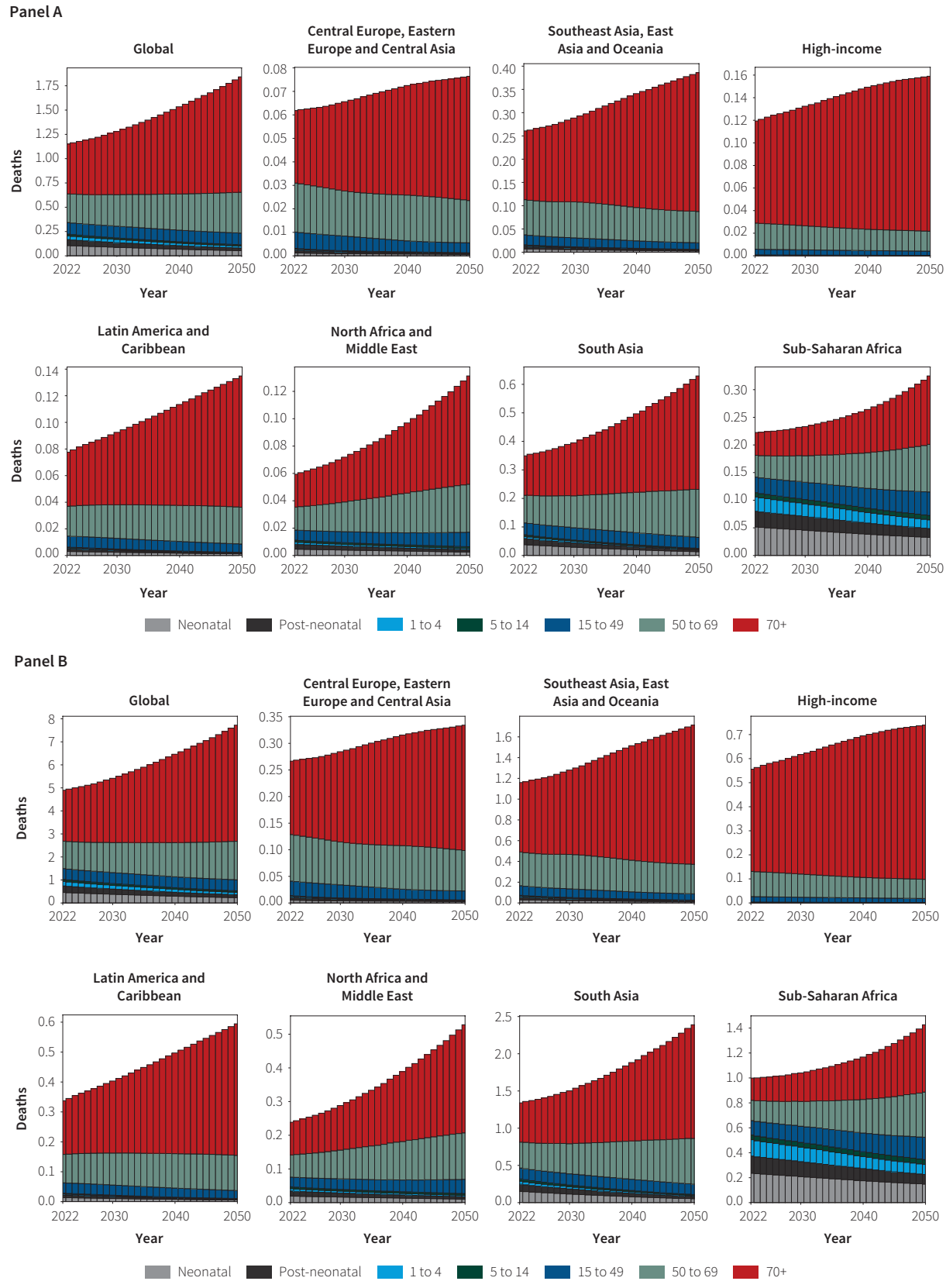
AGE PATTERNS

These overall death numbers conceal opposite trends by age. Globally and in every super-region, deaths under 5 years of age are decreasing, most pronounced in absolute numbers in Sub-Saharan Africa and South Asia. For deaths of people 70 years and older, we forecast an increase from 2022 to 2050 in every super-region (Figure 4). The increase in the 70+ age groups was 131% globally and ranged between 51% in the high-income and 230% in the North Africa and the Middle East super-regions. These diverging trends in younger and older ages contribute to the increases seen in all-age death rates and counts globally, as the population shifts toward older ages over time.

TABLE 2 Cumulative AMR associated and attributable death and DALY counts in millions, globally and by super-region in the reference scenario, 2025–2050

	Attributable deaths	Associated deaths	Attributable DALYs	Associated DALYs
Global	38.52 (32.02, 45.30)	162.37 (138.32, 184.91)	1,102.63 (906.30, 1,346.92)	4,694.30 (3,919.37, 5,636.79)
Central Europe, Eastern Europe and Central Asia	1.83 (1.51, 2.13)	7.95 (6.80, 8.97)	41.55 (34.50, 49.29)	177.29 (153.86, 202.19)
Southeast Asia, East Asia and Oceania	8.50 (6.90, 9.93)	37.73 (31.04, 43.51)	179.70 (148.87, 211.73)	790.56 (666.31, 917.40)
High-income	3.74 (2.86, 4.30)	17.41 (13.44, 19.81)	58.12 (47.64, 65.12)	268.36 (225.47, 295.50)
Latin America and Caribbean	2.82 (2.30, 3.33)	12.34 (10.30, 14.32)	63.02 (52.29, 75.87)	273.61 (231.19, 325.31)
North Africa and Middle East	2.40 (1.97, 2.94)	9.65 (8.10, 11.62)	70.46 (55.97, 88.96)	284.03 (228.90, 353.52)
South Asia	12.42 (9.51, 16.53)	47.15 (38.32, 56.87)	353.65 (262.87, 475.78)	1,368.18 (1,091.93, 1,695.67)
Sub-Saharan Africa	6.81 (5.27, 8.59)	30.15 (23.83, 37.41)	336.13 (243.50, 445.76)	1,532.27 (1,121.10, 2,049.80)

FIGURE 4 Deaths due to (A) and associated with (B) AMR by age group and location in the reference scenario, 2022–2050, in millions



Note: units are in millions.

In the under-5 age group, the number of AMR attributable deaths decreased from 206 thousand (95% UI: 152–273) to 100 thousand (64–150) globally, a decrease of 51.46% (36.90–62.84). Among the super-regions, the decreases ranged from 39.31% (21.72–53.89) in Sub-Saharan Africa to 67.08% (56.68–76.00) in South Asia.

IMPACT OF SCENARIOS

We assessed the impact of four alternative scenarios on the future AMR burden. A Gram-Negative Drug scenario explored the potential impact of establishing a pipeline for innovation of new drugs that are effective on gram-negative bacteria. Assuming that the pipeline would be fully effective by 2036, with a reduction of the gram-negative burden by 50%, we estimated that a total of 10.23 million (95% UI: 8.46–12.31) cumulative deaths between 2025 and 2050 could be averted (Table 3). The impact would be largest in South Asia, followed by Southeast Asia, East Asia and Oceania, and Sub-Saharan Africa (Table 3; Figure 5, Panel A). A Better Care scenario was forecast to avert 89.84 million (80.79–99.51) deaths, with the largest impacts in Sub-Saharan Africa, South Asia, and Southeast Asia, East Asia and Oceania (Table 3; Figure 5, Panel B). A Combined scenario assessed the impact that could be achieved by combining the Better Care and Gram-Negative Drug scenarios plus the gradual elimination of WASH risk factors, plus 100% vaccine coverage by 2050 for the modelled vaccines. The combined effects of these scenarios were forecast to amount to averting 110.02 million (44.19–153.19) deaths cumulatively from 2025 to 2050. Again, the impacts were largest in the super-regions of Sub-Saharan Africa; South Asia; and Southeast Asia, East Asia and Oceania (Table 3; Figure 5, Panel C). A pessimistic scenario on past rates of change in the inputs to the forecasting models of the cause Level 2 AMR PAFs indicated an excess of cumulative deaths from 2025 to 2050 of 6.69 million (6.05–7.33) (Table 3; Figure 5, Panel D).

Scenario impact by age

The Better Care scenario was forecast to have the largest overall impact on the burden measured in cumulative number of deaths averted from 2025 to 2050. Globally, 10.50 million (95% UI: 8.22–13.32) of these averted deaths (11.67% [9.57–13.86]) were forecast to occur in the under-5 age group. Close to two-thirds of the forecast averted burden of under-5 deaths (6.89 million [5.17–8.85]) were in Sub-Saharan Africa (Figure 6).

TABLE 3 Cumulative total deaths avoided/excess in millions, globally and by super-region and scenario, 2025–2050

	Gram-Negative Drug	Better Care	Combined	Pessimistic
Global	10.23 (8.46, 12.31)	89.84 (80.79, 99.51)	110.02 (44.19, 153.19)	–6.69 (–6.05, –7.33)
Central Europe, Eastern Europe and Central Asia	0.49 (0.40, 0.57)	2.28 (2.04, 2.56)	2.91 (–3.65, 7.57)	–0.29 (–0.27, –0.32)
Southeast Asia, East Asia and Oceania	1.83 (1.49, 2.20)	18.27 (13.95, 22.36)	19.99 (–2.1, 38.48)	–2.34 (–2.09, –2.60)
High-income	0.63 (0.48, 0.73)	2.56 (1.59, 3.77)	2.58 (–1.66, 6.47)	–0.98 (–0.83, –1.06)
Latin America and Caribbean	0.71 (0.57, 0.85)	7.00 (6.13, 7.95)	8.05 (1.54, 11.28)	–0.58 (–0.51, –0.65)
North Africa and Middle East	0.65 (0.54, 0.80)	3.99 (3.31, 4.82)	4.96 (–4.93, 10.52)	–0.49 (–0.43, –0.55)
South Asia	3.91 (2.93, 5.35)	31.11 (26.32, 36.60)	37.01 (25.94, 42.17)	–0.93 (–0.78, –1.07)
Sub-Saharan Africa	2.00 (1.54, 2.55)	24.63 (20.67, 29.12)	34.53 (31.90, 36.60)	–1.08 (–0.92, –1.27)

FIGURE 5 Cumulative deaths averted (in millions) by scenario compared to reference by location, 2025–2050

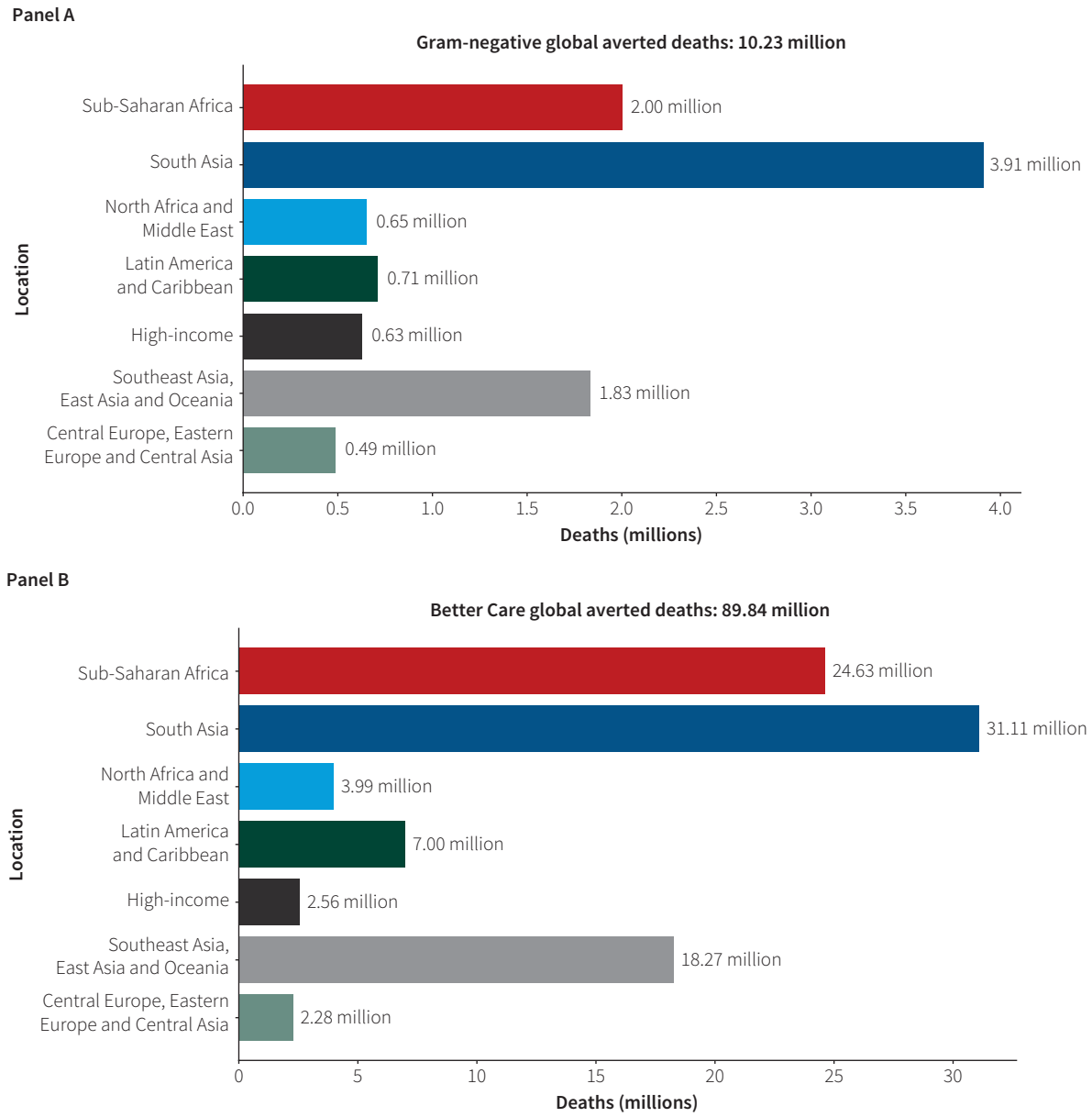
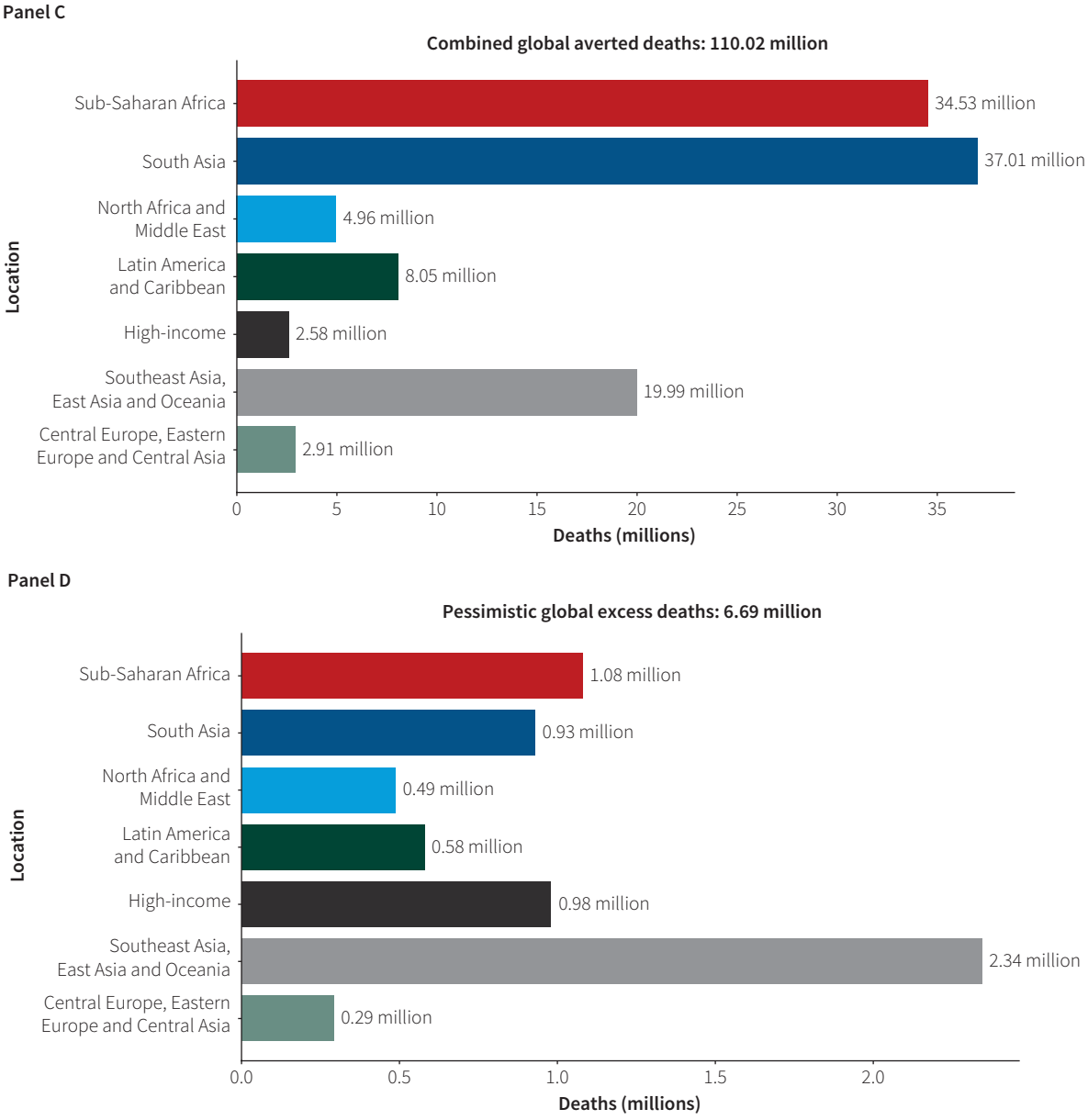


FIGURE 5 *(Continued)*



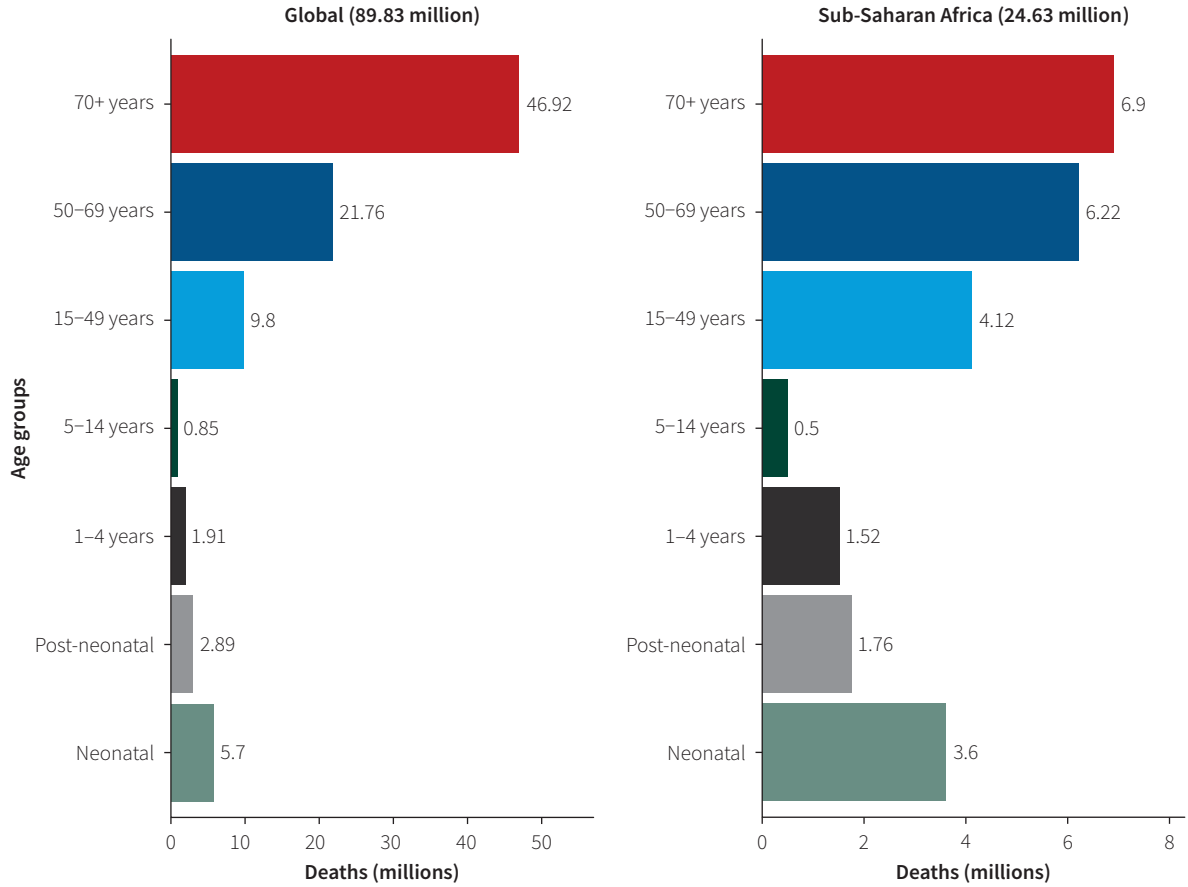
Note: pessimistic scenario depicts excess deaths (in millions) compared to reference.

Globally, more than half (52.27% [45.90–56.97]) of the potentially averted deaths are forecast to occur in the 70+ age group. Among super-regions, with the exception of Sub-Saharan Africa and North Africa and the Middle East, the percentages range from 55.70% (49.61–60.29) in South Asia to 80.54% (70.16–87.64) in the high-income super-region. In Sub-Saharan Africa, 28.17% (24.52–32.19) of the potentially averted deaths in the Better Care scenario are forecast to occur in persons aged 70 or older, and 27.88% (24.27–31.49) of averted deaths were forecast to happen in children under 5 years of age, the majority of these in the neonatal age group with 14.62% (12.58–16.99) (Figure 6).

THE DALY BURDEN OF AMR

We also computed the DALY burden of AMR. The number of DALYs attributable to AMR increased only moderately (4.68%) from 2022 to 2050, from 42.37 million (35.81–50.68) to 44.35 million (35.59–56.14). The relative increase was similar in DALYs associated with AMR (Table 1). As for deaths associated with or attributable to AMR, the largest cumulative DALY burden occurred in South Asia; Sub-Saharan Africa; and Southeast Asia, East Asia and Oceania. However, a larger share of the burden was forecast in Sub-Saharan Africa relative to Southeast Asia, East Asia and Oceania (Table 2).

FIGURE 6 Cumulative deaths averted (in millions) in the Better Care scenario by age, global *versus* Sub-Saharan Africa, 2025–2050



Discussion

Our forecasts suggest an increasing burden from antimicrobial resistance in the coming decades, with 1.84 million (95% UI 1.50–2.20) deaths attributable (due) to AMR and 7.73 million (6.45–8.97) associated with AMR in 2050. Cumulatively, AMR is forecast to be responsible for 38.52 million (32.02–45.30) deaths from 2025 to 2050 and associated with 162.37 million (138.32–184.91) deaths globally. Increases from 2022 to 2050 are projected to be largest among older adults (131.29% [112.43–151.27] increase in AMR deaths among those aged 70 and older) and outpace the declines that are predicted in children under the age of 5 (51.44% [36.90–62.84] reduction in AMR deaths). Similar increases are projected for deaths associated with AMR, with 7.73 million (6.45–8.97) deaths associated with AMR burden in 2050, 5.04 (4.08–5.77) among adults 70+, and 0.46 (0.29–0.69) among children under 5. An increase in total burden and a continued shift in the burden toward older adults is driven by increases in population size and a shift in the age structure of the population toward older ages over time, as age-standardised rates of AMR deaths are projected to decline from 14.49 (12.44–16.72) deaths per 100,000 in 2022 to 12.14 (9.56–15.66) deaths per 100,000 in 2050.

Regionally, South Asia is forecast to experience the most deaths due to AMR (629.46 thousand [473.44–856.95] deaths in 2050), followed by Southeast Asia, East Asia and Oceania (386.02 thousand [307.04–453.20] deaths in 2050) and Sub-Saharan Africa (324.87 thousand [254.42–413.27] deaths in 2050). These patterns also reflect the large shifts in the age structure of the populations forecast in these regions, where the proportion of the population above the age of 70 is forecast to increase from 4.05% in 2022 to 10.15% in 2050 in South Asia. We forecast an even stronger shift in the population above the age of 70 in Southeast Asia, East Asia and Oceania from 7.36% in 2022 to 18.38% in 2050, and only minor ageing in Sub-Saharan Africa. For Sub-Saharan Africa we forecast the strongest growth in the population size of 82.3% from 2022 to 2050 and only a moderate increase in South Asia of 12.8% and a minor decrease in population size of Southeast Asia, East Asia and Oceania of 3.7% (suppplemental results can be found in Figure S9 in Vollset *et al.* [7]).

The same forecast aging and population growth trends explain the contrast between AMR death and DALY burden. More than 95% of the DALY burden is from YLLs. YLLs are computed from deaths weighted by the expected remaining life years at the time of death calculated from the GBD reference life table. This means that the increasing AMR deaths above 70 years of age are strongly down-weighted in the DALY measure compared to counting deaths equally at any age. This explains the relatively flat future trend in AMR DALY counts *versus* the strong increase in death counts. Furthermore, the strong global reduction in under-5 deaths that has been observed from 1990 to the present from 11.28 million (10.72–11.84) to 4.66 million (3.98–5.50) in 2020 is a major driver behind the decrease in AMR deaths under 5 years of age [10].

Our forecasts suggest the 10-20-30 targets [4,16] are unlikely to be met without significant, concerted efforts on infection prevention, equitable access to antibiotics and stewardship [17]. Findings from our alternative scenarios highlight the opportunity for progress. Effective development and distribution of new gram-negative drugs could result in 10.23 million (95% UI 8.46–12.31) deaths averted from 2025 to 2050, accounting for approximately one-third of the 38.52 million (32.02–45.30)

deaths forecast under the reference scenario. Our Better Care scenario estimates a substantially larger impact, with 89.84 million (80.79–99.51) cumulative deaths averted from 2025 to 2050, as efforts to prevent infection, strengthening of the health care systems including increased access to antibiotics, particularly in low- and middle-income settings, will prevent deaths above and beyond those caused by resistance. Further, increasing vaccination coverage and improvements to sanitation, clean water and hygiene, combined with improved access to antibiotics and gram-negative drugs, could result in 110.02 million (44.07–153.19) averted deaths by 2050.

LIMITATIONS

As with any modelling or forecasting analysis, there are several limitations to these projections that are important to consider. First, this analysis used historical estimates of disease burden of AMR from the Global Research on Antimicrobial Resistance (GRAM) project. GRAM uses data from around the world on deaths related to infections, prevalence of resistance and pathogen-drug combinations, and the distribution of pathogens by infectious syndrome. These estimates are subject to data quality and availability limitations, particularly in low- and middle-income settings, which lead to reduced accuracy in the estimates. Hence, the forecasts carry those same limitations forward. Also, the GRAM project focused on bacterial AMR leading to under-estimation of the total AMR burden as resistance associated with HIV and other viral diseases, fungal and parasitic diseases (e.g. malaria) are not included. Second, we forecast the cause-specific burden due to antimicrobial resistance as an aggregate entity rather than forecasting individual pathogens or drug-bug combinations. Future iterations of this work will attempt to expand the granularity of the forecast entities to include pathogen distributions. Third, our alternative scenarios include several assumptions: we assume that the proportion of AMR attributable deaths that are caused by gram-negative bacteria will remain constant in the future and that the impact of releasing new gram-negative drugs will result in a 50% decline in the gram-negative AMR deaths over the course of 15 years. Scale-up of these drugs may vary by region, and the effectiveness of these drugs may vary as well. Our Better Care scenario assumes improvements in case-fatality rates of infectious syndromes that reach levels observed in settings with a Healthcare Access and Quality (HAQ) Index [15] measure at the 85th percentile across locations globally. This reduction in case-fatality rates reflects not only an improvement in antibiotic access but also health system improvements and general development, such as improved WASH, health facility readiness or health workforce capacity. Because of data limitations, we have not been able to separate the impact of better access to antibiotics from other aspects of health care improvements. As with most scenario specifications some of these assumptions are arbitrary and other choices would have changed the results. Lastly, our combined scenario demonstrates the overall effect of the Better Care and Gram-Negative Drug scenarios plus gradual elimination of WASH risk factors and gradual attainment of 100% vaccine coverage by 2050. Both of the latter targets may seem unrealistic, but they were chosen to demonstrate the maximum opportunity for disease burden reduction rather than being attainable as real-world goals. Future iterations of this work could include scenarios focused on improved stewardship if sufficient data exists to estimate historic trends in these measures. Despite these limitations, this study represents the most comprehensive analysis forecasting the burden of antimicrobial resistance to population health under different scenarios and is an important tool for decision-makers to tackle this growing public health threat.

Conclusion

Antimicrobial resistance is a growing public health threat, and our forecasts suggest 38.52 million (95% UI: 32.02–45.04) cumulative deaths due to AMR by 2050, and 162.34 million (138.32–184.91) cumulative deaths associated with AMR in 2050. More than half of these deaths by 2050 will be among those 70 years or older, emphasising the need for a multipronged approach to addressing not only infection treatment and control but strategies targeting comorbidities that are associated with infectious complications, such as obesity and diabetes. Our alternative scenarios demonstrate the opportunity to drastically reduce the threat that AMR poses by strengthening health systems including access to antibiotics, scaling the development of a robust drug pipeline, and continuing to reduce infections through vaccination campaigns and improvements to water, sanitation and hygiene.

References

1 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet, 2022; 399: 629-55. https://doi.org/10.1016/S0140-6736(21)02724-0

2 O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. London, UK: Review on Antimicrobial Resistance, 2014. Available at: https://wellcomecollection.org/works/rdpck35v (accessed on 9 September 2024).

3 O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London, UK: Review on Antimicrobial Resistance, 2016. Available at: https://wellcomecollection.org/works/thvwsuba (accessed on 9 September 2024).

4 Okeke IN, de Kraker ME, Boeckel TPV, *et al.* Lancet Series on Sustainable Access to Effective Antibiotics. Available at: https://www.thelancet.com/series/antibiotic-resistance (accessed on 9 September 2024).

5 Foreman KJ, Marquez N, Dolgert A, *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet, 2018; 392: 2052-90. https://doi.org/10.1016/S0140-6736(18)31694-5

6 Vollset SE, Goren E, Yuan C-W, *et al.* Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. Lancet, 2020; 396: 1285-306. https://doi.org/10.1016/S0140-6736(20)30677-2

7 Vollset SE, Ababneh HS, Abate YH, *et al.* Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the Global Burden of Disease Study 2021. Lancet, 2024; 403: 2204-56. https://doi.org/10.1016/S0140-6736(24)00685-8

8 GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet, 2024; 403: 2162-203. https://doi.org/10.1016/S0140-6736(24)00933-4

9 GBD 2021 Fertility and Forecasting Collaborators. Global fertility in 204 countries and territories, 1950–2021 with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. Lancet, 2024; published online March 20. https://doi.org/10.1016/S0140-6736(24)00550-6

10 GBD 2021 Demographics Collaborators. Global age-sex-specific mortality, life expectancy, and population estimates in 204 countries and territories and 811 subnational locations, 1950–2021, and the impact of the COVID-19 pandemic: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. Lancet, 2024; published online March 11. https://doi.org/10.1016/S0140-6736(24)00476-8

11 GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet, 2024; published online April 17. https://doi.org/10.1016/S0140-6736(24)00757-8

12 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet; Submitted.

13 Bhattacharjee NV, Schumacher AE, Aali A, *et al.* Global fertility in 204 countries and territories, 1950–2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. Lancet, 2024; 0. https://doi.org/10.1016/S0140-6736(24)00550-6

14 Zheng P, Barber R, Sorensen RJD, Murray CJL, Aravkin AY. Trimmed Constrained Mixed Effects Models: Formulations and Algorithms. J. Comput. Graph. Stat., 2021; 30: 544-56. https://doi.org/10.1080/10618600.2020.1868303

15 GBD 2019 Healthcare Access and Quality Collaborators. Assessing performance of the Healthcare Access and Quality Index, overall and by select age groups, for 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Glob. Health, 2022; 10: e1715-43. https://doi.org/10.1016/S2214-109X(22)00429-6

16 Mendelson M, Lewnard JA, Sharland M, *et al.* Ensuring progress on sustainable access to effective antibiotics at the 2024 UN General Assembly: a target-based approach. Lancet, 2024; 403: 2551-64. https://doi.org/10.1016/S0140-6736(24)01019-5

17 Lancet T. Antimicrobial resistance: an agenda for all. Lancet, 2024; 403: 2349. https://doi.org/10.1016/S0140-6736(24)01076-6

This report is part of the EcoAMR series. As of September 2024, the series features these other publications:

- Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Humans
- Forecasting the Fallout from AMR: Economic Impacts of Antimicrobial Resistance in Food-Producing Animals
- Forecasting the Fallout from AMR: Averting the Health and Economic Impacts through One Health Policy and Investment


World Organisation for Animal Health
AID
Animal Industry Data
CGD
CENTER FOR GLOBAL DEVELOPMENT
Institute for Health Metrics and Evaluation
RAND EUROPE
THE WORLD BANK
IBRD • IDA | WORLD BANK GROUP