# Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021

GBD 2021 Causes of Death Collaborators

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## Summary

### Background

Regular, detailed reporting on population health by underlying cause of death is fundamental for public health decision making. Cause-specific estimates of mortality and the subsequent impact on life expectancy worldwide are valuable metrics to gauge progress in reducing mortality rates. This is uniquely useful following the COVID-19 pandemic and for other large-scale mortality shocks in the future. When systematically analysed, mortality rates and life expectancy allow comparisons of the consequences of causes of mortality globally and over time, providing a more nuanced understanding of their impact on global populations.

### Methods

The GBD 2021 cause of death analysis estimated mortality and years of life lost (YLLs) from 288 causes of death by age-sex-location-year in 204 countries and territories and 811 subnational locations for each year from 1990 through 2021. The analysis used 56 604 total sources of data, including data from vital registration and verbal autopsy as well as surveys, censuses, surveillance systems, and cancer registries, among others. As with previous GBD rounds, cause-specific death rates for most causes were estimated using the Cause of Death Ensemble model (CODEm)—a modelling tool developed for GBD to evaluate the out-of-sample predictive validity of different statistical models and covariate permutations and combine those results to produce cause-specific fatal burden estimates—with alternative strategies adapted to model causes with very limited data, substantial changes in reporting over the study period, or unusual epidemiology. YLLs were computed as the product of the number of deaths for each cause-age-sex-location-year and the standard life expectancy at each age. As part of the modelling process, uncertainty intervals (UIs) were generated using the 2.5th and 97.5th percentiles from a 1000-draw distribution for each metric. We decomposed life expectancy by cause of death, location, and year to show cause-specific effects on life expectancy from 1990 to 2021. We used the coefficient of variation and the fraction of population affected by 90% of deaths, to highlight concentrations of mortality that may inform cause-specific policy-relevant insights. Findings are reported in counts and age-standardised rates. Methodological improvements for cause of death estimates in GBD 2021 include the expansion of under-5 ages to include four new age groups, enhanced methods to account for stochastic variation of sparse data, and the inclusion of pandemic-specific mortality from COVID-19 and “other pandemic-related mortality” (OPRM)—which includes excess mortality associated with the pandemic, excluding COVID-19, lower respiratory infections, measles, malaria, and pertussis causes. For this analysis, 199 new country-years of vital registration cause of death data, five country-years of surveillance data, 21 country-years of verbal autopsy data, and 94 country-years of other data types were added to those used in previous GBD rounds.

### Findings

The leading causes of age-standardised deaths globally were the same in 2019 as in 1990; these were, in descending order, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lower respiratory infections. In 2021, however, COVID-19 replaced stroke as the second-leading age-standardised cause of death, with 94.0 deaths (95% UI 89.2–100.0) per 100 000. The COVID-19 pandemic shifted the rankings of the leading five causes, lowering stroke and chronic obstructive pulmonary disease to the third and fourth places, respectively. In 2021, the highest age-standardised death rates from COVID-19 occurred in sub-Saharan Africa (271.0 deaths [250.1–290.7] per 100 000) and Latin America and the Caribbean (195.4 deaths [182.1–211.4] per 100 000). The lowest age-standardised death rates from COVID-19 were observed in the high-income super-region (48.1 deaths [47.4–48.8] per 100 000) and southeast Asia, east Asia, and Oceania (23.2 deaths [16.3–37.2] per 100 000). Globally, trends in life expectancy showed steady improvements between 1990 and 2019 for 18 of the 22 investigated causes. Decomposition of global and regional life expectancy demonstrates the positive impact that reductions in enteric infections, lower respiratory infections, stroke, and neonatal deaths, among others, have contributed to increased survival. Despite these improvements in causes of death until 2019, a net drop of 1.6 years occurred in global life expectancy between 2019 and 2021, primarily due to elevated death rates due to COVID-19 and OPRM. Examining the impact of COVID-19 on life expectancy between 2019–2021 is crucial because each of the seven GBD super-regions showed an overall improvement from 1990 to 2021, obscuring the negative impact on life expectancy isolated in the years of pandemic. There was high variability between super-regions, with southeast Asia, east Asia, and Oceania gaining 8.3 years (6.7–9.9) of life expectancy overall, while displaying the smallest reduction in life expectancy due to COVID-19 of 0.4 years. The largest decline in life expectancy due to COVID-19 occurred in Latin America and the Caribbean, which lost 3.6 years. In addition, we found that 53 of the 288 causes of death were highly concentrated in locations that contained less than 50% of the global population as of 2021, and that these causes of death became progressively more concentrated since 1990, when only 44 of 288 showed this pattern. The concentration phenomenon is discussed heuristically with respect to enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, tuberculosis, and measles.

### Interpretation

Longstanding gains in life expectancy and reductions in many of the leading causes of death have been disrupted by COVID-19, the adverse effects of which were spread unevenly among populations. Despite the pandemic, there has been continued progress in combatting several notable causes of death, leading to improved global life expectancy over the study period, with the biggest gains attributed to reductions in mortality due to enteric infections, lower respiratory infections, stroke, and neonatal deaths. Our findings about regional variation driving increases in life expectancy have clear policy utility, as does our analysis of changing mortality trends. Deaths from enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, tuberculosis, measles, and other causes that were once widespread globally are now increasingly concentrated. The changes to mortality concentration reveal marked regional differences in public health success, which alongside further investigation of changing risks, interventions, and relevant policy, provides an important opportunity to better understand how to reduce mortality. Translating these successes to locations where certain causes of death remain entrenched can inform policies that work to improve life expectancy for people everywhere. The pandemic highlighted inequities in existing health systems as well as health system preparedness, both of which were highly heterogenous globally in terms of population mortality outcomes. This has rightly prompted new calls for increasing equity in pandemic preparedness alongside calls for strengthening existing health systems.

### Funding

Bill & Melinda Gates Foundation.

## Research in context

### Evidence before this study

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has provided regular updates on the complex patterns and trends in population health around the world since the first GBD publication in 1993. With each subsequent iteration, there have been important methodological updates, new datasets included, and an expanded list of causes, risk factors, and locations for which burden of disease estimates are produced. In the 1993 World Bank Report, where GBD estimates were first published, mortality and years of life lost (YLLs) were reported for 107 categories of diseases that covered all possible causes of death, for eight regions. In the last GBD cycle—GBD 2019—mortality and YLL estimates were produced for 286 causes of death in 204 countries and territories, including all WHO member states, and for subnational locations in 21 countries and territories, for every year from 1990 to 2019. While many groups have reported on national-level cause-specific mortality and other population health metrics in recent years, including the WHO World Health Statistics reports, GBD is the most detailed and transparent research effort to date. Further, while estimates of COVID-19 deaths in 2020 and 2021 have been reported by numerous sources, including GBD studies that have quantified excess mortality due to the pandemic within a subset of GBD locations, there have been no prior publications to quantify the impact of COVID-19 on life expectancy, while comparing to the full spectrum of disease mortality and impact on life expectancy over the past three decades, across all countries and territories.

### Added value of this study

This study—GBD 2021—is the first of its kind to publish 2021 COVID-19 deaths and YLLs for 204 countries and territories in the context of the global burden of disease. While other publications have estimated deaths due to COVID-19, those deaths have not previously been comparable to deaths from other causes. By modelling COVID-19 deaths within a hierarchy of mutually exclusive and collectively exhaustive causes of death, this study provides policy makers with information that is essential for setting health priorities around the world. In addition, life expectancy at birth serves as a sensitive indicator that summarises overall mortality expectations of populations. To obtain more comprehensive insights from this measure, it is necessary to break it down into age-specific mortality, which is influenced by cause-specific mortality rates. Our analysis evaluated the impact of COVID-19 and other causes of death on life expectancy by decomposing death counts into different cause-specific mortality rates across various dimensions, including country or territory, region, super-region, and five distinct time periods: 1990–2000, 2000–2010, 2010–2019, 2019–2021, and 1990–2021. This allowed the impact of the COVID-19 pandemic to be systematically calibrated against other causes of mortality over the period 1990–2021. Finally, we identified causes of death that experienced increasing geographical concentration over this time period. This provides policy makers important information on regional variation and inequalities in cause-specific mortality. Also new to GBD 2021, we report on 12 additional causes of death: COVID-19 other pandemic-related mortality (OPRM), pulmonary arterial hypertension, and nine cancer types—hepatoblastoma; Burkitt lymphoma; other non-Hodgkin lymphoma; eye cancer; retinoblastoma; other eye cancers; soft tissue and other extraosseous sarcomas; malignant neoplasm of bone and articular cartilage; and neuroblastoma and other peripheral nervous cell tumours. Granularity of under-5 estimation was enhanced by the addition of four new age groups: 1–5 months, 6–11 months, 12–23 months, and 2–4 years.

### Implications of all the available evidence

Our study provides a full analysis of causes of death worldwide and across time, alongside the changing patterns in life expectancy precipitated by those causes. Increasing geographical concentration of mortality was observed for many causes of death, highlighting disparities between regions and significant differences in cause-specific contributions to life expectancy. On a global scale, this information provides an opportunity to examine if reductions in mortality were resilient to the onset of a novel pandemic. On a regional level, the estimates generated by our study provide important detail on the evolving impact of causes of death among countries, allowing crucial insight into differential success by geography, time, and cause. The comprehensive nature of GBD 2021 cause of death estimation provides valuable opportunities to learn from mortality gains and losses, helping to accelerate progress in reducing mortality.

## Introduction

For more than three decades, starting in 1993, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has been systematically and comprehensively recording and analysing causes of human death stratified by age, sex, and time across the world.1,2 As a global public good, this information has been used to guide policy solutions, reduce modifiable risk factors, monitor and evaluate national and subnational health interventions, and ultimately improve health recommendations at both regional and local levels.1 Assessing trends in cause-specific mortality is essential to inform health policy that must continuously evolve to account for rapid changes to the global health landscape such as the COVID-19 pandemic.3 Comprehensive updates to levels and trends in causes of death give insight into emerging global health challenges and can facilitate benchmarking in the case of a new pandemic or other events that can lead to a staggering loss of life.

Causes of death are not uniformly distributed between populations; rather, large variability in the leading causes often reflects important social and geographical differences.4 These differences can include access to and quality of health care, timeliness of health system responsiveness, and exposure to causes that are endemic to specific geographical locations.4 Patterns in the leading causes continually evolve, as some areas become successful in their efforts to reduce them, while other causes persist within specific locations. The past 30 years have seen improvements among many causes of mortality, some of which have significantly narrowed in scope and are now concentrated within smaller areas worldwide. This enables us to pinpoint the resulting mortality concentrations—areas where deaths from that cause are occurring within a limited fraction of the global population. Our analysis provides an opportunity to answer critical epidemiological questions that have been at the forefront of global and public health discourse, such as which causes have contributed to the largest increase or decrease in life expectancy, which locations are experiencing greater concentrations of preventable causes of death, and how has COVID-19 and other pandemic-related mortality impacted life expectancy and the overall fatal burden of diseases. Regional variation in many of the leading causes of death remains evident in these most recent estimates, representing important opportunities for creating tailored health policy to improve disparities and alleviate concentrations of mortality.

GBD 2021 provides an updated, comprehensive set of the fatal burden of disease summarised with cause-specific mortality metrics and years of life lost (YLLs) metrics for 288 causes by age and sex across 204 countries and territories from 1990 to 2021, an update from the previously published estimates covering 1990–2019. New in this study, we present mortality concentrations and a decomposition analysis of life expectancy due to different causes of death and illustrate the impact of causes of death on global, regional, and country-specific life expectancy, while highlighting locations that are most impacted by concentrated geographic mortality burden. As with previous iterations of the GBD, this cycle incorporates newly available data sources and improved methodological approaches to re-estimate the entire time series, providing updated estimates that supersede all prior GBD cause of death publications. GBD 2021 includes estimation of numerous different models for disease and injury outcomes. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.5

## Methods

### Overview

GBD 2021 produced estimates for each epidemiological quantity of interest for 288 causes of death by age-sex-location-year for 25 age groups from birth to 95 years and older; for males, females, and all sexes combined; in 204 countries and territories grouped into 21 regions and seven super-regions; and for every year from 1990 to 2021. GBD 2021 also includes subnational analyses for 21 countries and territories (see appendix 1 section 2.1 [note to editors and reviewers: these materials are available during peer review at: <https://cloud.ihme.washington.edu/s/Q7nnHz9CBbTErrx> password: 2021COD]). An international network of collaborators provides, reviews, and analyses the available data to generate these metrics; the 2021 GBD round drew on the expertise of more than 10 000 collaborators from more than 150 countries and territories.

The methods used to generate these estimates closely followed those for GBD 2019.6 These methods have been extensively peer-reviewed over previous rounds of the GBD study4,6–9 and concurrently as part of the peer review process for GBD 2021. Here we provide an overview of the methods with an emphasis on the main methodology changes since GBD 2019; a comprehensive description of the analytical methods for GBD 2021 is provided in appendix 1.

The GBD 2021 cause of death estimates described here include cause-specific mortality and premature death (YLL) metrics. YLLs were calculated as the number of deaths for each cause-age-sex-location-year multiplied by the standard life expectancy at each age. Standard life expectancy is calculated from lowest age specific mortality rate between countries.10 In brief, cause-specific death rates for most causes were estimated using the Cause of Death Ensemble model (CODEm), while alternative strategies were used to model causes with very limited data, substantial changes in reporting over the study period, or unusual epidemiology. The modelling strategy used for all causes of death can be found in appendix table 10. CODEm is a modelling tool developed specifically for GBD that evaluates the out-of-sample predictive validity of different statistical models and covariate permutations and then combines the results from those evaluations to produce cause-specific fatal burden estimates. Methodological improvements for cause of death estimates in the current round of estimation focused on several key areas. First, causes of death data were updated to retain age detail for the following under-5 age groups: 1–5 months, 6–11 months, 12–23 months, and 2–4 years. Second, enhanced methods were implemented to account for stochastic variation in causes of death data and improve the estimation of small cause fractions. Third, we added 199 new country-years of vital registration cause of death data, 5 country-years of surveillance data, 21 country-years of verbal autopsy data, and 94 country-years of other data types. Lastly, we incorporated COVID-19 and other pandemic-related mortality (OPRM)—which includes excess mortality associated with the COVID-19 pandemic, excluding COVID-19, lower respiratory infections, measles, malaria, and pertussis causes.

### The GBD disease and injury hierarchy

GBD classifies diseases and injuries into a hierarchy with four levels that include both fatal and non-fatal causes. Level 1 causes include three broad aggregate categories (communicable, maternal, neonatal, and nutritional diseases; non-communicable diseases; and injuries); Level 2 disaggregates those categories into 22 clusters of causes which are further disaggregated into Level 3 and Level 4 causes. At the most detailed level, 288 fatal causes are estimated. For a full list of causes of death by level, see appendix 1 (table S2). For GBD 2021, we separately report on 12 causes of death for the first time: COVID-19; OPRM, pulmonary arterial hypertension, and nine cancer types: hepatoblastoma; Burkitt lymphoma; other non-Hodgkin lymphoma; eye cancer; retinoblastoma; other eye cancers; soft tissue and other extraosseous sarcomas; malignant neoplasm of bone and articular cartilage; and neuroblastoma and other peripheral nervous cell tumours.

### Data sources, processing, and assessing for completeness

The GBD 2021 cause of death database included data sources identified in previous rounds of estimation in addition to 9248 new sources—these sources are detailed in appendix 1, table S5 (section 9) and can also be accessed through the GHDx [<http://ghdx.healthdata.org/gbd-2021>; *note to editors and reviewers that this link will be made available prior to publication but is not currently live*]. Multiple data types were included to capture the widest array of information including vital registration (VR) and verbal autopsy (VA) for all 288 causes as well as survey, census, surveillance, cancer registry, police record, open-source databases, and minimally invasive tissue sampling. To standardise these data so that they can be compared by cause, age, sex, location and time, a set of data processing corrections are applied. First deaths with insufficient age detail to estimate the GBD age groups or missing age and sex detail undergo age and sex splitting to assign GBD age groups as well as male or female (appendix 1 section 3.5). In addition, garbage codes, which are non-specific, implausible, or intermediate rather than underlying cause of death codes from the International Classification of Diseases (ICD), were redistributed to appropriate targets to assign the underlying cause of death.11 Data sources with more than 50% of all deaths assigned to major garbage codes (Class 1 or Class 2 garbage codes) in any location-year were excluded to mitigate the potential for bias from these sources (appendix 1 section 3.7). For GBD 2021, we established a buffer system so location-years that were included in the previous GBD cycle would not be dropped from the current cycle as long as less than 55% of all deaths were assigned to major garbage codes. This 5% buffer ensured greater consistency in data source inclusion from one cycle to the next.

Assessing data completeness illustrates the coverage from a data source on overall mortality for the country. VR and VA data completeness—a source-specific estimate of the percentage of total cause-specific deaths that are reported in a given location and year—was assessed by location-year, and sources with less than 50% completeness were excluded. We excluded 142 country years of data due to completeness. As with garbage codes, we employed a 5% buffer so sources included in the previous GBD cycle would not be excluded from the current cycle if they had at least 45% completeness allowing us to retain 24 country years that had previously been dropped. The estimated all-cause mortality for each age-sex-location-year was then multiplied by the cause fraction for the corresponding age-sex-location-year to adjust all included sources to 100% completeness. VA and VR data availability, completeness, and five-star quality rating for each location-year are available in the appendix 1 section 3. Full details on all data processing corrections can be found in appendix 1 section 3.

### Improvements in GBD 2021 to cause of death data processing and estimation

##### Adjustments for stochastic variation

In GBD 2021, two primary improvements were made to the methods used to reduce stochastic variation, most impacting causes of death with small sample size. First, the Bayesian algorithm used in the noise reduction of these data was updated to improve the preservation of real trends in data with large sample size, while imparting additional information from regional trends for data with small sample size. Second, the non-zero floor, a method that addresses distorted data shapes and non-sensical trends caused by small numbers when transformed to log space, was updated to be time-invariant and independent of demographic inputs. The full details of these two key improvements, as well as other improvements that address stochastic variation, can be found in appendix 1 section 3.14.

##### COVID-19 and other pandemic-related mortality (OPRM) estimation

COVID-19 and OPRM estimates were derived from an analysis of the overall excess mortality due to the COVID-19 pandemic from January 1, 2020, to December 31, 2021. Full details of the estimation of excess mortality, COVID-19 deaths, and OPRM are provided in appendix 1 section 5. To estimate excess mortality, we first developed a database of all-cause mortality by week and month after accounting for reporting lags, anomalies such as heat waves, and under-registration of death. Next, we developed an ensemble model to predict expected deaths in the absence of the COVID-19 pandemic for the years 2020 and 2021. In location and time combinations with data used for these models, excess mortality was estimated as observed mortality minus expected mortality. To estimate excess mortality for location-years without data, we developed a statistical model to directly predict the excess mortality due to COVID-19, using covariates that pertained to both the COVID-19 pandemic and background population-health-related metrics at the population level before SARS-CoV-2 emerged. Uncertainty was propagated through each step of this estimation procedure.12

To produce the final COVID-19 deaths used in GBD 2021, we use a counterfactual approach. The counterfactual estimates the number of deaths if infection detection rates were at the highest observed value for each location-year. Using the ratio of counterfactual over estimated excess deaths and the ratio of reported COVID-19 deaths over excess deaths, we calculate the ratio of total COVID-19 deaths over reported COVID-19 deaths and multiply this by reported COVID-19 deaths to arrive at our final estimates of COVID-19 deaths.12

To account for increases in excess mortality in 2020 and 2021 that could not be attributed to particular causes, we introduced a residual cause, OPRM. Four causes of death— lower respiratory infections, measles, malaria, and pertussis—were identified as related to the COVID-19 pandemic and having reliable enough estimates to not contribute to OPRM. Thus, OPRM was calculated as the difference between excess mortality and the sum of deaths due to COVID-19 and these four causes.12

### Presentation of cause-specific mortality estimates

Cause-specific mortality estimates for 2021 are given in death counts and age-standardised rates per 100 000 population, calculated using the GBD standard population structure.10 For changes over time, we present percentage changes over the period 1990–2021, and annualised rates of change (ARCs) as the difference in the natural log of the values at the start and end of the time interval divided by the number of years in the interval. Uncertainty intervals (UIs) for all metrics are computed using the mean estimate across 1000 draws (see appendix 1 section 2 and 3 for details), and 95% UIs are given as the 2.5th and 97.5th percentiles of that distribution.

### Life expectancy decomposition

The objective of life expectancy decomposition is to analyse the difference in life expectancy by age and location, quantifying contributions from specific causes. Full details of the life expectancy decomposition estimation of are provided in appendix 1 section 7. We examined temporal trends in causes over concatenated time periods across different locations. We aimed to identify the impact of causes of death on life expectancy by utilising three main decomposition steps. For this study, we investigated the top 20 Level 2 and Level 3 GBD causes contributing to change in life expectancy. The remainder of causes were then combined as “other communicable and maternal disorders”, or “other non-communicable diseases”. The first step involved decomposing the difference in life expectancy by age. Age-specific contributions were calculated to understand the variation in life expectancy across different age groups. In the second step, each age-specific contribution was further decomposed into cause-age-specific contributions. This analysis allowed for the identification of the specific causes of death that contributed to the differences in life expectancy within each age group. Finally, the cause-age-specific contributions were aggregated across age groups to produce cause-specific contributions to the overall difference in life expectancy. This aggregation provided a comprehensive understanding of how different causes of death contributed to the observed variations in life expectancy. By applying this decomposition approach, we gain insights into the relative impact of different causes of death on changes in life expectancy by age and location.

### Calculation of mortality concentration

Concentrated causes in GBD refer to causes that exhibit a disproportionate impact in a specific geographical subset of the data compared to the rest of the global observations. In GBD 2021, two different methods were employed to identify these concentrated causes: coefficient of variation and mortality concentration. These methods are described below.

#### *Coefficient of variation*

#### For each GBD cause, a coefficient of variation—a statistical measure used to assess the variability of a population relative its mean—was calculated from standard methods.13 The observations considered for this calculation were national, age-standardised, both-sex mortality rates, using the average mortality rate between 2019 and 2021. Causes with larger coefficients of variation have data that are less centered around the mean and indicate a greater likelihood of a concentrated cause.

#### *Mortality concentration*

In order to identify concentrations of mortality—geographic locations or groups of locations with populations that are disproportionately affected by a particular cause—we first calculated the total number of all-age, both-sex deaths in 2021 by cause in each of the 811 most detailed GBD locations and sorted these locations by deaths in descending order. We then calculated the cumulative percentage of deaths by dividing location-specific cumulative deaths by the global deaths for each cause. When the cumulative percentage reached or exceeded 90% for a given cause, we divided the population of the geographic subset included in that cumulative percentage by the total global population in 2021 using population estimates from the GBD population model described in previous publications.10,12 This identification of geographic subsets that contain at least 90% of deaths from a given cause but represent a comparatively small share of the global population is used to identify potential inequalities in the impact of mortality between locations and populations. In addition to identifying these concentrations of mortality in 2021, we repeated this same analysis for 1990. By comparing the respective proportions of affected global population in these two years, we were able to differentiate causes that showed increased, decreased, or static concentration of mortality. The causes highlighted in this study were those characterised by an age-standardised mortality rate greater than 0.5 per 100 000. We did not address causes that are inherently endemic to certain regions, such as Chagas.

### GBD research and reporting practices

This research is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting recommendations (GATHER);14 a completed GATHER checklist is provided in appendix 2 table S4. Software packages used in the causes of death analysis for GBD 2021 were Python version 3.10.4, Stata version 13.1, and R version 4.2.1. Statistical code used for GBD estimation is publicly available online [<http://ghdx.healthdata.org/gbd-2021/code>; *note to editors and reviewers, this link will be made available prior to publication but is not currently live*].

### Role of the funding source

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

## Results

### Global causes of death

From 1990 to 2019, the annual rate of change in global deaths from all causes ranged from -0.9% (95% UI –2.7 to 0.8) in 2006 to an increase of 2.4% (0.1–4.7) in 1994 (appendix 2 table S1 and figure S1). The corresponding annual rates of change in the global age-standardised mortality rate fell within a range of –3.3% (–5.0 to –1.6) to 0.4% (–1.9 to 2.5) from 1990 to 2019. In 2020, the total number of deaths worldwide increased by 10.8% (6.4–15.4) compared to 2019, from 57.0 million (54.9–59.5) deaths in 2019 to 63.1 million (60.6–65.9) deaths in 2020. This trend persisted in 2021, with an increase of 7.5% (3.1–12.4) relative to 2020, to 67.9 million (65.0–70.8) deaths. The age-standardised mortality rate followed a similar pattern, increasing 8.1% (3.9–12.4) in 2020 and an additional 5.2% (1.0–9.7) in 2021 (appendix 2 figure S1). In 2020 and 2021, deaths from COVID-19 and OPRM changed the pattern of mortality for the leading causes of age-standardised death (figures 1 and 2 and table 1). At Level 3 of the GBD cause classification hierarchy, the rankings of the four causes of death with the highest age-standardised mortality rates were the same in 2019 as they were in 1990, with each showing a steady decline in its age-standardised death rate (figure 1). These causes were, in descending order, ischaemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), and lower respiratory infections. In 2021, however, COVID-19 replaced stroke as the second-leading cause of age-standardised death globally (with 94.0 deaths [95% UI 89.2–100.0] per 100 000), pushing stroke down to the third position. COPD was consequently moved to the fourth rank. Additionally, OPRM—which includes excess mortality associated with the pandemic, excluding COVID-19, lower respiratory infections, measles, and pertussis causes—emerged as the fifth leading cause of age-standardised deaths in 2021; these changes shifted lower respiratory infections from the fourth to the seventh position. Table 1 and figure 2 show age-standardised death rates of the leading ten causes over the first two years of the pandemic. The impact of COVID-19 on age-standardised mortality was comparable to chronic obstructive pulmonary disorder in 2020 but increased by 60.2% (53.1–67.6) in 2021 to be comparable to stroke and ischaemic heart disease (figure 2).

### COVID-19 and other pandemic-related mortality

Our estimates show 4.80 million (95% UI 4.56–5.11) deaths globally due to COVID-19 occurred in 2020, and 7.89 million (7.49–8.40) occurred in 2021. Table 1 provides a breakdown of the number of deaths due to COVID-19 compared to the other leading ten causes of death, in addition to estimates of age-standardised rates—to account for differences in population size and age distribution—among each of the super-regions, in 2020 and 2021. Age-standardised death rates due to COVID-19 were highly variable among GBD super-regions, with the lowest in 2020 occurring in southeast Asia, east Asia, and Oceania (6.0 deaths [2.0–12.0]) per 100 000, and the highest in sub-Saharan Africa (159.0 deaths [148.0–170.0] per 100 000) (figure 3). In 2021, the rankings among super-regions, from highest to lowest, were sub-Saharan Africa (271.0 deaths [250.1–290.7] per 100 000); Latin America and the Caribbean (195.4 deaths [182.1–211.4] per 100 000); north Africa and the Middle East (172.4 deaths [150.3–191.5]) per 100 000; central Europe, eastern Europe, and central Asia (168.8 deaths [150.6–186.1] per 100 000); south Asia (156.5 deaths [150.4–164.4] per 100 000); high-income (48.1 deaths [47.4–48.8] per 100 000); and southeast Asia, east Asia, and Oceania (23.2 deaths [16.3–37.2]) per 100 000.

Deaths from both COVID-19 and OPRM also varied substantially by age, with older ages being disproportionately impacted (table 2). The 70–74 age group had the highest number of deaths from both COVID-19 and OPRM in 2020 and again in 2021. The highest cause-fraction of deaths from COVID-19 was found in those aged 40–44, whereas the highest mortality rate occurred in those ages 95 years and over. Death rates from OPRM were high among older age groups, and among the youngest ages, with a rate of 141.2 deaths (95% UI 58.0–277.5) per 100 000 for infants 0–6 days old, and 77.3 deaths (44.0–118.0) per 100 000 in infants 7–27 days old. The age and sex distribution of COVID-19 and OPRM can be seen in appendix 2 figure S5. At a global scale, COVID-19 deaths and OPRM were slightly higher for males than for females in most age groups in 2021. Exceptions to this include older age groups: 90–94 and 95 and older.

### Leading causes of global YLLs

The causes of death with the highest age-standardised YLL rates show shifting epidemiological trends from communicable, maternal, neonatal, and nutritional (CMNN) diseases to non-communicable diseases (NCDs) at Level 3 of the cause hierarchy (appendix 2 figure S2). Globally, the leading three causes of age-standardised YLLs in 1990 were all CMNN diseases; ranked in descending order, these were neonatal disorders, lower respiratory infections, and diarrhoeal diseases. In 2019, neonatal disorders remained the leading cause of age-standardised YLLs, but the second and third causes were replaced by NCDs: ischaemic heart disease (ranked second) and stroke (ranked third). Two years later, COVID-19 was the second-leading cause of global age-standardised YLLs, making the leading two causes CMNN diseases (with neonatal disorders ranked first), and ischaemic heart disease ranked third. Among the leading causes of age-standardised YLLs, malaria was the only cause to show an increase in age-standardised YLL rates between 2019 and 2021 (ranking ninth in 2019 and seventh in 2021).

### Decomposition of global life expectancy

Longstanding positive trends in global life expectancy were observed since the early 1990s, with steady increases occurring across each decade between 1990 and 2019 (appendix 2 table S4). Altogether, the global increase from 1990 to 2019 totalled 7.8 years (95% UI 7.1–8.5). In the years from 2019 to 2021, however, there was a global decline in life expectancy of 2.2 years due to deaths from COVID-19 and OPRM combined. This decrease was partially offset by reductions in other diseases for a net reduction in global life expectancy of 1.6 years. Despite this notable drop, we can observe an overall increase in life expectancy across the entire study period of 6.2 years (5.4–7.0). This decomposition analysis provides insights into the specific causes that influenced changes in life expectancy over the defined time periods. A detailed breakdown of the leading causes responsible for either an improvement or a decline in global life expectancy over the decades between 1990 and 2021 is visually represented in figure 4. Among the various contributing factors, the cause with the greatest impact on the rise in life expectancy worldwide was the reduction in deaths caused by enteric infections. This category includes diarrhoeal, typhoid, and paratyphoid diseases. A reduction in deaths from these diseases is responsible for a substantial increase in life expectancy of 1.1 years during the period from 1990 to 2021, but this increase was most pronounced between 1990 and 2000 compared to other time periods. The second-largest effect on increasing life expectancy is attributed to the reduction in lower respiratory infectious deaths, contributing 0.9 years of added life expectancy from 1990 to 2021. Other leading factors include reduced mortality from stroke, CMNN diseases, neonatal deaths, ischaemic heart disease, and neoplasms, each of which increased global life expectancy between 0.6 and 0.8 years over the study period. Changing rates of HIV/AIDS and malaria mortality both contributed positively to the overall global life expectancy in some years but negatively impacted it in others. Beginning in 2000, reductions in HIV/AIDS mortality were evident following substantial negative impacts in earlier years. Reductions in deaths from malaria, however, were less sustained, increasing life expectancy by 0.1 years from 2010 to 2019 but having no effect from 2019 to 2021. Across all causes, the most significant impact on the change in global life expectancy was due to COVID-19, which resulted in a decline of 1.6 years between 2019 and 2021.

### Decomposition of super-region, regional, and country-level life expectancy

Each of the seven super-regions experienced an overall increase in life expectancy between 1990 and 2021, despite progress in each being differentially impacted by COVID-19 (figures 3 and 5). Southeast Asia, east Asia, and Oceania showed the highest gain, with a net improvement of 8.3 years (95% UI 6.7–9.9), while also being the least impacted by COVID-19, which contributed a loss in life expectancy of just 0.4 years. The overall increase in life expectancy in southeast Asia, east Asia, and Oceania can largely be attributed to reduced mortality from chronic respiratory diseases, contributing to a gain of 1.2 years, while reduced mortality from stroke, lower respiratory infections, and neoplasms were among other causes that contributed to the 8.3-year (6.7–9.9) increase. The second-largest gain occurred in south Asia, where life expectancy increased by 7.8 years (6.7–8.9), which can be largely attributed to reduced mortality from enteric infectious diseases, contributing a substantial gain of 3.1 years in life expectancy. The most significant reduction in overall life expectancy due to COVID-19 occurred in the Latin America and the Caribbean super-region, which experienced a loss of 3.6 years. Reductions in deaths due to malaria throughout sub-Saharan Africa led to an increase in life expectancy of 0.8 years for the super-region.

The differential impact of COVID-19 on reduced life expectancy can be observed across regions (figure 6). Although most regions experienced overall improvements in life expectancy between 1990 and 2021, a reduction occurred in southern sub-Saharan Africa, which faced the greatest impact of HIV and was also heavily impacted by COVID-19. The overall decrease in life expectancy of 4.3 years (95% UI 3.0–5.8) included a reduction of 2.4 years due to HIV and 3.4 years due to COVID-19, which were only partially offset by declines in mortality due to other causes. Notably, COVID-19 reduced life expectancy in Andean Latin America by 4.9 years, although the region sustained an overall gain of 2.6 years (1.0–4.1) between 1990 and 2021. The impact of COVID-19 in eastern sub-Saharan Africa, which resulted in a decline of 2.7 years, was offset by steady improvements across many different causes, which resulted in the highest overall increase in life expectancy among GBD regions: 10.7 years (9.0–12.2). Control of enteric infections in this region contributed to an increase of 1.9 years, along with reductions in lower respiratory infections and tuberculosis, each of which contributed to an additional 1.6 years. Each region in sub-Saharan Africa experienced reductions in enteric infections, which improved life expectancy in those regions between 0.8 and 2.4 years.

HIV/AIDS had a substantial negative impact on life expectancy trends in southern sub-Saharan Africa from 1990 to 2021 (appendix 2 figure S27). Despite improvements in each of the time periods 2000–2010, 2010–2019, and 2019–2021, this region has been unable to recover the 9.0 years lost during the years from 1990 to 2000. Although there was a net decline in deaths due to HIV/AIDS between 2000 and 2019, improvements slowed substantially from 2019 to 2021, when only 0.2 years in life expectancy were gained as a result of reduced HIV/AIDS mortality. Conversely, eastern sub-Saharan Africa demonstrated the highest level of recovery to their life expectancy among the regions, gaining 1.5 years of life expectancy over the entire study period.

In 1990, malaria-related deaths had a minimal impact on life expectancy in eight out of the 21 GBD regions (appendix 2 figure S13). By 2021, however, 90% of malaria deaths across all age groups occurred in locations with only 12% of the global population. Over the years, efforts to control malaria in various regions of sub-Saharan Africa have yielded modest gains in life expectancy. Central sub-Saharan Africa gained 0.7 years between 2000 and 2010, western sub-Saharan Africa saw an increase of 0.9 years during 2010–2019, and eastern sub-Saharan Africa gained 0.7 years in the period of 2000–2010. Despite these advancements, it is evident that many regions with malaria transmission experienced a decline in life expectancy from 2019 to 2021. The most noticeable reductions were observed in eastern sub-Saharan Africa, with a decrease of 0.2 years, followed by western sub-Saharan Africa, which lost 0.1 years over the same period.

At the national level, some of the highest gains in life expectancy between 1990 and 2021 occurred in the eastern region of sub-Saharan Africa (appendix 2 figure S12). Life expectancy in Ethiopia increased 18.2 years (95% UI 16.3–19.8) as a result of reductions in deaths from many causes, most notably other communicable and maternal disorders, tuberculosis, and enteric infectious diseases. Reductions in these three causes alone increased the country’s life expectancy by 3.2 years, 3.1 years, and 2.4 years, respectively. The largest decline in life expectancy occurred in Lesotho, at 12.9 years (95% UI 10.1–15.7), largely attributed to increased HIV, which resulted in a loss of 7.3 years (appendix 2 figures S12, S27 and table S4).

### Communicable, maternal, neonatal, and nutritional diseases (CMNN) impact on life expectancy and trends in mortality concentration

Among CMNN causes, several key trends emerge in their impact on global life expectancy and the localisation of deaths over time. First, enteric disease mortality control had a significant impact on global life expectancy, with notable regional variations (figure 7). As 160 countries and territories made progress in controlling this cause of mortality, mortality concentration emerged. Deaths became more concentrated into certain countries or regions, persisting alongside advancements made in other parts of the world. An illustrative example is the shift in under-5 deaths due to enteric diseases, with 90% of deaths occurring in locations containing 63% of the under-5 population in 1990, decreasing to locations containing 51% of the population by 2021 (appendix 2 figure S28). Second, the control of lower respiratory infections yielded positive impacts on life expectancy in some regions. Regions such as Andean Latin America and western and eastern sub-Saharan Africa achieved gains of 1.6 years in life expectancy due to reduced lower respiratory infection deaths. This progress is further underscored by the transformation from 90% of under-5 lower respiratory infection deaths occurring in locations with 71% of the under-5 population in 1990 to 90% occurring in locations with 58% of the under-5 population by 2021, signalling significant improvements in some regions and increased concentration of this cause in others (figure 8 and appendix 2 figure S29). Third, (appendix 2, figure S27 and S30). Despite its prominent level of concentration, it is notable that HIV was less concentrated in 2021 than in 1990. Fourth, efforts to control malaria in sub-Saharan Africa resulted in modest gains in life expectancy. Likewise, 90% of malaria deaths in 2021 occurred in locations containing only 12% of the entire population and 20% of the under-5 population, illustratin HIV/AIDS had a substantial impact on life expectancy trends, particularly in southern sub-Saharan Africa, and also showed evidence of mortality concentration, with 90% of deaths concentrated in locations containing 46% of the entire population. As well as all age, in under-5-year age, 90% of death due to HIV/AIDS in this age group concentrated in locations with 39% of the under-5 population in 2021 (figure 5 and appendix 2 figure S13 and S31). Fifth, reductions in tuberculosis deaths had a positive effect on life expectancy across all regions, and changes in death mortality rates indicated mortality concentration, with 90% of deaths occurring in locations containing 66% of the entire population in 1990, decreasing to 62% by 2021 (figure 9 and appendix 2 figure S14). Lastly, while measles had a relatively small global impact on life expectancy, it showed high mortality concentration. The disease remained contained globally, with 90% of deaths concentrated in locations containing only 15% of the entire population and 24% of the under-5 population in 2021 (figure 4 and appendix 2 figure S15).

Reductions in neonatal deaths contributed to a substantial 0.6-year increase in global life expectancy. There was also a shift towards concentration, as 90% of neonatal deaths were concentrated in locations containing 71% of the population in 1990, decreasing to 51% by 2021 (appendix 2, figure S16 and S34). Finally, nutritional deficiencies had a relatively small global impact on life expectancy but significant effects on specific regions: eastern sub-Saharan Africa, central sub-Saharan Africa, and south Asia saw notable increases. Over time, there was a shift towards mortality concentration, with 90% of nutritional deficiency deaths in children under the age of 5 concentrated in locations containing 49% of the population in this age group by 2021, compared to 59% in 1990 (appendix 2, figure S18 and S35). Overall, trends from CMNN diseases exhibit a large degree of mortality concentration.

### Non-communicable diseases impact on life expectancy and trends in mortality concentration

Among non-communicable diseases (NCDs), there are several findings that reflect their impact on global life expectancy and death concentration. Stroke control and prevention strategies led to a notable gain of 0.8 years, but stroke deaths displayed a lack of concentration, with 90% occurring in locations containing 84% of the global population (appendix 2 figure S23 and S36). Similarly, ischaemic heart disease had a substantial impact on improvement to life expectancy, contributing 0.6 years to global life expectancy; yet, like stroke, ischaemic heart disease showed limited mortality concentration, with 90% of deaths concentrated in locations containing 84% of the population in 2021 (appendix 2 figure S17 and S37). Neoplasms added 0.6 years to life expectancy, with high-income regions significantly benefiting; like other NCDs, 90% of neoplasms deaths occurred in locations containing 86% of the population in 2021, indicating a consistent risk of dying from cancer regardless of geography (appendix 2 figure S19 and S38). Chronic respiratory diseases contributed an increase of 0.5 years to life expectancy, with east Asia contributing the most to this increase through significant improvements in China. Like other NCDs, chronic respiratory diseases exhibited limited mortality concentration, with 90% of deaths occurring in locations containing 79% of the population (appendix 2 figure S20 and S39). Digestive diseases and cirrhosis had a substantial negative effect on life expectancy, with minimal improvement from 2010 to 2019, and showed little mortality concentration, representing 90% and 88% of the population respectively (appendix 2 figure S21 and S40). Diabetes and kidney diseases had a negative impact on life expectancy, resulting in a global loss of 0.1 years. This cause also displayed limited mortality concentration, with 90% of deaths occurring in locations representing 89% of the population (appendix 2 figure S22, and S41). Overall, trends from NCDs did not exhibit a large degree of concentration, meaning that we do not observe mortality from these causes moving towards more restricted geographical areas (appendix 2 figure S42).

### Injuries impact on life expectancy and trends in mortality concentration

Key trends regarding the impact of injuries on global life expectancy and death concentration were observed. The reduction in transport injuries had a positive impact on life expectancy, contributing to a gain of 0.2 years. However, like NCDs, transport injuries did not display patterns of mortality concentration, with 90% of deaths concentrated in locations containing 88% of the population in 1990, decreasing slightly to 84% of the population by 2021 (appendix 2 figure S24 and S43). Unintentional injuries also showed limited mortality concentration, with 90% of deaths occurring in locations containing 88% of the population in 2021 (appendix 2 figure S26 and S44). Lastly, the overall reduction in mortality rates from self-harm and interpersonal violence contributed to a 0.2-year increase in life expectancy with variable mortality concentration, showing concentration in central and tropical Latin America and South Africa, but not exclusively these locations (appendix 2 figure S25 and S45).

## Discussion

### High-level findings on causes of death

The COVID-19 pandemic has emerged as one of the most defining global health events of recent history. Our latest comprehensive estimates of cause-specific mortality give insight into the global landscape of disease prior to and during the first two years of the pandemic, revealing the important changes in disease burden patterns that followed. After more than three decades of relatively consistent improvements in global life expectancy and declining age-standardised death rates, COVID-19 reversed longstanding progress and disrupted trends in the epidemiological transition. As the second-leading cause of age-standardised deaths in 2021, COVID-19 had a pronounced influence on the drop in global life expectancy that occurred. The heterogeneous influence of the virus across the globe provides important insights for improving future pandemic preparedness and ensuring that nations are equitably equipped to respond to new outbreaks. In addition, our analysis of geographical and temporal trends in mortality enables us to observe the changing patterns in causes of death worldwide. Many causes have exhibited a reduced geographical reach—a reflection of dedicated and persistent mitigation efforts to reduce them, as well as potential changes to risk factor exposure.15 This study offers an opportunity to apply the lessons learned from these successes to further reduce deaths from causes that are now present within smaller, more concentrated areas throughout the world.

### TThe COVID-19 pandemic

The emergence and spread of COVID-19 follows a similar pattern of regional heterogeneity that is common among many leading communicable causes of death, with higher rates of infection and increased fatalities occurring in lower-resource settings.6,16,17 While heterogeneity in COVID-19 outcomes in 2020 and 2021 varied by the income status of a country or territory, it was also directly related to age, government actions to close borders, and the implementation of transmission reduction policies.18 This general pattern did not always hold true at the national level, however, where estimates from some high-income countries showed a much greater burden than would have been expected, indicating significant opportunities for better pandemic preparedness and response in these nations.19 The varying degree of impact across locations emphasises the complexity of the pandemic’s effects. Diverse social, economic, and political influences contributed to the variations in death rates observed between locations. In general, areas with advanced health-care systems and robust medical facilities were better able to manage abrupt increases in the number of COVID-19 cases. In contrast, locations with limited health-care infrastructure were less equipped to handle the surge in infections that occurred,20 although strong health-care systems did not singularly determine the outcome of the pandemic.19 It has been suggested that improving preparedness for future pandemics should also include engagement strategies to enhance the trust that individuals place in public health recommendations.19 In addition, identifying methods to enhance death reporting systems3 and overcome political obstacles to ensure accurate reporting will be crucial steps for monitoring COVID-19 and future pandemic occurrences.21,22

Our study confirms that COVID-19 was one of the leading global causes of death during the first two years of the pandemic and provides an opportunity to delineate between its direct and indirect mortality effects as well as its impact on life expectancy. As previously predicted,3 COVID-19 shifted baseline patterns of mortality for diseases and injuries that were impacted by social distancing measures and other government-mandated restrictions. Deferred care-seeking during the height of the pandemic also likely contributed to shifts in patterns of mortality for some diseases and injuries, and likewise may have contributed to the emergence of pandemic-related deaths not attributable directly to COVID-19, lower respiratory infections, measles, malaria, or pertussis (OPRM). Deferred care-seeking may also have been a contributing factor in the notable divergence in the age-distribution in deaths between COVID-19 and OPRM, where COVID-19 deaths were dramatically higher in older ages, while the highest mortality of OPRM were seen in both the older ages as well as in children under 23 months. The youngest ages may have experienced higher mortality as caregivers may have hesitated to seek medical care during the peak of the virus’s spread. Understanding these disparities is imperative for shaping future health policies and preparedness efforts.

### Important trends in life expectancy

Advancements over the past three decades in the prevention and control of infectious diseases have contributed to prolonged life in many locations, resulting in lengthening life expectancies and an enhanced need to support populations living with NCDs.23 The global decline in life expectancy that occurred in 2020 and 2021, confounds the secular trend of increase.10 Our decomposition analysis suggests that this decline was predominantly a result of the pandemic (combined COVID-19 and OPRM), but the degree of severity varied dramatically by location. Although large improvements in many causes—including HIV/AIDS and lower respiratory and enteric infections—somewhat counterbalanced the decline, the decrease in life expectancy was also compounded by increasing rates of mortality from other causes, like diabetes and kidney diseases (figure 1 and figure 4).

The impact of COVID-19 on life expectancy shows varying degrees of severity, ranging from a large loss of 4.9 years in Andean Latin America, to comparatively minimal change in east Asia (figure 9). From 1990 to 2021, reductions in many of the leading causes of death resulted in overall life expectancy increases across most regions, despite heavy setbacks for many, because of the pandemic. We found that despite Andean Latin America suffering the largest regional decline in life expectancy due to the pandemic, overall life expectancy declines across the region were tempered by improvements in other causes, with declines in rates of death from lower respiratory infections and neonatal disorders allowing the region to gain 2.6 years overall between 1990 and 2021. The impressive reductions in neonatal disorders throughout many countries in Andean Latin America have been attributed to the improvements made in implementing effective maternal and neonatal health intervention strategies.24

The decline in life expectancy in southern sub-Saharan Africa also exceeded the global average by a substantial margin, with a loss of 3.4 years due to COVID-19. While life expectancy in the region was substantially impacted by the pandemic, the decline was also attributable to high mortality rates from HIV/AIDS. Some nations with high pandemic-related death tolls were among those already burdened by high rates of other infectious diseases. Several countries in southern sub-Saharan Africa navigated the challenges of the pandemic, alongside long histories of combatting some of the highest HIV/AIDS prevalence rates anywhere in the world.25,26 A subset of countries were faced with a triple burden of COVID-19, HIV, and tuberculosis simultaneously.27 The combined burden of these causes across southern sub-Saharan Africa was not offset by sufficient improvements in mortality from other causes, leading to an overall decline in the region’s life expectancy of more than four years over the entire study period.

### Cause-specific patterns of mortality concentration

Estimates of mortality concentration reflect shifting patterns of disease over time, from cosmopolitan impacts to more geographically reduced subsets of the global population. These changes highlight differences between populations and their progress toward reducing mortality due to diseases and injuries. They also provide an important opportunity to apply best public health practices more strategically to further disease reduction. Broadly, widespread declines in many communicable diseases resulted in mortality from these causes exhibiting more concentrated geographical distributions in 2021, relative to patterns seen in 1990. The degree of mortality concentration estimated by this study for enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, and tuberculosis reflects substantial global progress in reducing mortality from these causes over the study period, underscoring the success of numerous public health campaigns, global commitments, and improvements in communicable disease programmes.28–30 Estimates of mortality concentration can be used to examine where disease mitigation strategies have been successful, where they can be further implemented to reduce inequality, and where more research may be needed to develop effective treatment and intervention strategies.

Notably, our estimates show deaths from malaria exhibit an increasing degree of concentration over the study period and are now particularly concentrated within western sub-Saharan Africa, with an additional corridor running through central Africa and into Mozambique.31 Countries in western sub-Saharan Africa with the highest under-5 death rates from malaria in 2021 included Burkina Faso, Sierra Leone, and Niger. This malaria mortality concentration reflects both differential rates of population growth across Africa, as well as the varying rates of progress in reducing transmission, most notably by long lasting insecticide treated nets and in strengthening case management.32 At a time of growing threats to progress against malaria, including emerging parasite and vector resistance and budgetary pressures, but also promising new tools such as the recently approved second vaccine for malaria, it is more important than ever that changing patterns of mortality are quantified and understood.33,34

Enteric infections showed significant disease concentration, particularly in under-5 populations, with 90% of deaths occurring in locations containing 63% of the under-5 population in 1990, decreasing to 51% of the population by 2021. Under-5 deaths from enteric infections are now largely concentrated within sub-Saharan Africa and south Asia. Countries in sub-Saharan Africa and south Asia with the highest under-5 death rates from enteric infections in 2021 included Chad, South Sudan, and Central African Republic. There are many contributing factors that should be examined when evaluating how to reduce enteric infections in the remaining concentrated locations. Alongside the provision of oral rehydration solution and rotavirus vaccines, critical public health improvements such as in WaSH may have contributed to decreases in enteric deaths in recent years.35,36 Childhood growth failure, also a leading risk factor for lower respiratory infections, malaria, and measles deaths, must be addressed through interventions to improve women’s health including anaemia, promotion of early exclusive breastfeeding, and management of acute malnutrition, among others.37,38 There is substantial overlap in geographies with the highest burden of infectious disease mortality in children under-5, suggesting multisectoral approaches are necessary to successfully continue decreasing mortality in the countries with the highest rates.39

A broad and recurring theme from this study is that reductions in enteric infections contributed to improved life expectancies over the past several decades. The reductions in childhood mortality associated with diarrhoeal diseases that have occurred across many parts of Africa35,40–42 can also be partially explained by many combined local efforts in improved immunisation;43 access to water, sanitation, and hygiene (WaSH) facilities;12,44 breastfeeding;45 oral rehydration therapy;46 and zinc supplementation,15 alongside global initiatives like the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD).47 Given that enteric disease mortality and specifically diarrhoeal disease mortality continued to decline during the pandemic, the post-pandemic period may offer opportunities to accelerate progress on prevention and treatment. Diarrhoeal diseases are particularly amenable to public health intervention, and given its high burden among children, it is imperative that we continue to direct resources towards its prevention.47,48 Several locations still lack the needed financing, governance, and political commitment to improve rates of enteric infections.49 To accelerate progress in reducing enteric disease mortality, it will be especially important to strengthen and expand routine and catch-up immunisation programmes. This includes building on the global success of the rotavirus roll-out50 and countering disruptions in childhood immunisation during the pandemic.51 Additionally, efforts should focus on advancing candidate vaccines against enterotoxigenic *E. coli* (ETEC), norovirus, and shigella.51–55

Our study also found that some vaccine preventable diseases, such as measles, have shown widespread decreases in mortality rates and were geographically concentrated. 90% of measles deaths were concentrated in locations containing only 15% of the global population and 24% of the under-5 population in 2021. Under-5 deaths from measles are now concentrated within western and eastern sub-Saharan Africa. While multiple factors contribute to decreases in infectious disease burden, improvements in measles mortality have largely been attributable to the global availability of a safe and effective vaccine against measles, producing life-long immunity with two-dose efficacy exceeding 95%.56 Measles incidence has decreased dramatically where vaccination efforts have been successful, including North and South America, Europe, and Australia,57–61 although, since 2016, endemic measles transmission has been re-established in ten countries that previously had achieved measles elimination.61 We found that, as of 2021, measles mortality was concentrated in countries and regions with more limited access to the measles vaccine, particularly in sub-Saharan Africa. While valuable insights can be drawn from countries that have achieved measles control through effective vaccination programmes and surveillance systems, interventions still must be tailored to the impacted communities and countries for successful reductions in mortality.62

Some infectious diseases, such as HIV/AIDS and tuberculosis, also showed mortality concentration, with 90% of deaths from HIV/AIDS concentrated in locations containing 46% of the entire population and 39% of the under-5 population. Deaths from HIV/AIDS are now largely concentrated within sub-Saharan Africa, most notably southern sub-Saharan Africa. Countries in sub-Saharan Africa with the highest age-standardised mortality rate in 2021 included Lesotho, Eswatini, and Botswana. Countries in sub-Saharan Africa with the highest under-5 death rates from HIV in 2021 included Lesotho, Equatorial Guinea, and Guinea-Bissau. This concentration highlights how HIV control campaigns, preventative measures,63,64 improved treatment with the emergence of ART,65 access to testing and healthcare,66 and research advancements may have contributed to the reduced global mortality of HIV. Despite these successes, significant barriers remain to reducing HIV mortality, such as stigma discouraging people from accessing treatment and care,67,68 limited health-care infrastructure,69 access to testing,70 coverage of ART treatments,71 and complications due to co-occurring diseases like tuberculosis and HIV.72 Preventative measures are particularly important for the reduction of HIV mortality because HIV prevalence is the primary contributor to high mortality rates. While countries can learn from successful HIV campaigns and strategies, global support is needed to ensure HIV treatment and preventative measures are accessible to all populations at risk.70,73,74 Additionally, changes in death patterns of tuberculosis indicated mortality concentration, with 90% of deaths occurring in locations containing 66% of the entire population in 1990, decreasing to 62% by 2021. Deaths from tuberculosis are now largely concentrated within south Asia, southeast Asia, and sub-Saharan Africa.

In many high-income nations, the overall rate of neonatal deaths decreased between 1990 and 2021, becoming more concentrated over time. Neonatal deaths were concentrated in locations containing 71% of the global population in 1990, decreasing to 51% by 2021. Deaths from neonatal disorders are now concentrated within sub-Saharan Africa and south Asia.75 Countries in sub-Saharan Africa and south Asia with the highest under-5 death rates from neonatal disorders in 2021 included Mali with a mortality rate of 846.9 deaths (95% UI 712.0–997.7) per 100 000, South Sudan with 840.1 deaths (624.5–1105.8) per 100 000, and Sierra Leone with 754.2 deaths (588.8–932.5) per 100 000. However, the disparity in mortality between high- and low-income countries and regions highlights inequality in progress. Newborn care that can decrease mortality consists of resuscitation, prevention of hypothermia, infection, in-facility delivery, and exclusive breastfeeding.76,77 It may be possible to reduce neonatal mortality globally, if policy makers examine the strategies that led to successes elsewhere.78

Conversely, although many NCDs have also been on the decline, they have typically not followed the same pattern of mortality concentration seen in CMNNs. These trends emphasise a key distinction in the spatial dynamics of NCDs compared to many communicable diseases. While non-communicable causes may not exhibit the same degree of concentration, the mortality burden has changed in distribution, reducing over time in high-income countries and regions, while persisting in low-income countries and regions. Age-standardised mortality rates due to NCDs decreased in most locations within the high-income, Latin America and the Caribbean, north Africa and the Middle east, and central Europe, eastern Europe, and central Asia super-regions between 1990 and 2021. However, NCDs in the south Asia, sub-Saharan Africa, and southeast Asia, east Asia, and Oceania super-regions have either increased, or decreased at notably lower levels, in 2021 when compared with 1990. Examples of this include ischaemic heart disease, neoplasms, and stroke, all of which largely declined over the study period—though their reductions have been widely dispersed and not as targeted as the CMNN causes. These trends underscore that NCDs do not appear to be moving towards more condensed geographical locations over time in the same way that many CMNNs are, which could make interventions and policies more complex to implement.

Ultimately, the extent of mortality concentration reflects both the progress achieved in health-care advancements and the shortcomings that persist in their equitable implementation. Disease concentration is evidence that there are effective interventions and policies that have successfully reduced disease burden in many locations, but these innovations have not been equitably distributed throughout the world or have been ineffective at addressing the specific challenges certain populations face. There remains a global need to improve access to new interventions and vaccines, to invest in the implementation of validated public health policies, and to strategise with geographical sources of disease in mind. Future efforts should continue the ongoing mitigation of communicable diseases, focusing on locations where they have become more geographically concentrated, while also initiating efforts to combat chronic causes within low-resourced settings. Additionally, patterns of high geographical concentration among infectious causes and low geographical concentration among chronic ones reflect the global epidemiological transition, wherein mortality rates of infectious deaths declined throughout most years of our study. The increased concentration of a cause of death, particularly communicable diseases, illustrates success in mitigation that can be adapted within the countries and regions with mortality concentration identified in our study, with the potential to greatly reduce mortality from those causes of death.

### Limitations

Recent methodological advancements have enabled GBD 2021 to produce cause-specific estimates of mortality more easily; however, as with any study of this scope, there are several important limitations to acknowledge. Cause-specific limitations for every cause of death in GBD are detailed in appendix 1 section 3. Here, we describe cross-cutting limitations with applicability across many causes. First, sparsity of data and/or unreliability of data from specific regions, time periods, or age groups can influence the accuracy of our estimates, particularly poor data quality and coverage from western, eastern, southern, and central sub-Saharan Africa and south Asia. Second, the quality of cause of death and verbal autopsy data rely on accurately coded death certificates to the international standards set by the ICD and are subject to the practice of the physician completing the death certificate, who may or may not have received training to facilitate comparability of reporting underlying causes of death. This process is further complicated by comorbidities at the time of death, which may affect the accuracy of both VR and VA data sources. A key data processing method for GBD is the reallocation of incorrectly or vaguely assigned deaths—referred to as garbage codes11—to a more accurate, plausible underlying cause of death. This is an impactful step in our modelling process, creating comparable cause-specific estimates of mortality by underlying cause. Third, GBD evaluates quality of causes of death data in part by examining levels of completeness, which indicates the accuracy with which the VR can capture deaths that occur in a location-year, irrespective of the percentage of garbage coding. Data completeness depends on the percentage of well-certified data, which is not necessarily indicative of low garbage coding. Fourth, some sources of uncertainty, including the covariates used in models, are not captured in our estimation process. Fifth, we used a negative binomial modelling approach to improve our estimation of deaths for some causes with over-dispersed data, but do not have a standardised empirical approach for selecting causes to which we apply this method. Sixth, to provide estimates for locations with low levels of completeness, as well as to address the lags in data reporting that occur, our estimates for the most recent years depend more heavily on the modelling process. For causes where data are limited, providing estimates with appropriate uncertainty is preferable to providing no information. Seventh, in the calculation of life expectancy decomposition, there is instability when the difference in all-cause deaths is too small. In this case, we use the reduced Das Gupta equation, explained in appendix 1 section 7. Additionally, to avoid assigning positive life expectancy contributions to COVID-related causes, if the signs for the change in life expectancy and all-cause deaths are the same, we use the same reduced Das Gupta formula, except in the case that the cause in question is COVID-related (either COVID-19 or OPRM), where a modified version is used. When viewing life expectancy decomposition, it important to understand the effects of fatal discontinuity events, such as earthquakes or conflict. If life expectancy decomposition is calculated for 2 consecutive years, we can see the effect of unique, stochastic events, but for the longer time periods, the interpretation on the effect of these events will be misleading. This method works well with causes that have continuous time trends, and not for causes that have mortality spikes in select years and locations. This type of event confounds true health trends within a time period because the absence or presence of a disaster is seen as a change in life expectancy. Finally, this cycle of GBD contains additional limitations that pertain to modelling deaths and related mortality from the COVID-19 pandemic. The limitations of the methods used to calculate COVID-19 have been fully outlined in previous publications,12 but it is critical to reiterate that COVID-19 estimates are limited by data source availability. The methods to estimate COVID-19 were especially limited in certain regions, such as sub-Saharan Africa, which means our estimates in these areas are solely driven by relationships with covariates. Future development of these data sources is crucial because estimates improve as the quality of the underlying data sources improves. Subsequent GBD cycles will provide revised estimates after additional data for recent years become available.

### Future directions

In the next iteration of GBD, we will include over 100 location-years of vital registration and other data types that have been reported since GBD 2021 estimates were produced. Additionally, we will continue to expand the estimation of causes of death by disaggregating broad categories of causes of death into more detailed causes where available. These improvements aim to enhance precision and timeliness of the COVID-19 and other cause of death estimates. We also plan to simplify our approach to estimating COVID-19. In lieu of the residual OPRM category reported in GBD 2021, we will use all available location years of cause of death data to attribute mortality to specific causes, removing this residual category. We anticipate that this will facilitate more timely and actionable insights for public health planning and policy making, especially as we expect to observe more regular and modellable mortality patterns in the post-pandemic years. Through these advancements, we will improve the utility and accuracy of the GBD study as a critical tool for effective public strategies.

### Conclusion

The emergence of the COVID-19 pandemic has changed global mortality, causing 7.8 million deaths in 2021 and replacing stroke as the second leading cause of death. COVID-19 negatively impacted life expectancy in two years almost as much as the positive gains to life expectancy have improved it over the past decade. COVID-19, through reversing consistent improvements in life expectancy made through the reduction of communicable and non-communicable diseases, exposed gaps in health systems and highlighted the need for adequate emergency preparedness. The changes in mortality caused by the COVID-19 pandemic were not predictable through the standard GBD estimation methods and required the development and application of novel estimation methods as the pandemic emerged in real time. Despite the losses to life expectancy and mortality, GBD 2021 shows that better life expectancy outcomes may be achieved by analysing past successes in mortality reduction. If future policy efforts are guided by the successes made in countries and regions with effective disease mitigation programmes, they may be able replicate such achievements in locations where high mortality persists. While COVID-19 and other health challenges continue, GBD 2021 can offer valuable guidance for public health investment and policy making.

### Data sharing

To download the data used in these analyses, please visit the Global health Data Exchange GBD 2021 website (<https://ghdx.healthdata.org/gbd-2021/sources> [*note to editors and reviewers that this tool is currently password protected (password:* 2021AllSources*. Please do not share this password. The link will be made available to the public prior to publication*]).

### List of main text figures and tables

**Figure 1: Leading Level 3 causes of global deaths and age-standardised death rate per 100 000 for 1990, 2019, and 2021 for males and females combined**

Each column represents a year and displays the top 20 causes in descending order. Causes are connected by lines between time periods; solid lines represent an increase or lateral shift in ranking, dashed lines are decreases in rank. Communicable, maternal, neonatal, and nutritional diseases are shown in red; non-communicable causes in blue; and injuries in green. COPD=chronic obstructive pulmonary disease. OPRM=other pandemic-related mortality.

**Figure 2: Age-standardised mortality rate for leading ten causes of death globally, 2019–2021**

Whisker plot where the *y*-axis represents the age-standardised mortality rate and the *x*-axis represents a selected cause-year. The best estimate for a given cause-year is displayed in red, where the lower estimate is shown with the green whisker and the upper estimate is shown with the blue whisker. The whiskers represent the 95% uncertainty interval.

**Figure 3: Age-standardised mortality rate of COVID-19 and OPRM, 2021**

Global choropleth maps of COVID-19 and other pandemic-related mortality (OPRM) for 2021 that show subnational detail where available. The colour scale represents the age-standardised mortality rate per 100 000 population, where red indicates high and blue indicates low.

**Figure 4: Change in life expectancy attributable to leading causes of death in 1990–2000, 2000–2010, 2010–2019, and 2019–2021 for males and females combined**

Each row represents the change in global life expectancy from 1990 to 2021 for a given cause. The total change in life expectancy is further broken down by different colours to represent changes over time periods. Blue represents the 1990s, red 2000s, green 2010s, and purple since 2019. A bar to the right of zero represents an increase in life expectancy due to changes in the given cause, and a bar to the left of zero represents a decrease in life expectancy due to a given cause.

**Figure 5: Change in life expectancy attributable to leading causes of death in 1990–2021 among super-regions**

Each row represents the change in life expectancy from 1990 to 2021 for a given super-region. The total change in life expectancy is further broken down by different colours and patterns to represent the change attributed to specific causes. A bar to the right of zero represents an increase in life expectancy due to changes in the given cause, and a bar to the left of zero represents a decrease in life expectancy for a given super-region.

**Figure 6: Impact of COVID-19 on life expectancy by four periods of time and GBD regions**

This graph shows a bar chart that represents the total change in life expectancy due to COVID-19 over the period 2019-2021 by GBD regions. Each row shows a GBD region that is broken down by color to indicate the change in life expectancy by different year ranges. Yellow shows the change from 2019-2021.

**Figure 7: Impact of enteric infectious diseases on life expectancy by four periods of time and GBD regions**

This graph shows a bar chart that represents the total change in life expectancy due to enteric infections over the period 1990–2021 by GBD regions. Each row shows a GBD region that is broken down by colour to indicate the change in life expectancy by different year ranges. Blue shows the change from 1990 to 2000, red 2000 to 2010, green 2010 to 2019, and purple 2019 to 2021.

**Figure 8: Impact of lower respiratory infections on life expectancy by four periods of time and GBD regions**

This graph shows a bar chart that represents the total change in life expectancy due to lower respiratory infections over the period1990–2021 by GBD regions. Each row shows a GBD region that is broken down by colour to indicate the change in life expectancy by different year ranges. Blue shows the change from 1990 to 2000, red 2000 to 2010, green 2010 to 2019, and purple 2019 to 2021.

**Figure 9: Change in life expectancy attributable to leading causes of death in 1990–2021 among GBD regions**

Each row represents the change in life expectancy from 1990 to 2021 for a given region. The total change in life expectancy is further broken down by different colours and patterns to represent the change attributed to specific causes. A bar to the right of zero represents an increase in life expectancy due to changes in the given cause, and a bar to the left of zero represents a decrease in life expectancy for a given region.

**Table 1: Number of deaths and age-standardised death rate for the leading ten causes in 2020 and 2021, globally and by super-region, all ages, all sexes combined**

**Table 2: Number of deaths, age-standardised death rate, and percentage of total deaths due to COVID-19 and OPRM by age, global**

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