

Global, regional, and national age-sex-specific burden of diarrhoeal diseases, their risk factors, and aetiologies, 1990–2021, for 204 countries and territories: a systematic analysis for the Global Burden of Disease Study 2021

GBD 2021 Diarrhoeal Diseases Collaborators*



Summary

Background Diarrhoeal diseases claim more than 1 million lives annually and are a leading cause of death in children younger than 5 years. Comprehensive global estimates of the diarrhoeal disease burden for specific age groups of children younger than 5 years are scarce, and the burden in children older than 5 years and in adults is also understudied. We used results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 to assess the burden of, and trends in, diarrhoeal diseases overall and attributable to 13 pathogens, as well as the contributions of associated risk factors, in children and adults in 204 countries and territories from 1990 to 2021.

Methods We used the Cause of Death Ensemble modelling strategy to analyse vital registration data, verbal autopsy data, mortality surveillance data, and minimally invasive tissue sampling data. We used DisMod-MR (version 2.1), a Bayesian meta-regression tool, to analyse incidence and prevalence data identified via systematic reviews, population-based surveys, and claims and inpatient data. We calculated diarrhoeal disability-adjusted life-years (DALYs) as the sum of years of life lost (YLLs) and years lived with disability (YLDs) for each location, year, and age–sex group. For aetiology estimation, we used a counterfactual approach to quantify population-attributable fractions (PAFs). Additionally, we estimated the diarrhoeal disease burden attributable to the independent effects of risk factors using the comparative risk assessment framework.

Findings In 2021, diarrhoeal diseases caused an estimated 1·17 million (95% uncertainty interval 0·793–1·62) deaths globally, representing a 60·3% (50·6–69·0) decrease since 1990 (2·93 million [2·31–3·73] deaths). The most pronounced decline was in children younger than 5 years, with a 79·2% (72·4–84·6) decrease in diarrhoeal deaths. Global YLLs also decreased substantially, from 186 million (147–221) in 1990 to 51·4 million (39·9–65·9) in 2021. In 2021, an estimated 59·0 million (47·2–73·2) DALYs were attributable to diarrhoeal diseases globally, with 30·9 million (23·1–42·0) of these affecting children younger than 5 years. Leading risk factors for diarrhoeal DALYs included low birthweight and short gestation in the neonatal age groups, child growth failure in children aged between 1–5 months and 2–4 years, and unsafe water and poor sanitation in older children and adults. We estimated that the removal of all evaluated diarrhoeal risk factors would reduce global DALYs from 59·0 million (47·2–73·2) to 4·99 million (1·99–10·0) among all ages combined. Globally in 2021, rotavirus was the predominant cause of diarrhoeal deaths across all ages, with a PAF of 15·2% (11·4–20·1), followed by norovirus at 10·6% (2·3–17·0) and *Cryptosporidium* spp at 10·2% (7·03–14·3). In children younger than 5 years, the fatal PAF of rotavirus was 35·2% (28·7–43·0), followed by *Shigella* spp at 24·0% (15·2–37·9) and adenovirus at 23·8% (14·8–36·3). Other pathogens with a fatal PAF greater than 10% in children younger than 5 years included *Cryptosporidium* spp, typical enteropathogenic *Escherichia coli*, and enterotoxigenic *E coli* producing heat-stable toxin.

Interpretation The substantial decline in the global burden of diarrhoeal diseases since 1990, particularly in children younger than 5 years, supports the effectiveness of health interventions such as oral rehydration therapy, enhanced water, sanitation, and hygiene (WASH) infrastructure, and the introduction and scale-up of rotavirus vaccination. Targeted interventions and preventive measures against key risk factors and pathogens could further reduce this burden. Continued investment in the development and distribution of vaccines for leading pathogens remains crucial.

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Introduction

Diarrhoeal diseases, caused by various pathogens such as bacteria and viruses, are a major public health issue

worldwide, responsible for more than 1 million deaths each year.¹ These diseases are among the leading causes of death in children younger than 5 years, particularly in

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Research in context

Evidence before this study

The burden of diarrhoeal diseases, risk factors, and aetiologies in children younger than 5 years, often considered a homogeneous group, has been extensively studied by several groups, including WHO and the Maternal and Child Epidemiology Estimation Group (WHO-MCEE) and the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). The GBD 2017 diarrhoeal diseases study evaluated the impact of risk factors and interventions on the burden of diarrhoeal diseases in children younger than 5 years across 195 countries and territories. Evidence suggests that the diarrhoeal disease burden might vary within this age group due to factors such as differences in age-specific susceptibility and immune system development. Yet, global diarrhoeal disease burden estimates for specific age groups among children younger than 5 years, attributed to various risk factors and pathogens, have been largely unavailable due to studies aggregating data for all children younger than 5 years. We searched PubMed using the terms “diarrhea”[MeSH] AND (“burden” OR “estimates”) AND (“age” OR “sex” OR “gender”) AND “global” AND “risk”, without applying any language restrictions, for articles published from Jan 1, 1990, to Jan 27, 2024. The search yielded 70 studies. We did not identify any studies that evaluated global levels of, and trends in, diarrhoeal disease burden and corresponding risk factors by granular age groups in children younger than 5 years, or in older children and adults by age and sex.

Added value of this study

GBD 2021 included new data sources, compared with previous GBD iterations (including GBD 2019 and GBD 2017), for diarrhoeal mortality and morbidity and corresponding aetiologies, including pathogen-specific data from the Global Pediatric Diarrhoea Surveillance Network. This study also

differentiated the specific burdens of enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-EPEC) and typical enteropathogenic *E coli* (tEPEC), which were previously aggregated as all EPEC and all EPEC, respectively, in past GBD publications focusing on diarrhoeal diseases. Our study examines the burden of, and trends in, diarrhoeal diseases in children younger than 5 years across nuanced age categories and expands the scope of previous research by assessing the burden of diarrhoea in older children and adults, as well as analysing the burden attributable to risk factors by more granular age groups. Last, we provide risk-deleted burden estimates for the first time, representing the diarrhoeal disease burden that would occur if the effects of all evaluated risk factors were removed.

Implications of all the available evidence

The results of our study highlight the considerable progress made in reducing the burden of diarrhoeal diseases worldwide, with the most notable improvements observed in children younger than 5 years. This success reflects the effectiveness of concerted public health interventions, including the water, sanitation, and hygiene (WASH) initiative, rotavirus vaccination, and oral rehydration therapy. Our study underscores the important role of continued investment and innovation in vaccine development for leading pathogens and emphasises the importance of implementing comprehensive public health strategies that encompass improvements in WASH practices, nutrition, and access to health-care services. Effective implementation of these strategies could substantially accelerate the decline in the global burden of diarrhoeal diseases, particularly in the most vulnerable populations, and help bridge the gap in health disparities across different regions.

low-income and middle-income countries.² Recognising this crucial issue, global health initiatives such as WHO and UNICEF's Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea have been established, setting ambitious goals such as ending preventable deaths from diarrhoeal diseases in children younger than 5 years by 2025.³ Available evidence indicates the uneven distribution of the diarrhoeal disease burden in children younger than 5 years, potentially due to factors such as differences in age-specific susceptibility and immune system development.^{4–6} Although a granular understanding of the age-specific burden can enhance refinement and prioritisation of interventions towards achieving the global goals, existing literature⁷ on the global burden of diarrhoeal diseases has predominantly reported combined results for all children younger than 5 years as a homogeneous group. Whereas diarrhoeal episodes tend to be milder in older children and adults,⁸ the diarrhoeal burden continues to put a strain on economies,^{9,10} health-care systems, and the overall health

of communities around the world.¹¹ Although previous studies have highlighted the growing burden of diarrhoeal diseases in older people,^{2,12} the burden in older children and adult age groups has not been comprehensively studied. Expanding the analytical focus to include both granular age groups aged younger than 5 years along with those aged 5 years and older (child and adult age groups) aligns with Sustainable Development Goal 3 of ensuring healthy lives and promoting wellbeing for all ages.¹³

Previous research reports diarrhoea as the fifth leading cause of death among children younger than 5 years, with rotavirus as the leading aetiology for diarrhoea mortality among both children aged younger than 5 years and all ages combined.² Although the results presented in this study continue to report rotavirus as a leading pathogen, it is important to explore other aetiologies with a high burden. Previous publications of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) focused on diarrhoeal diseases aggregated data for the heat-stable toxin (ST) and heat-labile toxin (LT) genotypes of

enterotoxigenic *Escherichia coli* (ETEC).^{2,14} However, the Global Enteric Multicenter Study (GEMS) showed that ETEC strains producing ST, whether alone or alongside LT, substantially contributed to moderate-to-severe diarrhoea in children in low-income to middle-income countries.¹⁵ GEMS also indicated that both ST-ETEC and typical enteropathogenic *E coli* (tEPEC) strains were associated with an increased risk of diarrhoeal mortality in infants after adjusting for other pathogens and study sites,¹⁵ yet these were grouped under ETEC and all EPEC, respectively, in previous GBD studies.^{2,14}

To address crucial gaps in our understanding of diarrhoeal diseases, we used data from GBD 2021 to assess the burden of, and trends in, diarrhoeal diseases and risk factors across all age groups, including granular age groups in children younger than 5 years, by sex, for 204 countries and territories from 1990 to 2021. We also aimed to assess the burden of diarrhoeal diseases attributable to 13 pathogens, including ST-ETEC and tEPEC separately, to better assess their individual burdens and inform targeted interventions against pathogen-specific diarrhoeal diseases. Additionally, by reporting the risk-deleted burden, we offer an opportunity to assess what the theoretical burden of diarrhoea might be in ideal scenarios, in which the impact of risk factors has been removed. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.

Methods

Overview

GBD is a systematic, scientific effort to quantify the comparative magnitude of health loss caused by diseases, injuries, and risk factors by age, sex, and geography over time. The GBD geographical hierarchy includes 204 countries and territories, which are grouped into 21 regions based on epidemiological similarities and geographical closeness. These regions are further aggregated into seven super-regions according to cause-of-death patterns. Detailed methods for GBD have been published elsewhere.^{1,16} Here, we describe the methods and estimation strategies used for diarrhoeal diseases and their corresponding risk factors and pathogens.

Burden of diarrhoeal diseases overall and due to specific aetiologies

Input data for estimating mortality from diarrhoeal diseases comprised vital registration data spanning 24181 site-years (ie, the total number of years of data available for all locations with data), 825 site-years of sample-based vital registration data, 1785 site-years of verbal autopsy data, 575 site-years of mortality surveillance data, and nine site-years of minimally invasive tissue sampling data. The data were adjusted for incomplete death registration and garbage coding.^{1,17} Using these input data, we estimated diarrhoeal disease mortality using the Cause of Death Ensemble modelling (CODEm) strategy.^{1,18}

This approach involves analysing a diverse array of sub-models, each using different combinations of predictive covariates, such as access to improved water sources, coverage of oral rehydration therapy, and the Socio-demographic Index.¹⁹ The covariates used in our analysis are detailed in appendix 1 (p 14). These sub-models include mixed-effects regression models and spatiotemporal Gaussian process regression models with cause fractions and mortality rates as the outcome variables. We tested the out-of-sample predictive validity of the sub-models, which were then combined into an ensemble with the best out-of-sample predictive performance.

Input data for estimating diarrhoeal disease morbidity included incidence and prevalence data identified via systematic reviews, population-based surveys, claims data, and inpatient data (appendix 1 pp 15–18). Before modelling, we enhanced the comparability of the data from different sources (appendix 1 pp 16–17). We used DisMod-MR (version 2.1),^{1,20} a Bayesian meta-regression tool that imposes coherence between data for different parameters, to produce incidence and prevalence estimates.

For aetiology (pathogen) estimation, we used a counterfactual approach consistent with previous GBD cycles^{1,2} that incorporated the pathogen-specific risk of diarrhoeal disease and the prevalence of the pathogen in diarrhoea episodes (appendix 1 pp 21–29). We estimated population attributable fractions (PAFs) for the following pathogens: adenovirus, *Aeromonas* spp, *Campylobacter* spp, *Clostridium difficile*, *Cryptosporidium* spp, *Entamoeba histolytica*, norovirus, rotavirus, non-typhoidal *Salmonella* spp, *Shigella* spp, ST-ETEC, tEPEC, and *Vibrio cholerae*. We calculated disability-adjusted life-years (DALYs) for diarrhoeal diseases—a composite measure of burden that captures both premature mortality and the prevalence and severity of diarrhoea—as the sum of years of life lost (YLLs) due to premature mortality and years lived with disability (YLDs) from GBD 2021.

Risk factors

Detailed methods for GBD risk factor estimation have been published elsewhere.¹⁶ In summary, we first selected risk–outcome pairs (eg, diarrhoeal disease attributable to suboptimal breastfeeding) based on evidence of a convincing or probable causal relationship between the risk and the outcome. The list of diarrhoeal disease risk factors and the mechanism through which each risk factor could result in diarrhoeal diseases is summarised in appendix 1 (p 74). The PAFs of risk factors were quantified by estimating the risk factor exposure distributions and the relative risk of the association between each risk factor and outcome and determining the theoretical minimum risk exposure level (TMREL). More details of these methods are provided in appendix 1 (pp 31–71). The PAF is the fraction of diarrhoeal disease DALYs that would have been reduced if the exposure to the risk factor had been at the TMREL. The attributable burden was computed by multiplying the location–year–age–sex-specific PAFs of

See Online for appendix 1

risk factors by corresponding diarrhoeal disease DALYs. We also calculated risk-deleted diarrhoeal disease DALYs to represent the DALYs that would have been observed had the risk factors been set to their corresponding TMREs.

Uncertainty intervals, age standardisation, percentage changes, and result presentation

We computed 95% uncertainty intervals (UIs) based on 1000 draws from the posterior distribution of each quantity of interest using the 2·5th and 97·5th percentiles of the 1000 ordered values. We used the GBD world population age standard²¹ to calculate age-standardised diarrhoeal disease mortality and DALY rates. The

percentage change was calculated by subtracting the initial value (eg, for the year 1990) from the final value (eg, for the year 2021), then dividing the result by the initial value and multiplying by 100. Count estimates are presented to three significant figures, and percentages and rates are presented to 1 decimal place. We present results in aggregated age groups (all ages, <5 years, 5–14 years, 15–49 years, 50–69 years, and ≥70 years) and more granular age groups for those aged younger than 5 years (early neonatal, late neonatal, 1–5 months, 6–11 months, 12–23 months, 2–4 years) for the years 1990 to 2021. Additional age–sex-specific results for diarrhoea and aetiologies can be found in the GBD Results Tool.

For the GBD Results Tool see
<https://vizhub.healthdata.org/gbd-results/>

	Male				Female			
	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021
Global								
All ages	561 000 (365 000 to 841 000)	14·2 (9·2 to 21·2)	–62·4% (–71·0 to –51·6)	–74·5% (–80·3 to –67·2)	605 000 (346 000 to 966 000)	15·4 (8·8 to 24·6)	–58·0% (–71·2 to –43·8)	–71·7% (–80·6 to –62·2)
<5 years	185 000 (128 000 to 271 000)	54·5 (37·6 to 79·7)	–78·6% (–84·5 to –70·6)	–79·9% (–85·5 to –72·4)	155 000 (116 000 to 209 000)	48·7 (36·4 to 65·7)	–79·9% (–86·0 to –71·8)	–81·0% (–86·8 to –73·4)
5–14 years	18 000 (8 030 to 32 200)	2·6 (1·1 to 4·6)	–65·3% (–78·9 to –49·1)	–71·4% (–82·7 to –58·2)	15 800 (6 420 to 31 200)	2·4 (1·0 to 4·8)	–69·3% (–80·3 to –54·0)	–74·5% (–83·6 to –61·8)
15–49 years	58 700 (25 500 to 106 000)	2·9 (1·3 to 5·3)	–46·9% (–61·7 to –25·1)	–63·6% (–73·7 to –48·6)	47 800 (18 100 to 92 200)	2·5 (0·9 to 4·7)	–50·2% (–65·0 to –26·4)	–65·8% (–76·0 to –49·5)
50–69 years	92 400 (41 700 to 170 000)	13·1 (5·9 to 24·1)	–49·9% (–62·8 to –31·8)	–76·1% (–82·2 to –67·4)	94 200 (37 300 to 187 000)	12·9 (5·1 to 25·5)	–47·6% (–61·5 to –27·0)	–75·3% (–81·9 to –65·6)
≥70 years	206 000 (110 000 to 363 000)	94·8 (50·7 to 167·0)	–25·8% (–45·1 to –0·5)	–71·8% (–79·1 to –62·1)	292 000 (135 000 to 534 000)	105·4 (48·8 to 192·7)	–15·1% (–39·4 to 24·5)	–63·4% (–73·9 to –46·4)
Central Europe, eastern Europe, and central Asia								
All ages	2 270 (1890 to 2760)	1·1 (0·9 to 1·4)	–75·3% (–80·3 to –70·3)	–75·1% (–80·2 to –70·1)	2760 (2380 to 3210)	1·3 (1·1 to 1·5)	–66·2% (–71·4 to –60·0)	–65·9% (–71·1 to –59·7)
<5 years	1070 (701 to 1520)	8·1 (5·3 to 11·5)	–87·2% (–92·0 to –82·2)	–82·4% (–89·0 to –75·4)	919 (638 to 1310)	7·4 (5·1 to 10·6)	–87·6% (–91·5 to –82·4)	–82·5% (–87·9 to –75·2)
5–14 years	29 (17 to 47)	0·1 (0·1 to 0·2)	–74·0% (–82·6 to –60·8)	–67·4% (–78·2 to –50·8)	28 (17 to 45)	0·1 (0·1 to 0·2)	–72·5% (–81·1 to –59·7)	–64·6% (–75·6 to –48·1)
15–49 years	121 (96 to 156)	0·1 (0·1 to 0·2)	–45·0% (–53·5 to –33·1)	–43·0% (–51·9 to –30·7)	78 (65 to 98)	0·1 (0·1 to 0·1)	–46·3% (–53·3 to –37·0)	–43·8% (–51·1 to –34·1)
50–69 years	292 (263 to 325)	0·6 (0·6 to 0·7)	12·1% (3·4 to 22·2)	–9·0% (–16·1 to –0·9)	252 (230 to 275)	0·5 (0·4 to 0·5)	34·3% (24·5 to 44·3)	16·4% (7·8 to 25·1)
≥70 years	755 (684 to 838)	5·5 (5·0 to 6·1)	320·6% (270·4 to 365·0)	132·8% (105·0 to 157·3)	1480 (1260 to 1640)	5·7 (4·9 to 6·4)	409·1% (341·5 to 462·4)	248·2% (202·0 to 284·7)
High income								
All ages	12 100 (10 800 to 13 000)	2·3 (2·0 to 2·4)	321·1% (283·1 to 348·1)	249·1% (217·6 to 271·5)	17 700 (14 100 to 20 000)	3·2 (2·5 to 3·6)	337·9% (284·0 to 376·2)	266·2% (221·1 to 298·2)
<5 years	208 (180 to 239)	0·7 (0·6 to 0·9)	–74·5% (–78·5 to –70·4)	–71·0% (–75·6 to –66·3)	179 (154 to 205)	0·7 (0·6 to 0·8)	–71·2% (–75·2 to –66·6)	–67·4% (–71·9 to –62·2)
5–14 years	21 (19 to 24)	0·0 (0·0 to 0·0)	–34·5% (–50·2 to –18·9)	–32·5% (–48·6 to –16·4)	19 (17 to 21)	0·0 (0·0 to 0·0)	–22·0% (–42·9 to –1·5)	–19·6% (–41·2 to 1·5)
15–49 years	220 (204 to 238)	0·1 (0·1 to 0·1)	65·3% (43·8 to 90·4)	60·2% (39·4 to 84·5)	174 (163 to 184)	0·1 (0·1 to 0·1)	107·2% (79·4 to 137·3)	101·6% (74·5 to 130·9)
50–69 years	1490 (1410 to 1600)	1·1 (1·0 to 1·2)	284·4% (251·6 to 318·2)	135·7% (115·6 to 156·4)	1380 (1310 to 1460)	1·0 (0·9 to 1·0)	351·6% (309·8 to 391·8)	192·6% (165·5 to 218·7)
≥70 years	10 200 (8930 to 11 000)	15·5 (13·5 to 16·6)	573·6% (519·8 to 617·5)	191·1% (167·8 to 210·0)	16 000 (12 400 to 18 200)	18·3 (14·2 to 20·9)	430·5% (372·2 to 478·5)	188·4% (156·7 to 214·5)

(Table continues on next page)

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Global trends in diarrhoeal disease mortality

Globally in 2021, diarrhoeal diseases accounted for 1·17 million (95% UI 0·793–1·62) deaths, a 60·3% (50·6–69·0) decline from the 2·93 million (2·31–3·73) estimated deaths in 1990. During this period, the reduction

in diarrhoeal mortality rates per 100 000 population across age–sex groups varied from a 79·2% (72·4–84·6) decrease in children younger than 5 years (both males and females) to a 63·4% (46·4–73·9) decrease in women aged 70 years and older (table, figure 1).

The global estimated total YLLs due to diarrhoeal diseases decreased substantially, from 186 million (95% UI 147–221) in 1990 to 51·4 million (39·9–65·9) in 2021 (figure 2). Children younger than 5 years showed the most significant drop in YLLs during this period, from 146 million (114–172) in 1990 to 30·3 million (22·3–41·3) in 2021. Declines were also seen in older age groups

	Male				Female			
	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021
(Continued from previous page)								
Latin America and Caribbean								
All ages	12 600 (10 400 to 15 500)	4·3 (3·6 to 5·3)	–80·4% (–83·9 to –76·6)	–87·0% (–89·3 to –84·5)	13 000 (11 200 to 15 400)	4·3 (3·7 to 5·1)	–76·1% (–79·5 to –71·7)	–84·4% (–86·7 to –81·6)
<5 years	4610 (3290 to 6150)	19·1 (13·6 to 25·5)	–90·9% (–93·5 to –87·9)	–90·5% (–93·3 to –87·4)	3580 (2550 to 4700)	15·5 (11·0 to 20·3)	–91·3% (–93·9 to –88·6)	–90·9% (–93·5 to –88·0)
5–14 years	312 (225 to 434)	0·6 (0·5 to 0·9)	–81·4% (–85·7 to –76·1)	–81·8% (–86·0 to –76·7)	258 (194 to 355)	0·5 (0·4 to 0·8)	–83·6% (–86·7 to –79·6)	–83·6% (–86·7 to –79·6)
15–49 years	1160 (933 to 1490)	0·8 (0·6 to 1·0)	–60·7% (–66·5 to –52·4)	–75·3% (–78·9 to –70·1)	881 (719 to 1140)	0·6 (0·5 to 0·7)	–60·6% (–66·6 to –52·8)	–74·9% (–78·7 to –70·0)
50–69 years	2030 (1690 to 2500)	4·1 (3·4 to 5·1)	–41·7% (–48·8 to –32·6)	–78·2% (–80·8 to –74·7)	2020 (1740 to 2480)	3·7 (3·2 to 4·5)	–26·9% (–35·5 to –17·9)	–74·1% (–77·1 to –70·9)
≥70 years	4470 (3860 to 5240)	29·6 (25·5 to 34·7)	–23·8% (–30·4 to –16·6)	–74·7% (–76·9 to –72·3)	6240 (5230 to 7340)	32·2 (27·0 to 37·8)	–0·3% (–10·0 to 8·5)	–69·8% (–72·7 to –67·1)
North Africa and Middle East								
All ages	8840 (5880 to 13700)	2·7 (1·8 to 4·2)	–83·1% (–88·3 to –77·7)	–90·9% (–93·7 to –88·0)	7160 (5030 to 9840)	2·4 (1·7 to 3·3)	–84·1% (–88·4 to –78·2)	–91·2% (–93·6 to –88·0)
<5 years	6400 (3970 to 11100)	20·3 (12·6 to 35·2)	–86·8% (–91·2 to –81·4)	–89·0% (–92·7 to –84·5)	5070 (3580 to 7170)	17·1 (12·1 to 24·2)	–87·9% (–91·4 to –83·5)	–89·8% (–92·8 to –86·1)
5–14 years	305 (97 to 641)	0·5 (0·2 to 1·0)	–63·8% (–84·2 to –34·7)	–73·7% (–88·6 to –52·5)	243 (90 to 536)	0·4 (0·2 to 0·9)	–66·5% (–82·9 to –26·9)	–75·4% (–87·4 to –46·3)
15–49 years	387 (131 to 710)	0·2 (0·1 to 0·4)	–34·8% (–53·1 to –4·8)	–69·4% (–78·0 to –55·3)	303 (101 to 599)	0·2 (0·1 to 0·4)	–31·0% (–52·5 to 15·1)	–66·2% (–76·7 to –43·5)
50–69 years	454 (163 to 822)	1·0 (0·4 to 1·9)	–33·4% (–52·1 to 0·1)	–75·7% (–82·5 to –63·5)	372 (137 to 799)	0·9 (0·3 to 1·9)	–28·6% (–52·1 to 5·3)	–73·5% (–82·2 to –61·0)
≥70 years	1290 (497 to 2610)	13·0 (5·0 to 26·2)	–16·5% (–38·5 to 22·7)	–69·9% (–77·8 to –55·8)	1160 (442 to 2520)	11·2 (4·3 to 24·2)	–18·6% (–51·5 to 21·6)	–71·5% (–83·0 to –57·4)
South Asia								
All ages	249 000 (143 000 to 448 000)	26·4 (15·2 to 47·6)	–64·9% (–74·8 to –53·3)	–78·8% (–84·8 to –71·8)	323 000 (151 000 to 612 000)	35·7 (16·7 to 67·6)	–58·5% (–74·4 to –39·5)	–75·9% (–85·2 to –64·9)
<5 years	30 700 (15 200 to 50 000)	37·1 (18·4 to 60·5)	–89·4% (–95·0 to –83·7)	–89·6% (–95·1 to –83·9)	25 500 (16 400 to 37 200)	33·6 (21·6 to 49·0)	–92·1% (–94·7 to –88·5)	–92·1% (–94·7 to –88·5)
5–14 years	6000 (2480 to 11 300)	3·3 (1·4 to 6·2)	–81·2% (–88·0 to –73·6)	–85·1% (–90·5 to –79·1)	6980 (2650 to 13 000)	4·2 (1·6 to 7·8)	–79·3% (–86·8 to –69·4)	–83·5% (–89·5 to –75·7)
15–49 years	22 300 (8910 to 45 100)	4·4 (1·7 to 8·8)	–65·6% (–73·7 to –55·4)	–81·6% (–85·9 to –76·2)	23 400 (9000 to 46 900)	4·7 (1·8 to 9·5)	–60·3% (–71·8 to –46·4)	–79·5% (–85·5 to –72·4)
50–69 years	49 200 (21 400 to 95 500)	38·0 (16·5 to 73·7)	–60·1% (–69·7 to –48·9)	–82·4% (–86·6 to –77·5)	59 100 (22 600 to 124 000)	45·4 (17·4 to 95·4)	–51·8% (–66·1 to –36·4)	–81·3% (–86·9 to –75·4)
≥70 years	141 000 (73 100 to 264 000)	404·4 (210·1 to 757·9)	–29·3% (–47·7 to –2·0)	–75·6% (–81·9 to –66·2)	208 000 (92 400 to 403 000)	541·1 (240·4 to 1048·2)	–13·2% (–42·9 to 24·0)	–74·1% (–83·0 to –63·0)

(Table continues on next page)

	Male				Female			
	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021	Number of deaths in 2021	Mortality rate (per 100 000 population) in 2021	Percentage change in number of deaths, 1990–2021	Percentage change in mortality rate (per 100 000 population), 1990–2021
(Continued from previous page)								
Southeast Asia, east Asia, and Oceania								
All ages	40 900 (21 800 to 59 800)	3.7 (2.0 to 5.4)	–80.7% (–87.4 to –71.0)	–85.0% (–90.3 to –77.5)	42 500 (18 000 to 64 800)	4.0 (1.7 to 6.0)	–78.7% (–89.3 to –65.7)	–83.6% (–91.7 to –73.6)
<5 years	9060 (6100 to 12 900)	12.4 (8.4 to 17.6)	–93.2% (–95.6 to –89.0)	–91.5% (–94.4 to –86.1)	7200 (5610 to 9140)	11.0 (8.6 to 14.0)	–93.5% (–95.7 to –90.1)	–91.7% (–94.5 to –87.4)
5–14 years	918 (475 to 1750)	0.6 (0.3 to 1.1)	–85.9% (–92.0 to –73.8)	–85.2% (–91.6 to –72.5)	634 (263 to 1360)	0.4 (0.2 to 0.9)	–89.1% (–93.1 to –79.7)	–88.1% (–92.4 to –77.8)
15–49 years	4270 (1800 to 7940)	0.8 (0.3 to 1.4)	–71.6% (–83.2 to –51.1)	–75.5% (–85.5 to –57.8)	2650 (1010 to 5760)	0.5 (0.2 to 1.1)	–77.7% (–86.6 to –56.0)	–80.4% (–88.2 to –61.3)
50–69 years	9090 (3590 to 15 500)	3.5 (1.4 to 6.0)	–58.2% (–76.0 to –26.5)	–82.9% (–90.2 to –69.9)	8050 (2600 to 14 200)	3.1 (1.0 to 5.4)	–64.2% (–81.8 to –16.4)	–86.1% (–92.9 to –67.4)
≥70 years	17 500 (6660 to 26 300)	25.4 (9.6 to 38.1)	–49.2% (–71.6 to –7.7)	–84.1% (–91.1 to –71.0)	24 000 (7440 to 38 100)	28.3 (8.8 to 45.0)	–50.7% (–76.5 to 12.0)	–83.6% (–92.2 to –62.7)
Sub-Saharan Africa								
All ages	235 000 (156 000 to 333 000)	42.1 (28.0 to 59.7)	–46.8% (–62.8 to –24.8)	–76.8% (–83.8 to –67.2)	199 000 (129 000 to 278 000)	34.5 (22.3 to 48.3)	–43.5% (–60.9 to –21.1)	–75.6% (–83.1 to –66.0)
<5 years	133 000 (87 100 to 199 000)	151.9 (99.2 to 226.6)	–60.1% (–73.2 to –41.8)	–79.4% (–86.1 to –70.0)	113 000 (76 700 to 163 000)	132.4 (90.2 to 191.2)	–53.9% (–70.6 to –29.4)	–76.0% (–84.7 to –63.1)
5–14 years	10 400 (4510 to 18 800)	6.8 (3.0 to 12.3)	–3.3% (–54.2 to 68.6)	–57.3% (–79.8 to –25.6)	7620 (3070 to 15 600)	5.1 (2.0 to 10.4)	–19.6% (–53.6 to 66.6)	–64.0% (–79.2 to –25.4)
15–49 years	30 200 (13 300 to 54 800)	11.4 (5.0 to 20.6)	12.9% (–37.7 to 78.0)	–54.6% (–75.0 to –28.5)	20 300 (7520 to 39 600)	7.2 (2.7 to 14.1)	–8.6% (–46.1 to 81.5)	–63.5% (–78.5 to –27.5)
50–69 years	29 800 (12 900 to 51 900)	69.4 (30.0 to 120.7)	–14.2% (–55.2 to 37.2)	–61.0% (–79.6 to –37.6)	23 100 (8360 to 43 800)	48.5 (17.6 to 92.0)	–25.8% (–55.9 to 42.2)	–70.4% (–82.4 to –43.3)
≥70 years	31 200 (14 000 to 51 900)	358.1 (160.2 to 595.1)	–11.8% (–51.3 to 30.5)	–56.4% (–75.9 to –35.4)	35 100 (13 200 to 64 500)	323.2 (121.3 to 593.2)	–20.8% (–53.1 to 41.5)	–64.1% (–78.8 to –35.9)

Data in parentheses are 95% uncertainty intervals. Each section represents estimates at the global or super-region level. All ages is an aggregate of all child and adult age groups. The <5 years category is an aggregate of all granular age groups aged <5 years. Count estimates are presented to three significant figures, and percentages and rates are presented to 1 decimal place. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Table: Diarrhoeal deaths and mortality rates in 2021 and percentage change in deaths and mortality rates between 1990 and 2021 by age, sex, and GBD super-region

between 1990 and 2021: YLLs decreased from 8.39 million (4.94–12.0) to 2.73 million (1.58–4.49) in those aged 5–14 years, from 11.8 million (7.22–19.0) to 6.04 million (3.41–9.84) in those aged 15–49 years, from 10.8 million (6.76–17.5) to 5.48 million (3.10–8.59) in those aged 50–69 years, and from 9.15 million (5.86–13.8) to 6.92 million (4.11–10.6) in those aged 70 years and older.

Annualised rates of change in diarrhoeal disease mortality in 1990–2019 and 2019–2021

Before the COVID-19 pandemic, from 1990 to 2019, the global all-age diarrhoeal disease mortality rate changed at a rate of –4.2% (95% UI –5.0 to –3.5) per year, with substantial variation across regions and countries, indicating an increase, decrease, or no change in diarrhoeal disease mortality rates (appendix 2 table S1). From 2019 to 2021, the global all-age diarrhoeal disease mortality rate changed at a rate of –5.0% (–7.3 to –2.7) per year, showing similar variation across regions and countries (appendix 2 table S1).

Variation in diarrhoeal disease mortality in 2021

In 2021, when comparing diarrhoeal disease mortality rates across different age–sex groups in children younger than 5 years, the highest global mortality rates were estimated to be in the early neonatal age group (0–6 days old), with 471.0 (95% UI 286.2–812.0) deaths per 100 000 population in males and 348.7 (274.6–471.4) deaths per 100 000 population in females. As age increased, mortality rates declined, reaching 15.1 (9.2–23.9) deaths per 100 000 population in males and 14.2 (9.2–21.5) deaths per 100 000 population in females aged 2–4 years (appendix 2 table S2). Among other age groups, the highest global mortality rates due to diarrhoeal diseases in 2021 were estimated to be in those aged 70 years and older, with 94.8 (50.7–167.0) deaths per 100 000 population in males and 105.4 (48.8–192.7) deaths per 100 000 population in females (table). Those aged 5–14 years had the lowest mortality rates: 2.6 (1.1–4.6) deaths per 100 000 population in males and 2.4 (1.0–4.8) deaths per 100 000 population in females.

See Online for appendix 2

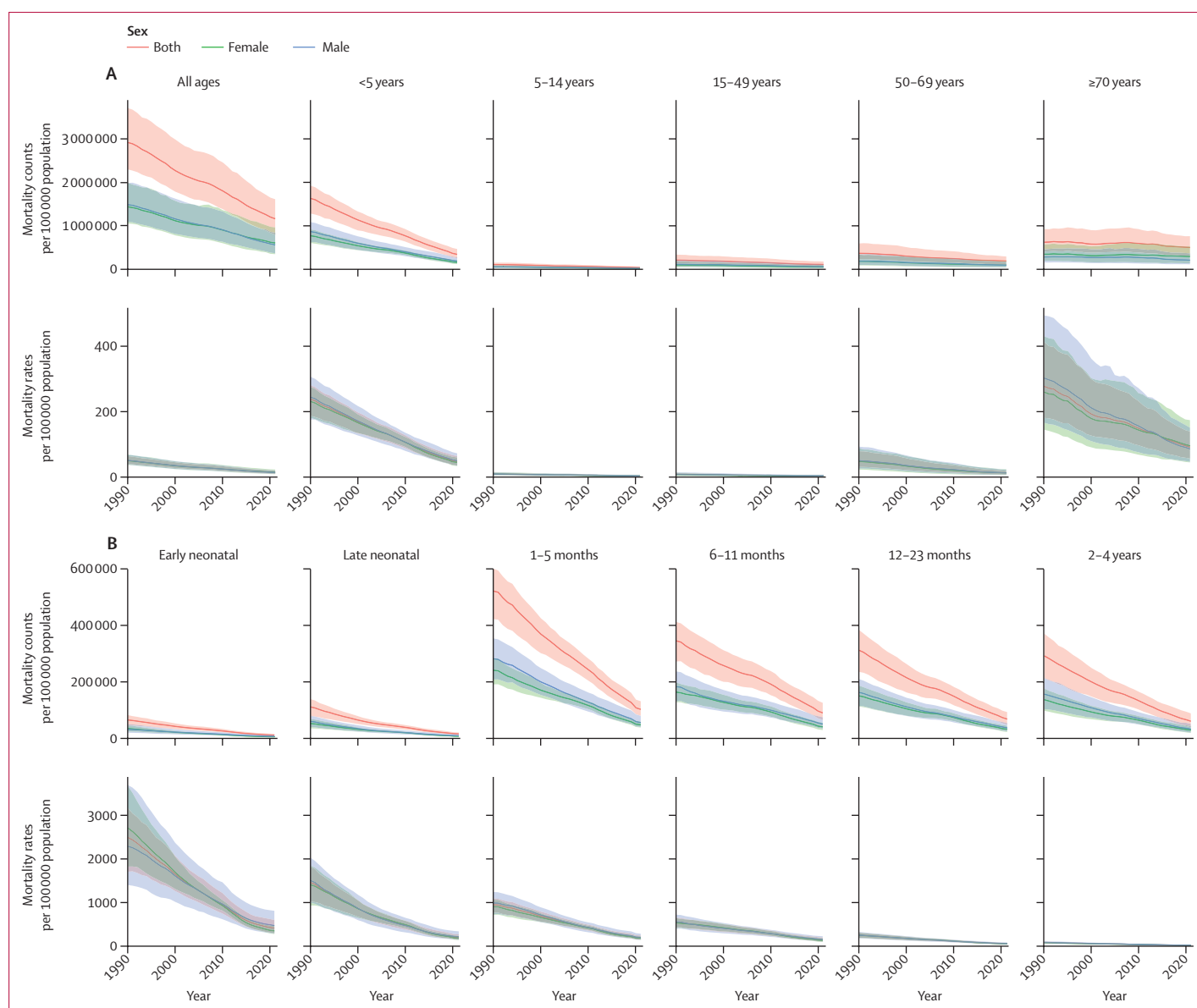


Figure 1: Diarrhoeal mortality rates per 100 000 and counts by broad age categories (A) and under-5 age groups (B), from 1990 to 2021

Shaded areas represent 95% uncertainty intervals. Early neonatal represents newborns aged 0–6 days. Late neonatal represents newborns aged 7–27 days.

Regionally, in 2021, sub-Saharan Africa had the highest mortality rates for children younger than 5 years (151·9 [95% UI 99·2–226·6] deaths per 100 000 population in males and 132·4 [90·2–191·2] deaths per 100 000 population in females), while south Asia had the highest rates in those aged 70 years and older (404·4 [210·1–757·9] deaths per 100 000 population in males and 541·1 [240·4–1048·2] deaths per 100 000 population in females; table). Although diarrhoeal mortality rates declined substantially across age groups in most super-regions, in the high-income super-region, as well as in central Europe, eastern Europe, and central Asia, the mortality rates from diarrhoea in adults aged 50–69 years

and those 70 years and older either did not change or increased between 1990 and 2021 (table). At the country level, age-standardised mortality rates per 100 000 population were greater than 100 in seven countries (South Sudan, Central African Republic, Chad, Somalia, Lesotho, Niger, and Eritrea) for males and in three countries (South Sudan, Chad, and Somalia) for females in 2021 (figure 3).

Diarrhoeal disease burden attributable to risk factors

In 2021, we estimated a global total of 59·0 million (95% UI 47·2–73·2) DALYs due to diarrhoeal diseases; 30·9 million (23·1–42·0) of these DALYs were in children

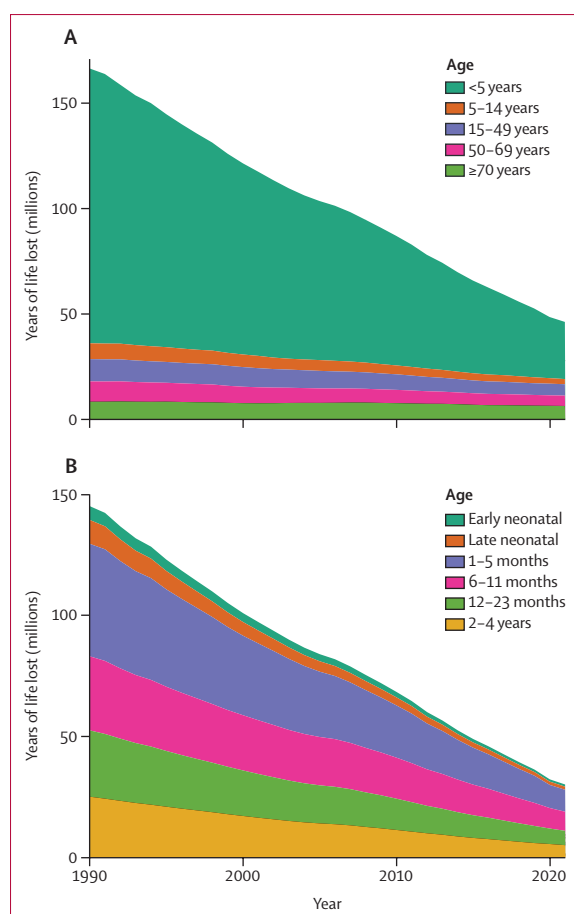


Figure 2: Years of life lost due to diarrhoeal diseases by broad age categories (A) and under-5 age groups (B), from 1990 to 2021

Years of life lost are shown in millions with each colour representing one age group. Early neonatal represents newborns aged 0–6 days. Late neonatal represents newborns aged 7–27 days.

younger than 5 years (appendix 2 table S3). Of the total DALYs, 54.0 million (42.2–67.1) were attributed to all evaluated diarrhoeal risk factors. Of the DALYs estimated for children younger than 5 years, 30.4 million (22.8–41.0) were attributed to all evaluated diarrhoeal risk factors.

A breakdown by age among children younger than 5 years reveals that in the early neonatal group (newborns aged 0–6 days), low birthweight and short gestation was the predominant risk factor, contributing to 683 000 (95% UI 493 000–1 030 000) DALYs (figure 4). This was closely followed by unsafe water, at 666 000 (365 000–1 060 000) DALYs. Unsafe sanitation practices resulted in about 523 000 (365 000–773 000) DALYs, while no access to handwashing facilities added another 217 000 (32 700–408 000) DALYs. The leading risk factors for the late neonatal group (newborns aged 7–27 days) remained similar to those in the early neonatal group, with the addition of suboptimal breastfeeding, which contributed 607 000 (428 000–845 000) DALYs.

For infants aged 1–5 months, the largest risk factor for diarrhoeal diseases was child growth failure, accounting for 7.34 million (95% UI 3.90–9.96) DALYs (figure 4A). Unsafe water was the second leading risk factor, contributing 6.73 million (3.66–9.41) DALYs. Poor sanitation practices followed as the third leading risk factor, contributing 5.27 million (3.94–6.85) DALYs, and suboptimal breastfeeding was the fourth, contributing 4.37 million (3.19–5.84) DALYs. In infants aged 6–11 months, child growth failure remained the most significant risk factor, with 6.51 million (3.66–9.32) DALYs attributed to diarrhoeal diseases. Unsafe water and unsafe sanitation practices continued to be major risk factors, accounting for 5.91 million (3.33–8.90) and 4.67 million (3.23–6.74) DALYs, respectively. This pattern of risk factors leading to the highest numbers of DALYs persisted in those aged 12–23 months and 2–4 years (figure 4A).

For children aged 5–14 years, unsafe water was the leading risk factor for diarrhoeal diseases, contributing 3.44 million (95% UI 1.62–5.24) DALYs. Poor sanitation followed, contributing 2.59 million (1.78–3.75) DALYs. The absence of handwashing facilities contributed 0.993 million (0.141–1.96) DALYs. Unsafe water continued to pose a major health risk in adults, with total DALYs attributed to diarrhoeal diseases of 6.45 million (3.00–10.2) in those aged 15–49 years, 4.31 million (1.72–7.00) in those aged 50–69 years, and 4.77 million (1.98–8.23) in those aged 70 years and older (figure 4B). Unsafe sanitation and lack of access to handwashing facilities were the second and third leading risk factors in these age groups. The corresponding PAFs of individual risk factors for diarrhoeal diseases are presented in appendix 2 for granular age groups aged younger and older than 5 years (appendix 2 table S4 and table S5).

When considering a scenario with all diarrhoeal risk factors removed, the global all-age DALYs would decrease from 59.0 million (95% UI 47.2–73.2) to 4.99 million (1.99–10.0), and among children younger than 5 years they would decrease from 30.9 million (23.1–42.0) to 556 000 (67 100–1 400 000; appendix 2 table S2). At the super-region level, the comparison of DALYs before and after the removal of risk factors in the top five regions with the highest diarrhoeal burden in 2021 showed a substantial decrease: from 30.9 million (23.0–40.9) to 894 000 (206 000–2 210 000) DALYs in sub-Saharan Africa; from 20.4 million (15.1–29.1) to 2.34 million (0.696–5.14) DALYs in south Asia; from 3.83 million (2.91–4.79) to 591 000 (194 000–1 380 000) DALYs in southeast Asia, east Asia, and Oceania; from 1.49 million (1.13–1.99) to 210 000 (91 600–357 000) DALYs in north Africa and the Middle East; and from 1.35 million (1.11–1.63) to 260 000 (117 000–451 000) DALYs in Latin America and the Caribbean. India, Nigeria, and Pakistan would experience the most gains due to their population sizes,

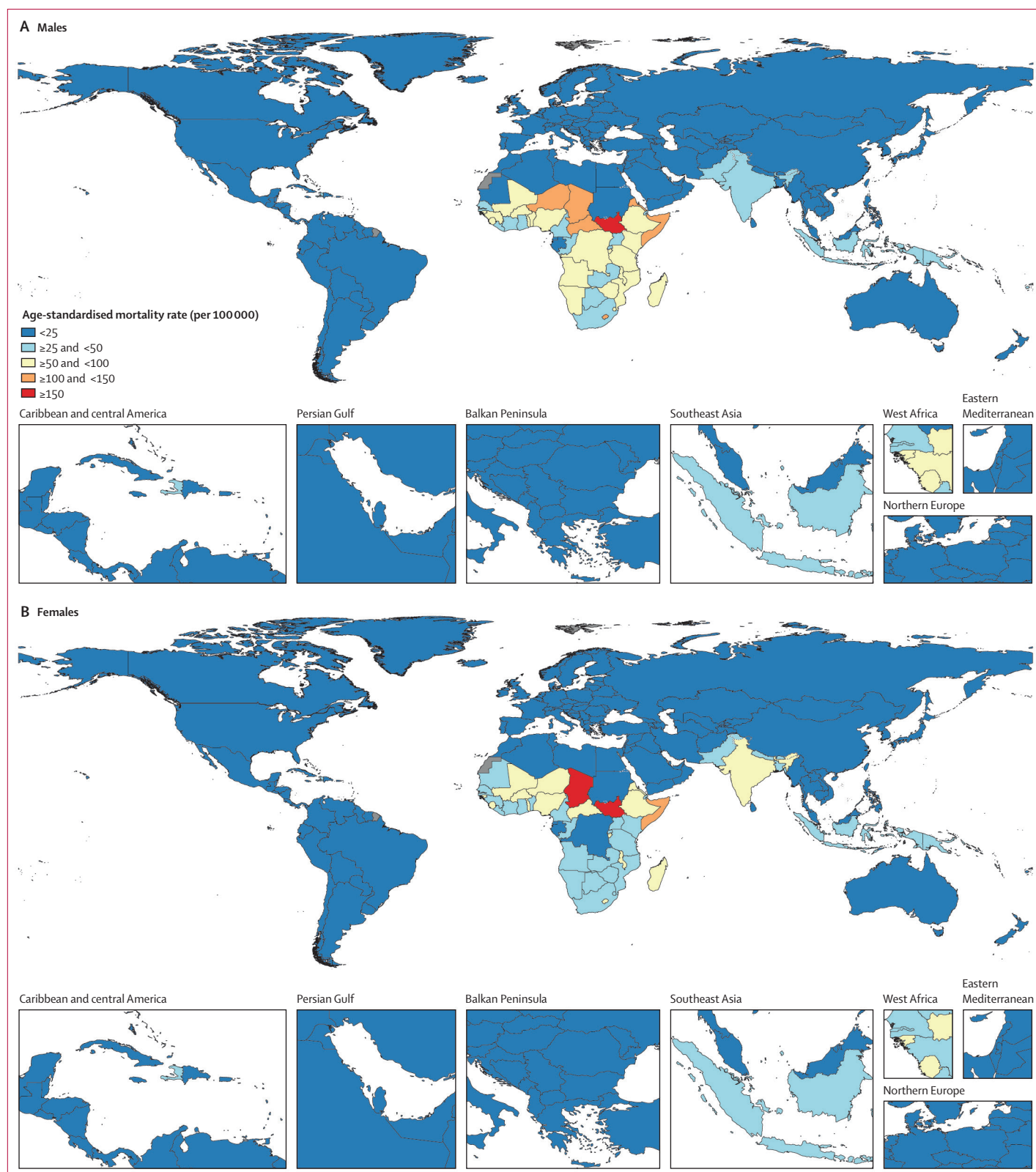


Figure 3: Age-standardised diarrhoeal mortality rates per 100 000 population in males (A) and females (B) in 2021
Grey shading indicates the location has no data.

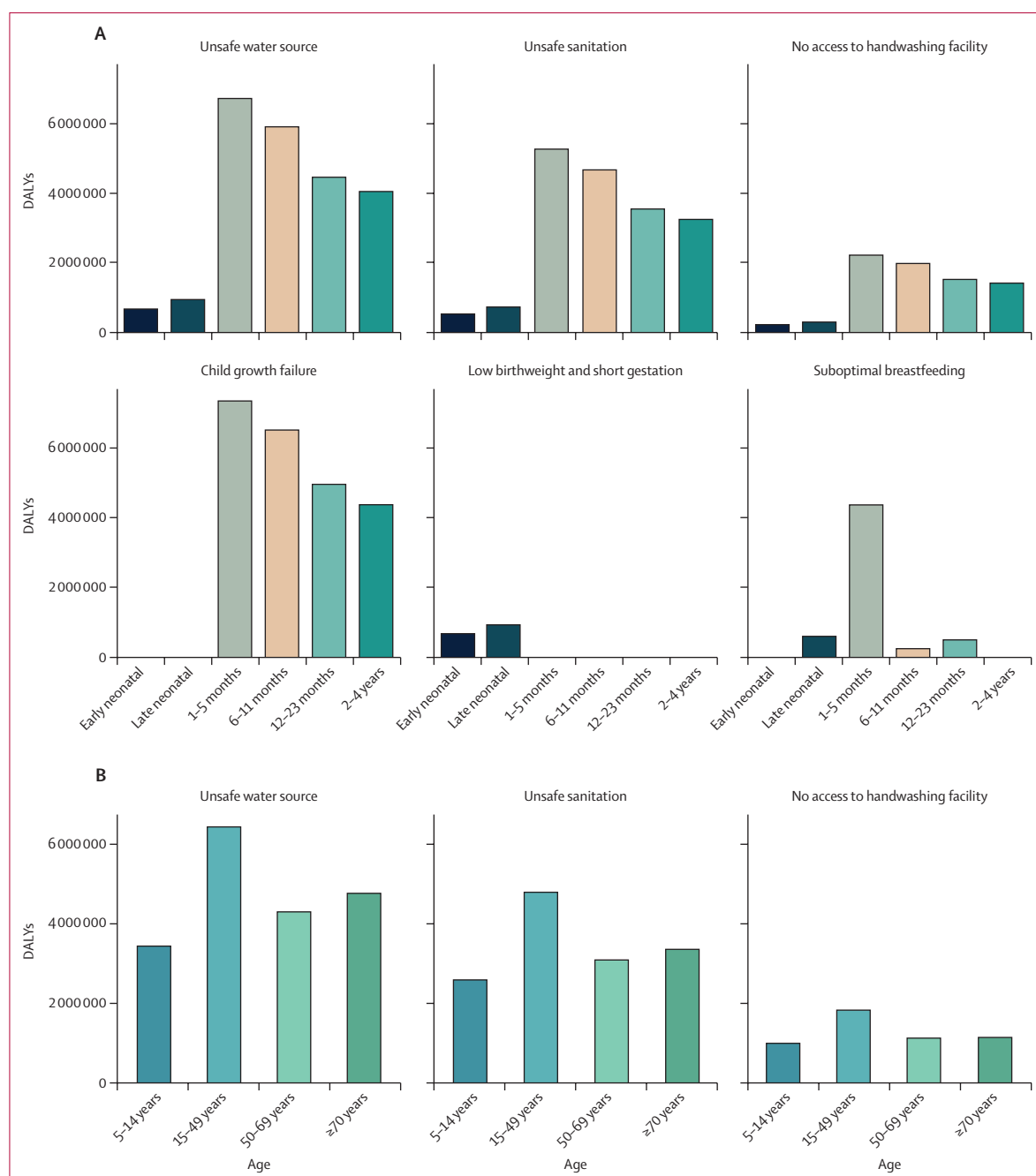


Figure 4: Diarrhoeal DALYs attributable to the leading risk factors in children younger than 5 years (A) and other age groups (B) in 2021

Charts represent DALYs in counts for children younger than 5 years (A) and those aged 5 years and older (B). Early neonatal represents newborns aged 0–6 days. Late neonatal represents newborns aged 7–27 days. Low birthweight is defined as any birthweight in 500 g units below the TMREL at 38 weeks or later but less than 40 weeks, and 3500 g or greater but less than 4000 g. Short gestation refers to any gestational age that falls below the gestational age TMREL at less than 37 completed weeks. Suboptimal breastfeeding includes the absence of breastmilk as a source of nourishment for children aged 6–23 months and the practice of non-exclusive breastfeeding among infants younger than 6 months. Child growth failure includes stunting, wasting, and underweight. DALY=disability-adjusted life-year. TMREL=theoretical minimum risk exposure level.

with a decrease in DALYs from 16·8 million (12·0–24·2) to 2·11 million (0·644–4·56) in India, from 10·1 million (6·93–13·9) to 164 000 (0–452 000) in Nigeria, and from 2·47 million (1·83–3·39) to 152 000 (35 600–363 000) in Pakistan.

Diarrhoeal disease burden attributable to aetiologies

Globally, in 2021, among all ages, rotavirus was the leading cause of diarrhoeal deaths, with a PAF of 15·2% (95% UI 11·4–20·1), followed by norovirus at 10·6% (2·3–17·0) and *Cryptosporidium* spp at 10·2% (7·03–14·3;

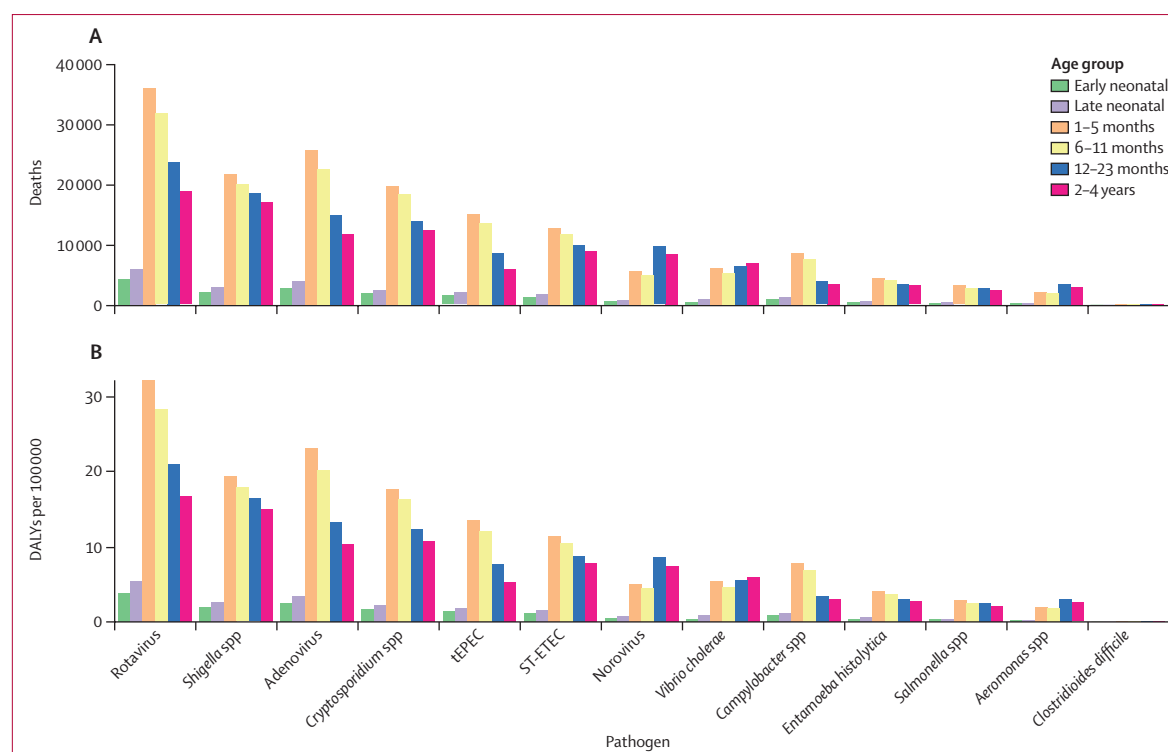


Figure 5: Number of diarrhoeal deaths (A) and DALYs (B) in specific age groups in children younger than 5 years attributable to 13 pathogens in 2021
Early neonatal represents newborns aged 0–6 days. Late neonatal represents newborns aged 7–27 days. DALY=disability-adjusted life-year. PAF=population attributable fraction. ST-EPEC=enterotoxigenic *Escherichia coli* producing heat-stable toxin. tEPEC=typical enteropathogenic *E. coli*.

appendix 2 table S8). Rotavirus accounted for an estimated 176 000 (131 000–230 000) diarrhoeal deaths and 13.4 million (9.85–17.9) DALYs in 2021. In the same year, norovirus was responsible for an estimated 124 000 (25 800–224 000) diarrhoeal deaths and 5.69 million (1.88–9.67) DALYs, whereas *Cryptosporidium* spp caused 118 000 (75 300–178 000) diarrhoeal deaths and 7.37 million (4.53–11.30) DALYs.

Among children younger than 5 years, rotavirus topped the list with a fatal PAF of 35.2% (95% UI 28.7–43.0), followed by *Shigella* spp at 24.0% (15.2–37.9) and adenovirus at 23.8% (14.8–36.3) (appendix 2 table S7). Other pathogens with a fatal PAF greater than 5% included *Cryptosporidium* spp (20.1% [13.3–30.9]), tEPEC (13.6% [8.1–21.0]), ST-EPEC (13.4% [8.3–21.1]), norovirus (8.7% [3.2–14.9]), *Vibrio cholerae* (7.7% [4.8–11.3]), and *Campylobacter* spp (7.4% [3.4–13.3]). The leading pathogen, rotavirus, contributed to an estimated 120 000 (83 100–169 000) diarrhoeal deaths and 10.8 million (7.52–15.2) DALYs in 2021. *Shigella* spp and adenovirus also posed a substantial burden, with *Shigella* spp contributing to 81 800 (47 900–138 000) diarrhoeal deaths and 7.34 million (4.32–12.4) DALYs, and adenovirus contributing to 81 100 (44 900–133 000) diarrhoeal deaths and 7.32 million (4.05–12.0) DALYs.

In children younger than 5 years, the 120 000 diarrhoeal deaths due to rotavirus were distributed across age groups

as follows: 4270 (95% UI 2810–6540) deaths in the early neonatal group, 5940 (4130–8630) in the late neonatal group, 35 800 (25 300–48 800) in infants aged 1–5 months, 31 600 (20 100–46 900) in those aged 6–11 months, 23 500 (14 800–35 100) in those aged 12–23 months, and 18 700 (11 100–29 700) in children aged 2–4 years. The 10.8 million diarrhoeal DALYs in children younger than 5 years were distributed as follows: 0.384 million (0.253–0.589) DALYs in the early neonatal group, 0.538 million (0.374–0.781) in the late neonatal group, 3.23 million (2.28–4.40) in infants aged 1–5 months, 2.84 million (1.81–4.21) in those aged 6–11 months, 2.11 million (1.33–3.13) in those aged 12–23 months, and 1.68 million (1.01–2.63) in children aged 2–4 years. The age distributions of deaths and DALYs for rotavirus and other pathogens are illustrated in figure 5.

Although not a leading pathogen globally, *C. difficile* was the main cause of diarrhoea-related deaths in high-income countries in 2021. We estimated 15 600 (95% UI 13 400–18 200) deaths and 284 000 (250 000–326 000) DALYs globally due to this pathogen (appendix 2 table S8). Specifically, in high-income regions, *C. difficile* was associated with 13 100 (11 400–15 200) deaths and 218 000 (197 000–243 000) DALYs (appendix 2 table S6), predominantly affecting individuals aged 70 years and older (12 100 [10 100–14 500] deaths and 156 000 [132 000–186 000] DALYs).

For GBD Compare see
<https://vizhub.healthdata.org/gbd-compare/>

More detailed diarrhoeal disease burden results by age and sex (including results for more granular age groups in adults) across locations and years are available in GBD Compare.

Discussion

The global burden of diarrhoeal diseases has substantially decreased between 1990 and 2021, with the number of deaths reduced by 60·3% during this period. The largest decline in diarrhoeal mortality rates was observed in children younger than 5 years, with a 79·2% decrease in deaths. Despite these global declines, there were still 51·4 million YLLs in 2021, including 30·3 million in children younger than 5 years. Neonates had the highest diarrhoeal disease mortality rates despite some inherent protection against diarrhoeal diseases from maternal antibodies and breastfeeding, which is likely to be due to factors such as immune system immaturity, poor access to clean water and sanitation, suboptimal breastfeeding practices, and restricted access to health care. Substantial variation remains across regions and countries in both the levels of, and trends in, mortality due to diarrhoeal diseases. In 2021, diarrhoeal diseases globally contributed to 59·0 million DALYs, which could have been reduced to 4·99 million DALYs had all evaluated risk factors been removed. Compared with previous GBD studies of the diarrhoeal disease burden,^{2,14} rotavirus and *Shigella* spp continued to be the leading pathogens causing diarrhoeal deaths in children younger than 5 years globally in 2021, while *C difficile* was the primary cause of diarrhoeal deaths in high-income countries, especially in people aged 70 years and older.

The remarkable decline in diarrhoeal mortality since 1990, especially in children younger than 5 years, represents a triumph for public health initiatives worldwide. This success can be attributed to a multipronged approach that includes widespread immunisation against rotavirus,^{22,23} the implementation of improved water, sanitation, and hygiene (WASH) practices, and broader access to oral rehydration therapies and health-care services.^{24,25} The rotavirus vaccines recommended by WHO and administered in more than 100 countries have contributed to marked reductions in both hospital admissions and deaths caused by diarrhoea.²³ Despite the oral vaccines' positive impact, challenges such as incomplete vaccine coverage²⁶ and the need for parenteral vaccines²⁷ persist. These live oral vaccines have shown reduced effectiveness in low-income countries compared with high-income countries, highlighting the need for additional research to identify factors that influence vaccine effectiveness in different settings.²⁸ Ongoing efforts aim to create new vaccines that do not rely on the oral route, which could potentially play a key role in achieving sustained control of rotavirus disease.²³

When it comes to vaccination against other diarrhoeal pathogens, oral killed cholera vaccines have been shown

to be effective in protection against cholera in endemic areas.²⁹ A highly effective cholera vaccine with more than 85% protective efficacy has yet to be introduced in endemic countries due to reduced efficacy and logistical storage challenges in field delivery.^{29,30} Vaccine research targeting diarrhoeal pathogens, such as *Shigella* spp, ETEC, norovirus, and *Campylobacter* spp, is ongoing and continues to address a complex array of challenges, including the genetic and antigenic heterogeneity of the pathogens.^{31–33} With the growing number of vaccines being added to WHO's Expanded Programme on Immunization, the development of combination vaccines is appealing, as such vaccines could not only reduce manufacturing costs but also streamline the immunisation schedule.³⁴ For instance, the development of a combined vaccine for *Shigella* spp, ETEC, and *Campylobacter* spp is seen as a potentially important advancement for reducing the diarrhoeal disease burden.³⁵

As bacterial antimicrobial resistance has emerged as a major public health threat, preventing infections through vaccination is crucial to minimising the need for antibiotics.³⁶ Improper use of antibiotics for treating conditions such as ETEC-induced diarrhoea can lead to increased antimicrobial resistance; an efficacious ETEC vaccine could decrease the number of infections requiring antibiotics and reduce the risk of developing antimicrobial-resistant strains.^{33,37} Additionally, the emergence of *Shigella* strains resistant to most antimicrobials is a growing global concern.^{38–40} The mass distribution of azithromycin to preschool children has been shown to reduce childhood mortality in sub-Saharan Africa, likely through reductions in respiratory infections, diarrhoea, and malaria, yet any policy advocating for mass azithromycin distribution should carefully consider the potential risk of antibiotic resistance.⁴¹

Although the overall decrease in diarrhoeal disease mortality is encouraging, the rise in diarrhoeal deaths attributable to *C difficile* infection among adults in certain regions, such as high-income North America and Europe, presents a new set of challenges. This trend might reflect the increasing use of antibiotics and subsequent disruption to the gut microbiome, leading to heightened susceptibility to *C difficile* infection.⁴² Addressing this issue requires a multifaceted response, including improved antibiotic stewardship, heightened infection control measures in health-care settings, and continued research into effective treatments and preventive measures for *C difficile* infection and recurrence.⁴³ Fidaxomicin is the primary treatment for *C difficile* infection,⁴⁴ while fecal microbiota transplantation has been shown to be the most cost-effective treatment option for recurrent *C difficile* infection.⁴⁵ A recent novel oral formulation of live fecal microbiota spores approved by the US Food and Drug Administration is a major advancement in gastroenterology, although

the availability of this treatment outside the USA and Canada is still uncertain, highlighting the need for international collaboration to ensure its economic viability and equitable distribution.⁴⁶ Although an efficacious vaccine for *C difficile* infection could help mitigate the disease, clinical trials of vaccines containing toxin-based antigens from *C difficile* have shown only modest efficacy, indicating the need for future vaccines to include bacterial or spore antigens to provide enhanced protection.⁴⁷

Regional disparities in diarrhoeal disease mortality rates are stark, with less than one death per 100 000 population in children younger than 5 years in the high-income super-region versus more than 130 deaths per 100 000 population in children younger than 5 years in sub-Saharan Africa. Despite the remarkable progress made in recent years—more than 90% of the world's population has access to improved water sources, and 2·1 billion people have gained access to improved sanitation—challenges remain, particularly in scaling up WASH infrastructure in resource-limited settings.⁴⁸ The new ambitious safely managed services framework by UNICEF, which considers factors such as on-premises availability of drinking water and its freedom from fecal and chemical contaminants, further highlights disparities in access to clean water.⁴⁹ In Niger, for example, while 66% of the population has access to an improved water source, only 10% have the convenience of having it available on their premises.⁴⁸ The refinement of WASH service definitions to include factors such as the absence of contaminants can highlight previously invisible issues, such as *E coli* contamination in piped water in some countries.⁵⁰

In addition to improving WASH infrastructure, reducing the diarrhoeal disease burden in the under-5 age groups requires interventions that address malnutrition, such as promoting exclusive breastfeeding, addressing food insecurity, and fortifying foods with essential nutrients. The link between malnutrition and increased vulnerability to diarrhoea is compounded by climate change, with extreme weather conditions such as heavy rainfall and high temperatures amplifying the risk of diarrhoeal diseases.⁵¹ According to a recent review, climate change can act as a triggering factor for the occurrence of diarrhoea, although the underlying causes are more complex, encompassing factors such as rainfall, human behaviour, water availability, immunity, and socioeconomic influences.⁵² It is also noteworthy that diarrhoea and malnutrition share a bidirectional relationship, with malnutrition predisposing individuals to diarrhoeal infections through impaired immune defences, and diarrhoea exacerbating malnutrition by impairing nutrient absorption.⁵³ Investing in the training of health professionals could empower them to lead interdisciplinary efforts, utilising the One Health framework, to address both the immediate and long-term

challenges posed by climate change and diarrhoeal risk factors.⁵⁴

The current study addressed multiple limitations identified in previous GBD diarrhoeal disease publications. Notably, it distinguished the specific burdens of ST-EPEC and tEPEC. These two pathogens were aggregated under the broader categories of all ETEC and all EPEC in previous publications.^{2,14} Additionally, our study incorporated pathogen-specific data from WHO's Global Pediatric Diarrhea Surveillance network for many high-burden countries; these data were unavailable for incorporation into earlier GBD publications. Consequently, this has led to a reshuffling in the ranking of some pathogens compared to previous findings.² While the leading three pathogens remain the same in children younger than 5 years, there has been a notable shift with tEPEC (formerly aggregated with all EPEC and ranked tenth) and ST-EPEC (formerly aggregated with all ETEC and ranked eighth), which now rank as the fifth and sixth most prevalent pathogens, respectively.

Despite these improvements, some data limitations persist, particularly the paucity of data to inform the estimation of overall diarrhoea mortality, especially for sub-Saharan Africa, and the scarcity of age-specific aetiological data for individuals older than 5 years. To address the limited availability of cause of death data, we incorporated covariates linked biologically or strongly associated with diarrhoeal diseases, sourced from population-based surveys such as Demographic and Health Surveys and Multiple Indicator Cluster Surveys. Additionally, we used spatial modelling to leverage data from neighbouring countries, which, while compensating for scarce information, expanded the uncertainty intervals in years with scarce data. We used verbal autopsy data to inform our estimates where reliable vital registration data were unavailable. Although verbal autopsy data might be prone to misclassification of causes of death, validation studies of verbal autopsies in children generally indicate reasonable sensitivity and specificity for diagnosing diarrhoeal diseases.^{55,56} The propagation of uncertainty from multiple sources, including sampling variance, non-sampling variance, and adjustment and standardisation methods applied to data has resulted in wide uncertainty intervals, which might have affected the accuracy of our estimates.

Currently, we assume the association between pathogen detection and odds of diarrhoeal diseases in children younger than 5 years from GEMS is applicable to older age groups. Efforts are ongoing to address this limitation by integrating more odds ratio data across different geographical locations and age groups in future GBD studies. Moreover, the availability and quality of *C difficile* data in low-income and middle-income countries are inadequate. Due to substantial variation in diagnostic and surveillance practices in these countries, there is a potential for underestimating the *C difficile*

burden, which might explain why increases in deaths due to *C difficile* were seen only in high-income countries.⁵⁷ The availability of more robust data in these countries, through enhanced diagnostic and surveillance infrastructure, could help to provide more accurate estimates.

Furthermore, although DALYs offer a composite measure of disease burden, combining premature mortality with the prevalence and severity of diarrhoeal diseases, in this study they account only for the acute effects of diarrhoea. The broader impact of diarrhoeal morbidity, which can lead to long-term consequences such as stunted physical growth and cognitive impairment, has not yet been accounted for in the DALY estimates. Studies that have attempted to quantify some of the long-term consequences suggest that diarrhoea might represent a larger burden of disease than is currently estimated by GBD.^{58,59} Addressing this gap in future iterations of GBD is crucial for a more comprehensive assessment of the true burden of diarrhoeal diseases.

Last, we did not quantify the indirect impact of the COVID-19 pandemic on the diarrhoeal disease burden for GBD 2021. Data from Demographic and Health Surveys show conflicting trends and do not provide a definitive indication of the impact of the COVID-19 pandemic on diarrhoeal prevalence (appendix 2 figure S1). Although some countries have reported a slight increase in diarrhoea prevalence from the pre-pandemic to the post-pandemic period, others have observed a decrease. It is noteworthy, however, that in countries where a decline has been reported, there was already an observable trend of declining diarrhoeal prevalence before the onset of the pandemic. Consequently, it remains uncertain whether the observed decrease can be directly attributed to the implementation of non-pharmaceutical interventions or whether it simply represents a continuation of pre-existing trends. This suggests the need for cautious interpretation of the pandemic's impact and calls for a more in-depth investigation as additional data become available.

In conclusion, the substantial decline in the diarrhoeal disease burden since 1990, especially in young children, reflects the dedicated efforts to enhance WASH infrastructure, vaccination programmes, and access to oral rehydration therapy. Yet, considerable regional disparities persist, and the emergence of antibiotic resistance presents new challenges, calling for sustained efforts in vaccine research. Our study highlights the need for the implementation of holistic public health strategies that integrate WASH, nutrition, vaccination, and health-care accessibility to further reduce the diarrhoeal disease burden and bridge global health disparities.

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Please see appendix 1 (pp 95–101) for more detailed information about individual author contributions to the research, divided into the following categories: managing the overall research enterprise; writing the first draft of the manuscript; primary responsibility for applying analytical methods to produce estimates; primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables; providing data or critical feedback on data sources; developing methods or computational machinery; providing critical feedback on methods or results; drafting the manuscript or revising it critically for important intellectual content; and managing the estimation or publications process. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. Members of the core research team (HHK, AV, RMVD, JM, SBA, ANo, CET, MCD, JRL, SBS, RGB, LRS, MCu, and SSP) for this topic area had full access to the underlying data used to generate estimates presented in this Article.

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Data sharing

In compliance with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER), we have made the input data sources and the code for each step of the estimation process publicly available on the Global Health Data Exchange at <https://ghdx.healthdata.org/gbd-2021>.

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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: GBD 2021 Diarrhoeal Diseases Collaborators. Global, regional, and national age-sex-specific burden of diarrhoeal diseases, their risk factors, and aetiologies, 1990–2021, for 204 countries and territories: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Infect Dis* 2024; published online Dec 18. [https://doi.org/10.1016/S1473-3099\(24\)00691-1](https://doi.org/10.1016/S1473-3099(24)00691-1).

Appendix 1

Supplementary Methods Appendix to “Global, regional, and national age-sex-specific burden of diarrhoeal diseases, its risk factors, and aetiologies, 1990-2021, for 204 countries and territories: a systematic analyses for the Global Burden of Disease Study 2021”

This appendix provides further methodological detail and results for “Global, regional, and national age-sex-specific burden of diarrhoeal diseases, its risk factors, and aetiologies, 1990-2021, for 204 countries and territories: a systematic analyses for the Global Burden of Disease Study 2021.”

All the material in the paper itself is novel. However, the parts of the supplemental methods appendix include sections adapted from the GBD Capstones published in *The Lancet*,¹⁻³ and references are provided for reproduced sections.

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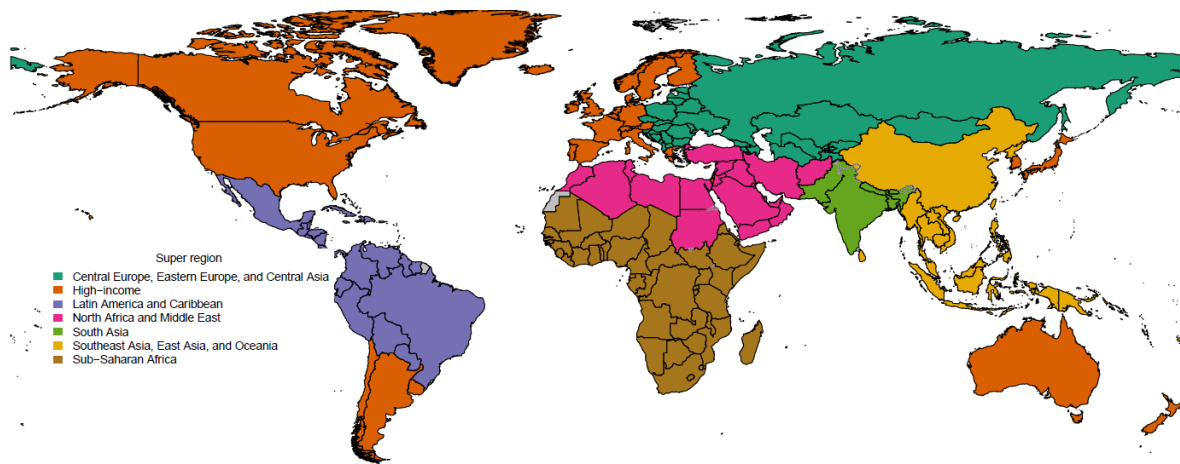
Table of Contents

GBD 2021 Super Regions.....	5
<i>Diarrhoeal disease mortality</i>	6
Flowchart	6
Input data.....	6
Causes of death data quality (star rating) calculation ¹	6
HIV/AIDS misclassification correction ¹	11
Modelling strategy.....	12
<i>Diarrhoeal disease morbidity.....</i>	15
Flowchart	15
Case definition.....	15
Input data.....	15
Modelling strategy.....	18
<i>Diarrhoeal Aetiologies</i>	21
<i>Diarrhoeal references</i>	29
<i>Unsafe water</i>	31
Flowchart	31
Input data and methodological summary	31
Exposure	31
Case definition	31
Input data	31
Modelling strategy	32
Theoretical minimum-risk exposure level	35
Relative risks	35
Input data	35
Modelling strategy	36
Unsafe Water References	38
<i>Unsafe sanitation</i>	38
Flowchart	38
Input data and methodological summary	39
Exposure.....	39
Modelling	39
Theoretical minimum-risk exposure level	40

Relative risks	40
Unsafe Sanitation References	42
No access to handwashing facility	43
Flowchart	43
Input data and methodological summary	43
Exposure	43
Case definition	43
Input data	43
Modelling strategy	43
Theoretical minimum-risk exposure level	44
Relative risks	44
Input data	44
Modelling strategy	44
No access to handwashing facility References.....	46
Child growth failure	47
Combined Flowchart for Child Growth Failure and Protein Energy Malnutrition	47
Input data and methodological summary	48
Exposure.....	48
Modelling strategy <i>Exposure estimation</i>	49
Theoretical minimum-risk exposure level	50
Relative risks	50
Child Growth Failure References.....	53
Low birthweight and short gestation	54
Flowchart	54
Input data and methodological summary	55
Case definition.....	56
Input data and data processing.....	57
Table 4. Input data for exposure models.....	58
Data processing.....	58
Modelling strategy	62
Relative risks and theoretical minimum risk exposure level	64
Causes	64
Input data	65
Modelling strategy	65
Population attributable fraction	66
Low Birthweight and Short Gestation References	66

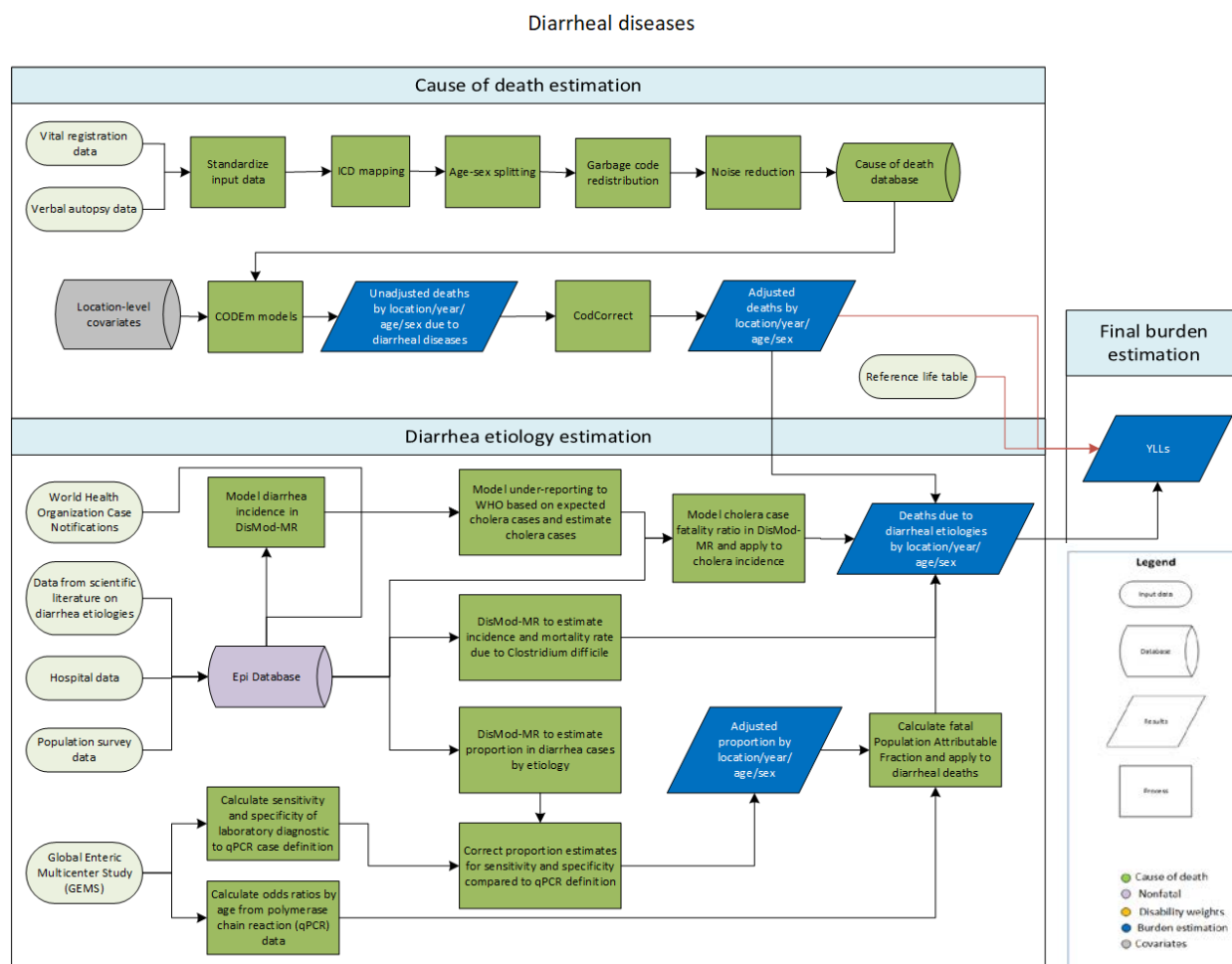
<i>Suboptimal breastfeeding.....</i>	<i>67</i>
Flowchart	67
Input data and methodological summary	67
Definition.....	67
Exposure.....	67
Input data.....	68
Exposure.....	68
Relative risk	69
Modelling strategy	69
Theoretical minimum-risk exposure level	70
Relative risk	70
Population attributable fraction	71
Suboptimal Breastfeeding References	71
Justification for the counterfactual approach.....	72
Counterfactual Approach References	72
Estimation of population attributable fractions³	72
Calculating the burden of multiple risk factors³	73
Risk factors and causal pathways leading to diarrhoeal diseases.....	74
Risk Factors and Causal Pathways: References	74
<i>Statement of GATHER Compliance.....</i>	<i>75</i>
<i>Ethics Statement.....</i>	<i>76</i>
<i>Authorship Material</i>	<i>77</i>
GBD 2021 Diarrhoeal Disease Collaborators.....	77
Affiliations.....	79
Authors' Contributions.....	95
Managing the overall research enterprise.....	95
Writing the first draft of the manuscript	95
Primary responsibility for applying analytical methods to produce estimates	95
Primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables	95
Providing data or critical feedback on data sources	95
Developing methods or computational machinery	96
Providing critical feedback on methods or results	97
Drafting the work or revising it critically for important intellectual content	99
Managing the estimation or publication process	101

GBD 2021 Super Regions



Diarrhoeal disease mortality

Flowchart



Diarrhoeal diseases are a cause of death in GBD. We also estimated the attributable deaths from 13 diarrhoeal aetiologies using an independent modelling strategy. These pathways are shown in the flowchart above and described in detail below in this report.

Input data

Cause of death. To estimate mortality from diarrheal diseases, the input data comprised vital registration data across 24,181 site-years (i.e., the total number of years of data available for each geography), 825 site-years of sample vital registration data, 1,785 site-years of data from verbal autopsy studies, 575 site-years from mortality surveillance, and 9 site-years from minimally invasive tissue sampling.

Causes of death data quality (star rating) calculation¹

GBD estimates are most accurate when computed with a full time series of complete VR with a low percentage of garbage codes. For GBD 2016, we developed a simple star-rating system from 0 to 5 to give

a picture of the quality of data available in a given country over the full time series used in GBD estimates. Countries improve in the star rating as they increase availability, completeness, and detail of their mortality data and reduce the percentage of deaths coded to ill-defined garbage codes or highly aggregated causes.

We assign star ratings to rate the quality of data for any given location-year. Two dimensions determine this star rating: (1) the level of completeness of death registration and (2) the percentage of total deaths determined to be major garbage or highly aggregated cause. These two values were used to create a “percentage well-certified” value between 0 and 1, determined as:

$$pct_{wellcertified} = completeness \times (1 - pct_{majgarbage})$$

Where:

$$completeness = \frac{registered\ deaths}{GBD\ mortality\ envelope}$$

$$pct_{majgarbage} = \frac{deaths\ coded\ to\ level\ 1\ or\ 2\ garbage\ or\ highly\ aggregated\ cause}{registered\ deaths}$$

For each verbal autopsy (VA) data source, percent well-certified is:

$$pct_{wellcertified} = VerbalAutopsyAdjustment \times (1 - pct_{majgarbage})$$

Where:

$$VerbalAutopsyAdjustment = SubAdj \times RegAdj \times AgeSexCoverage$$

And:

SubAdj represents 10% for subnationally representative studies, 100% for nationally representative studies. This adjustment, while arbitrary in its specific value, reflects the bias that can be associated with studies that only cover a potentially non-representative sample of a country’s population. *RegAdj* represents 64% for all VA data sources. This accounts for the inaccuracy of VA in assigning CoD compared to medically verified VR. The specific multiplier 0.64 is based on the chance-corrected concordance of Physician Certified Verbal Autopsy (PCVA) versus medical certification by the Population Health Metrics Research Consortium. *Age-Sex Coverage* reflects the number of deaths estimated in the GBD mortality envelope for the ages and sexes in the study for the country and year divided by the number of deaths estimated in the GBD mortality envelope for the country and year. Studies that only cover children under 5 or maternal mortality, for example, will be highly discounted by this multiplier. In the case of VA, all garbage codes are considered ill-defined, as redistribution for VA is highly imprecise.

Once percent well-certified is calculated for each location-year of VR and each VA study-year, we then combine these into one measurement for each five-year time interval and the full time series 1980–2020. For each five-year time interval, we take the maximum percent well-certified. Then for 1980–2020, we

take the average of the maximum percentages well-certified for the seven five-year time intervals, including any five-year time interval where no data were available as a zero.

Once these values are calculated, we assign stars as follows:

5 stars: 85%–100% well-certified

4 stars: 65%–84% well-certified

3 stars: 35%–64% well-certified

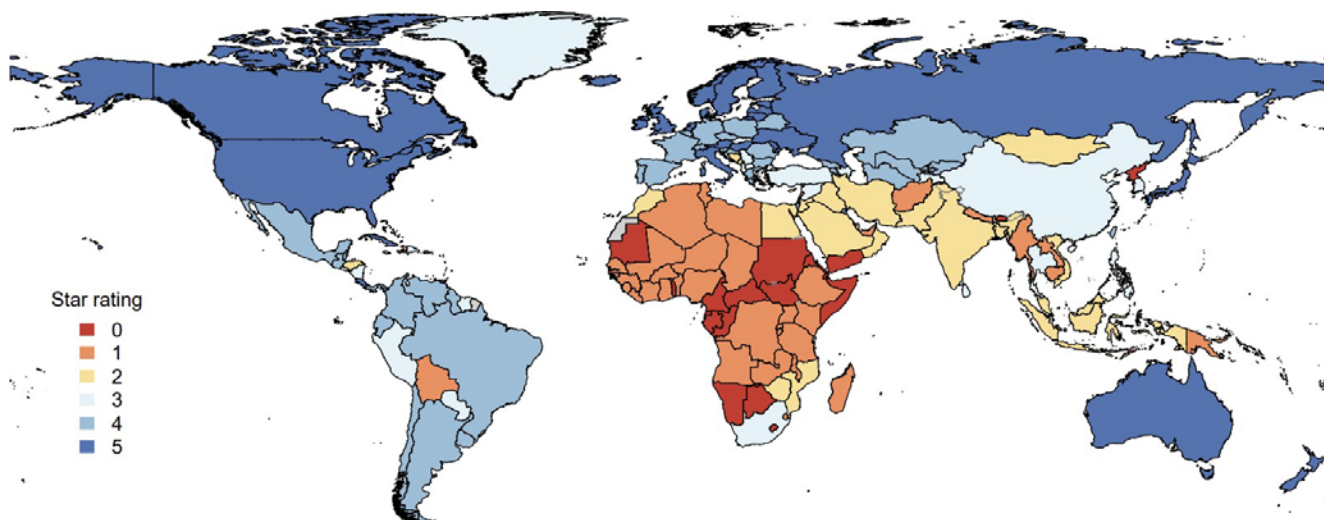
2 stars: 10%–34% well-certified

1 star: >0%–9% well-certified

0 stars: No VR or VA data available or 0% well-certified

While stars are calculated for each five-year time interval, as well as the full time series from 1980 to 2020, stars in the figure below are presented for the full time series.

Overall data quality by country



Processing cause of death data to enhance comparability and utility¹

Redistribution

A crucial aspect of enhancing the comparability of data for causes of death (CoD) is to deal with uninformative, so-called garbage codes. Garbage codes to which deaths were assigned should not be considered as the underlying CoD, for example: “heart failure”, “ill-defined cancer site”, “senility”, “ill-defined external causes of injuries”, and “septicaemia”. Redistribution is therefore the process of reallocating garbage-coded deaths to plausible underlying causes. For each group of diagnostically related garbage codes, we define a set of probable underlying causes of death and the proportion of garbage-coded deaths that are redistributed to each underlying cause, separately by GBD age group, sex, location, and

year. The methods for redistributing these garbage-coded deaths have been previously described in detail.¹ While our underlying algorithm has not changed significantly since GBD 2013, several improvements were made in GBD 2019 and GBD 2021.

For each redistribution package, we defined the “universe” of data as all deaths coded to either the package’s garbage codes or the package’s redistribution targets for each country, year, age, and sex. We then ran a regression based on the following equation, separately for each target group and sex:

$$TG_{crt} = \alpha + \beta_1 Gar_{crt} + \beta_2 Age_{crt} Gar_{crt} + \theta_r Gar_{crt} + \gamma_r + \varepsilon_{ct}$$

Where:

TG_{crt} = percentage of deaths within the given garbage code’s universe which were coded to a given target group, by country

Gar_{crt} = percentage of deaths within the given garbage code’s universe which were coded to a given set of garbage codes

α = constant

β_1 = slope coefficient describing the association between Gar_{crt} and TG_{crt}

β_2 = slope coefficient describing the association between the interaction $Age_{crt} Gar_{crt}$ and G_{crt}

γ_r = region-specific random intercept (or super-region if the random effect on region is not significant)

θ_r = region-specific random slope (or super-region if the random effect on region is not significant)

ε_{ct} = standard error, normally distributed and calculated by bootstrapping

This regression was adjusted from GBD 2013 to include fixed effects on the interaction of garbage and age to ensure smooth age patterns. The random effects on location were included to help capture geographic differences in garbage coding for various causes. The regressions were first run with a random effect on the region, and in the case of failed convergence, they were attempted again with a random effect on the superregion. When models using a random effect on the superregion failed to converge, a fixed effect model considering only age was settled upon. We made this decision after investigating diagnostic visualisations that showed unlikely gaps between proportions assigned to different age groups.

Computing redistribution uncertainty

We assigned redistribution variance to each data point by calculating residual variance from a regression predicting the percentage of garbage coded deaths redistributed to a cause, given the proportion of garbage codes we observed for that location, year, age, sex, cause, and the age standardized relative rate of major garbage codes across all causes. If there is a cause that has greater residual variance, we assume greater redistribution uncertainty.

In order to calculate variance, a dataset was generated containing percent garbage by location, year, age, sex and cause, where percent garbage is:

$$pct_{garbage} = \frac{deaths_{redistributed} - deaths_{raw}}{deaths_{redistributed}}$$

A mixed-effect linear regression model was then fit to predict the logit percent of deaths from redistribution by age-standardized relative rate of major garbage.

$$\begin{aligned} \text{logit}(pct_{garbage_{ij}}) \\ = \beta_0 + \beta_1 * \log(ASR_{majorgarbage_{ij}}) + \beta_2 * 15yearage_{ij} + \gamma_{1j} \\ * \log(ASR_{majorgarbage_{ij}}) + u_j + e_{ij}, \theta_{\{i\}} \sim N(0, \sigma^2) \end{aligned}$$

Where:

i indexes dataset-location-year-age-sex-cause data points nested within j groups by GBD region

ASR major garbage: age standardized relative rate of major garbage

Residual variance, as estimated by the median absolute deviation (MAD), was calculated for each cause, sex, and age. The next step was to use the residual variance to calculate uncertainty around each data point in the CoD database. First, we calculated the percent garbage of each data point, treating all deaths that could not be directly mapped to a GBD cause as garbage, including level four garbage. Percent garbage was calculated as:

$$pct_{garbage} = \frac{deaths_{redistributed} - deaths_{corrected}}{deaths_{corrected}}$$

Where:

death corrected: deaths post misdiagnosis correction (Appendix Section 2.6)

deaths redistributed: deaths post redistribution (Appendix Section 2.7)

Residual variance was matched to each data point and one hundred draws were sampled from a normal distribution using the cause, age, sex, specific residual variance and mean of zero. The logit transformed

percent garbage was added to each value in the distribution. Each draw was then transformed out of logit space and the post-redistribution deaths were calculated as:

$$deaths = \frac{deaths_{corrected}}{1 - pct_garbage}$$

Draws of deaths were processed through noise reduction before calculating the final redistribution variance passed to CODEm, which was added to the total data variance. The mean of the draws was not used as the final estimate, because it was found that the logit transformation biases the distribution of cause fractions higher than if only point estimates are used.

HIV/AIDS misclassification correction¹

In many location-years, certain causes of death known to be comorbid with HIV/AIDS (eg, tuberculosis, other infectious diseases) are seen to have age patterns that diverge from those observed in location-years without widespread HIV epidemics and are in fact more reflective of HIV mortality trends. In order to identify these instances, a global relative age pattern is generated using all VR deaths in countries with observed HIV prevalence less than 1% using the following:

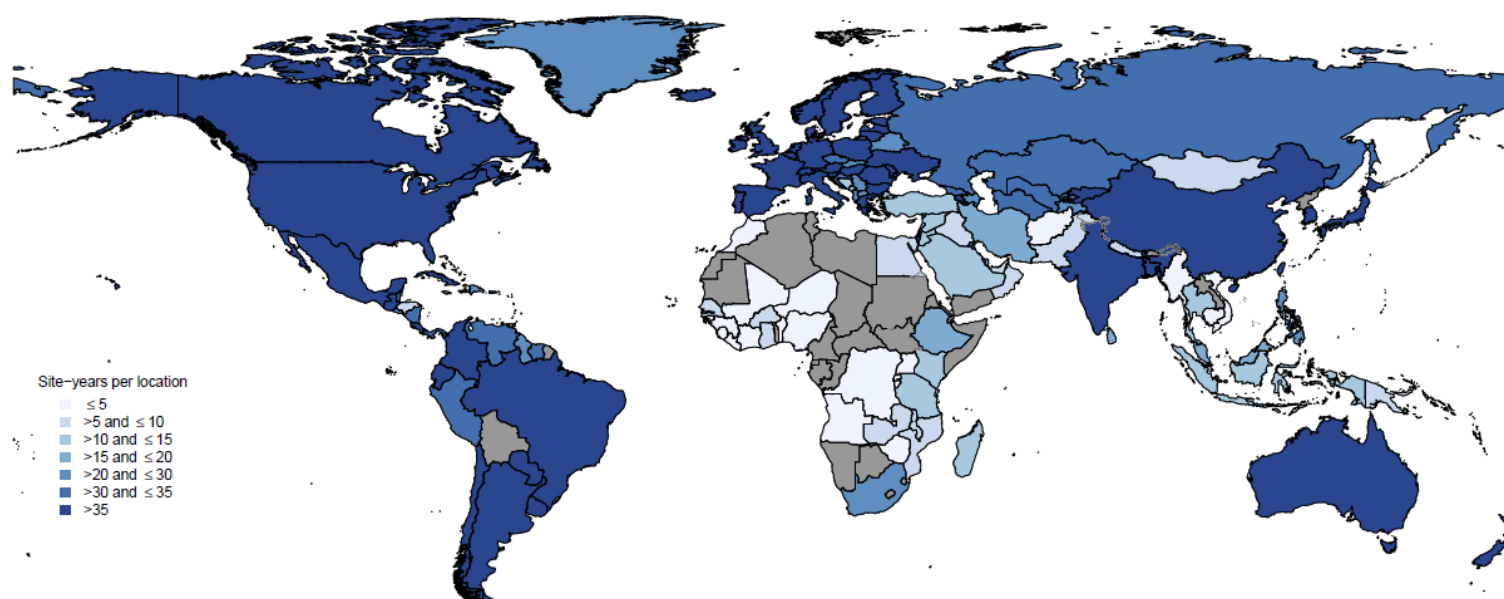
$$RR_{asc} = \frac{R_{asc}}{\bar{x}(R_{65sc}, R_{70sc}, R_{75sc})}$$

Where RR_{asc} is the relative death rate for age group a , sex s , and cause c ; R_{asc} is the rate for that age group; and $\bar{x}(R_{65sc}, R_{70sc}, R_{75sc})$ is the mean of the rates in ages 65–69, 60–74, and 75–79 for that sex and cause. This is preferable to comparing mortality rates because we are able to isolate divergence in age pattern while accounting for varying levels of overall mortality by fixing death rates to age groups that are unlikely to be confounded by the presence of HIV. Expected deaths for an identified cause were then determined to be:

$$ED_{lyasc} = \bar{x}(R_{ly65sc}, R_{ly70sc}, R_{ly75sc}) \times p_{lyasc} \times RR_{asc}$$

Where ED_{lyasc} are deaths for location l , year y , age group a , sex s , and cause c ; $\bar{x}(R_{l65sc}, R_{l70sc}, R_{l75sc})$ is the mean of the rates for ages 65–69, 60–74, and 75–79 for that location-year-sex-cause; p_{lyasc} is the population for that location-year-age-sex-cause; and RR_{asc} is the global standard relative rate determined in the previous step for that age-sex-cause. The expected deaths remain attributed to that particular cause, while the difference between observed and expected are reallocated to HIV/AIDS.

Diarrhoeal cause-of-death data availability



Modelling strategy

Cause of death. Diarrhoeal disease mortality was estimated in the Cause of Death Ensemble modelling platform (CODEm). We estimated diarrhoea mortality separately for males and females and for children under 5 years and older than 5 years. We used country-level covariates to inform our CODEm models (**Table 1**).

We modelled deaths due to diarrhoeal disease with two CODEm models, separately for each sex and two age categories (under 5 and 5 years and above), as the mortality trends differ substantially between these age groups. The final sex-specific models for deaths due to diarrhoeal disease were a hybridised model of separate global and data-rich models for males and females.

In the CODEm framework,¹ four families of statistical models are used: linear mixed effects regression (LMER) models of the natural log of the cause-specific death rate, LMER models of the logit of the cause fraction, spatiotemporal Gaussian process regression (ST-GPR) models of the natural logarithm of the cause-specific death rate, and ST-GPR models of the logit of the cause fraction (see the 2x2 table in Foreman et al).⁷ For each family of models, all plausible relationships between covariates and the response variable are identified. Based on the evidence of a causal relationship with diarrhoeal disease mortality, covariates are ranked from 1 (proximally related) to 3 (distally related). The direction of the association between each covariate and diarrhoeal disease mortality is assigned as a prior based on the literature (Appendix Tables 1A and 1B). Because all possible combinations of selected covariates are considered for each family of models, multi-collinearity between covariates may produce implausible signs on coefficients or unstable coefficients. Each combination is therefore tested for statistical significance (covariate coefficients must have a coefficient with p-value < 0.05) and plausibility (the coefficients must have the directions expected on the basis of the

literature). Only covariate combinations meeting these criteria are retained. This selection process is run for both cause fractions and death rates, then ST-GPR and LMER-only models are created for each set of covariates. For locations with sparse data, we leverage regional patterns and covariates to assist in making predictions for these areas. As a result, the estimates for such locations are associated with wider uncertainty intervals.

The families of models that go through ST-GPR incorporate information about data variance. The main inputs for a Gaussian process regression (GPR) are a mean function, a covariance function, and data variance for each data point. These inputs are described in detail in Foreman et al.⁷ Three components of data variance are now used in CODEm: sampling variance, non-sampling variance, and garbage code redistribution variance. The computation of sampling variance and non-sampling variance has not changed since previous iterations of the GBD and is also described in previous publications.^{1,7} Garbage code redistribution variance is computed in the CoD database process. Since variance is additive, we calculate total data variance as the sum of sampling variance, non-sampling variance, and redistribution variance. Increased data variance in GPR may result in the GPR draws not following the data point as closely.

The performance of all models (individual and ensemble) is evaluated by means of out-of-sample predictive validity tests. Thirty percent of the data are randomly excluded from the initial model fits. These individual model fits are evaluated and ranked by using half of the excluded data (15% of the total), then used to construct the ensembles on the basis of their performance. Data are held out from the analysis on the basis of the cause-specific missingness patterns for ages and years across locations. Out-of-sample predictive validity testing is repeated 20 times for each model, which has been shown to produce stable results. These performance tests include the root mean square error (RMSE) for the log of diarrhoeal disease death rate, the direction of the predicted versus actual trend in the data, and the coverage of the predicted 95% UI.

The component models are weighted on the basis of their predictive validity rank to determine their contribution to the ensemble estimate. The relative weights are determined both by the model ranks and by a parameter ψ , whose value determines how quickly the weights taper off as rank decreases. The distribution of ψ is described in more detail in Foreman et al. A set of ensemble models is then created by using the weights constructed from the combinations of ranks and ψ values. These ensembles are tested by using the predictive validity metrics described in the previous section on the remaining 15% of the data, and the ensemble with the best performance in out-of-sample trend and RMSE is chosen as the final model. Lastly, 1000 draws are created for the final ensemble, and the number of draws contributed by each model is proportional to its weight. The mean of the draws is used as the final estimate for the CODEm process, and a 95% UI is created from the 0.025 and 0.975 quantiles of the draws.

Similar to other models of mortality in GBD, diarrhoeal disease mortality models are single-cause, requiring that the sum of all mortality models must be equal to the all-cause mortality envelope. We correct diarrhoeal disease mortality estimates, and other causes of mortality, by rescaling them according to the uncertainty around the cause-specific mortality rate. This process is called CoDCorrect and is essential to ensure internal consistency among causes of death.

Table 1. Covariates used in diarrhoea mortality modelling. Table 1A shows the covariates used in the 0–4 years model, and Table 1B shows the covariates used in the 5–95+ years model. The *Level* represents the strength of the association between the covariate and diarrhoea mortality from 1 (proximally related) to 3 (distally related). The *Direction* indicates the positive or negative association between the covariate and diarrhoea mortality.

Table 1A. Covariates used in the 0–4 years model

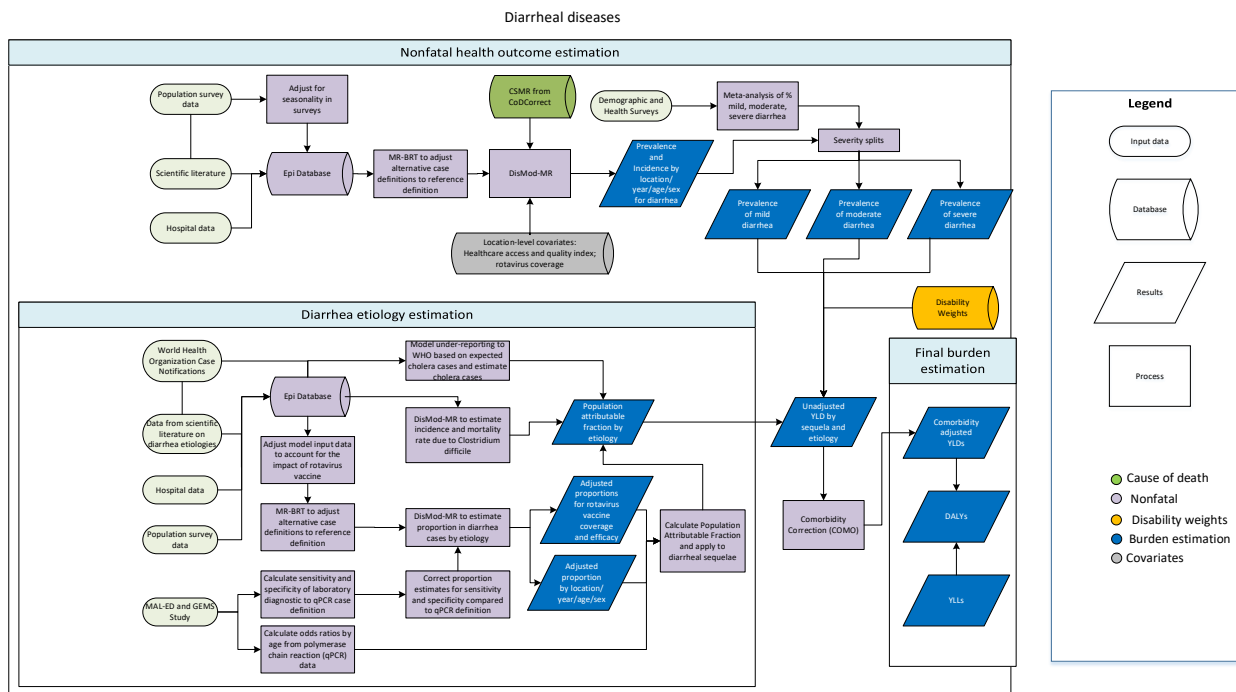
Level	Covariate	Direction
1	Oral rehydration solution treatment	-
	Rotavirus vaccine coverage (proportion)	-
	Sanitation (proportion with access)	-
	Improved water source (proportion with access)	-
2	Zinc deficiency	+
	Zinc treatment for diarrhoea	-
	Healthcare Access and Quality Index	-
3	Maternal education years	-
	Socio-demographic Index (SDI)	-
	Lag distributed income (LDI) per capita	-
	No access to handwashing facility	+

Table 1B. Covariates used in the 5–95+ years model

Level	Covariate	Direction
1	Sanitation (proportion with access)	-
	Improved water source (proportion with access)	-
2	Healthcare Access and Quality Index	-
	Rotavirus vaccine coverage (proportion)	-
	Oral rehydration solution treatment	-
3	Education years per capita	-
	Lag distributed income (LDI) per capita	-
	Adult underweight	+
	Socio-demographic Index (SDI)	-
	No access to handwashing facility	+

Diarrhoeal disease morbidity

Flowchart



Case definition

We defined diarrhoeal disease episodes as three or more loose stools in a 24-hour period. In the diarrhoea models, self-reported prevalence is the reference category for all data adjustments. Hospital input data use ICD-9 codes 001-009.9 and ICD-10 codes A00-A09.

The case definitions accepted for diarrhoea are shown below.

Quantity of interest	Reference or alternative	Definition
Incidence or prevalence of diarrhoea	Reference	Three or more abnormally loose stools in a 24-hour period. Self-reported or parental report for children.
Incidence of inpatient diarrhoea episodes	Alternative	Incidence of diarrhoea episodes that become inpatients reported in health care data.
Incidence of diarrhoea episodes in clinical claims data	Alternative	Incidence of diarrhoea episodes reported in claims data.

Input data

Model inputs

We used three main types of data in the diarrhoea non-fatal burden estimation: hospital data, population-based surveys, and data from scientific literature.

The first type of data is the incidence of diarrhoea in hospital settings, including inpatient, outpatient, and claims data. These data were identified using the ICD-9 codes 001-009.9 and ICD-10 codes A00-A09 and were adjusted prior to modelling for multiple admissions and multiple diagnoses. To be consistent with the population-based survey data, adjusted hospital data were transformed from incidence to prevalence using the following equation:

$$Prevalence = Incidence * \frac{duration(days)}{365}$$

The second type of data are from population-representative surveys, such as the Demographic and Health Surveys and the Multiple Indicator Cluster Surveys. We converted the prevalence of maternal-reported two-week period from surveys to point prevalence in one-year age groups using this equation:

$$Point\ Prevalence = Period\ Prevalence * \frac{Duration}{(Recall\ Period + Duration - 1)}$$

Where the mean duration was the duration in days, an average of 4.3 days (4.2–4.4) in both equations.¹⁴

Survey data were adjusted for seasonality. Surveys are frequently conducted over several months. To account for seasonal variation in diarrhoea prevalence, we fit a mixed-effects generalised additive model for each GBD region with a forced periodicity and a random intercept by country. The ratio between the monthly model-fit diarrhoea prevalence and the corresponding regional diarrhoea prevalence is a scalar to adjust survey data by month and geography.

The third type of data are from scientific literature. Inclusion criteria include diarrhoea as the case definition, studies with a sample size of at least 100, and a study duration of at least one year to avoid bias in the seasonal timing of diarrhoea. We excluded studies that reported on diarrhoeal outbreaks exclusively and studies that combined acute gastroenteritis with and without diarrhoea. We included all literature data sources used in GBD 2019 and conducted an updated review of literature for GBD 2021 covering the period 2/7/2019 to 1/3/2020 for diarrhoea prevalence, incidence, and all diarrhoea aetiologies.

Newly identified sources were added to studies and sources identified in previous rounds of the GBD, representing data from 199 countries (**Table 1**).

Table 1. Unique source counts for diarrhoeal diseases by measure

Measure	Total sources	Countries with data
Prevalence	1292	169
Other	450	116

Data crosswalks

One of the GBD core principles is to use all available data to inform our estimates. To account for differences between studies, we conducted a meta-regression of the ratio of reference to non-reference data using the

meta-regression—Bayesian, regularised, trimmed (MR-BRT) tool. When possible, crosswalks based on data matched within studies on age, sex, and location are used. When not possible, ratios between alternative and reference case definitions/methods were based on data matched between studies, nearby in age, year, with exact matches on sex and location. We adjusted inpatient data and claims data up to the level of self-reported data (our reference case definition) (**table 2**).

Table 2. Diarrhoeal disease crosswalk coefficients

Data input	Reference or alternative case definition	Gamma	Crosswalk covariate	Beta coefficient, logit (95% UI)
Self-reported diarrhoea	ref	--	--	--
Clinical and literature, inpatient	alt	0.36	intercept	−5.80 (−6.51 to −5.08)
Claims, MarketScan	alt	0	intercept	0.07 (−0.11 to 0.26)

Age-sex splits

Data were age- and sex-split based on population and a modelled age-curve generated using age-specific data as inputs in MR-BRT to better estimate the distribution of non-age-specific data.

Severity split inputs

Diarrhoeal diseases have three severity levels: mild, moderate, and severe (**Table 3**). The proportion of diarrhoea cases that are assigned to each comes from a systematic review of diarrhoea severity.¹³ Mild cases are the proportion of diarrhoea cases that did not seek medical care (64.8%); moderate cases are the proportion that sought medical care but did not have severe dehydration or bloody stool (28.9%); and severe cases are the proportion that sought medical care with severe dehydration or bloody stool (6.9%). These proportions are based on the frequency of dehydration and bloody stool among community-based studies reported in the systematic review.

Table 3. Severity splits, details on the severity levels for diarrhoea in GBD 2021 and the associated disability weight (DW) with that severity.

Severity level	Lay description	Disability weight (95% CI)	Proportion
Mild	Has diarrhoea defined as 3 or more loose stools in a 24-hour period with no dehydration.	0.074 (0.049–0.104)	64.8%
Moderate	Has diarrhoea defined as 3 or more loose stools in a 24-hour period with painful cramps and feeling thirsty and any dehydration.	0.188 (0.125–0.264)	28.9%

Severe	Has diarrhoea defined as 3 or more loose stools in a 24-hour period with painful cramps and is very thirsty or feels nauseated or tired and/or severely dehydrated.	0.247 (0.164–0.348)	6.9%
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Modelling strategy

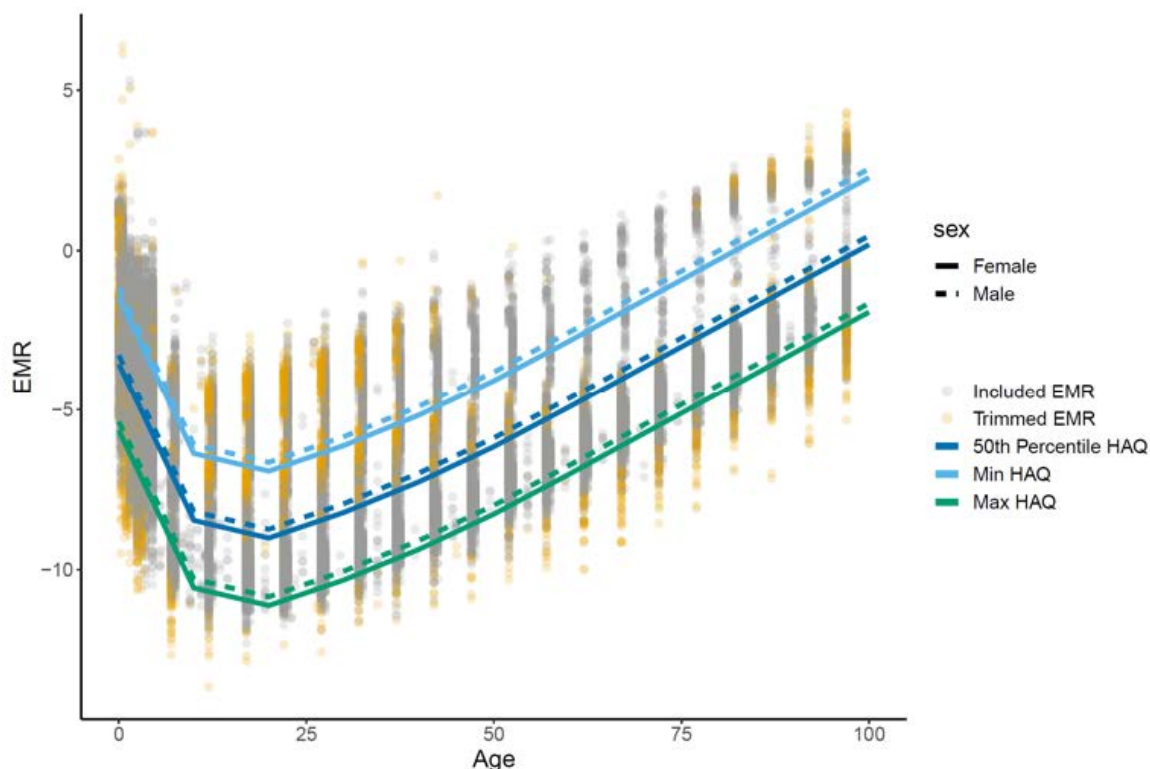
Diarrhoea incidence and prevalence

The non-fatal diarrhoeal disease burden is modelled in DisMod-MR 2.1, a Bayesian meta-regression modelling framework. DisMod-MR produces estimates of the incidence, prevalence, and remission of diarrhoea for each age, sex, geographical location, and year. The reference category for our input data is community-based diarrhoea episodes such as data from population-representative surveys or community cohorts. As described in the data crosswalks section above, input data that are from a different population, such as hospital inpatient groups, are adjusted before modelling by determining a meta-regression ratio of non-reference to reference data values, so that they are consistent with the reference category. Before modeling in DisMod, we ran the MR-BRT (Meta-Regression with Bayesian priors, Regularization, and Trimming) tool with excess mortality rate (EMR) computed as cause-specific mortality (CSMR) divided by prevalence as input data and healthcare access and quality index (HAQ), age, and sex as covariates to predict EMR prior data for all locations. We assumed higher HAQ to be associated with lower EMR. To examine this assumption, we analyzed the model fit across all available data, as illustrated in Figure 4. In Figure 4, there are three distinct sets of model fit lines, representing different HAQ values: light blue lines for the minimum HAQ values, darker blue lines for the 50th percentile HAQ values, and green lines for the maximum HAQ values. Within these sets, we further differentiated between genders, with solid lines representing females and dotted lines representing males. This detailed visualization clearly demonstrates the inverse relationship we hypothesized for both males and females: the light blue lines, corresponding to the lowest HAQ values, estimate higher EMR compared to the dark blue and green lines, which represent higher HAQ values. We then used location-year-age-sex specific EMR prior data as an input to DisMod, which simultaneously models prevalence, incidence, EMR, and CSMR to produce internally consistent estimates. Country-level covariates are used to inform the model (Table 4).

Table 4. Covariates. Summary of covariates used in the diarrhoea DisMod-MR meta-regression model

Covariate	Type	Parameter	Exponentiated beta (95% uncertainty interval)
RotaC vaccine lagged in five-year coverage	Country-level	Prevalence	0.20 (0.19 — 0.20)
Socio-demographic Index	Country-level	Prevalence	0.13 (0.12 — 0.14))
Sex	Study-level	Prevalence	1.05 (1.04 — 1.06)
Healthcare Access and Quality Index	Country-level	Excess mortality rate	0.94 (0.94–0.94)
Sex	Study-level	Excess mortality rate	1.33 (1.32 — 1.34)

Figure 4. Model predictions across HAQ levels against EMR input data (log space)



DisMod-MR 2.1 description²

The sequence of estimation in DisMod MR 2.1 occurs at five levels: global, super-region, region, country and, where applicable, subnational location. The super-region priors are generated at the global level with mixed-effects, nonlinear regression using all available data; the super-region fit, in turn, informs the region fit, and so on down the cascade. Subnational estimation was informed by the country fit and country covariates, plus an adjustment based on the average of the residuals between the subnational location's available data and its prior. This mimicked the impact of a random effect on estimates between subnationals. At each level of the cascade, the DisMod-MR 2.1 enforces consistency between all parameters. Analysts have the choice to branch the cascade in terms of time and sex at different levels depending on data density. We used the default option to model diarrheal disease, which is to branch by sex after the global fit but to retain all years of data until the lowest level in the cascade.

The coefficients for country covariates were re-estimated at each level of the cascade. For a given location, country coefficients were calculated using both data and prior information available for that location. In GBD 2021, we generated model fits for the years 1990, 1995, 2000, 2005, 2010, 2015, 2017, 2019, 2020 and 2021, and log-linearly interpolated estimates for the intervening years. The 95% uncertainty intervals were computed based on 1000 draws from the posterior distribution of the model using the 2.5th and 97.5th percentiles of the ordered 1000 values.

Analysts have the choice of using a Gaussian, log-Gaussian, Laplace or Log-Laplace likelihood function in DisMod-MR 2.0. The default log-Gaussian equation for the data likelihood is:

$$-\log[p(y_j|\Phi)] = \log(\sqrt{2\pi}) + \log(\delta_j + s_j) + \frac{1}{2} \left(\frac{\log(a_j + \eta_j) - \log(m_j + \eta_j)}{\delta_j + s_j} \right)^2$$

where, y_j is a 'measurement value' (i.e. data point); Φ denotes all model random variables; η_j is the offset value, eta, for a particular 'integrand' (prevalence, incidence, remission, excess mortality rate, with-condition mortality rate, cause-specific mortality rate, relative risk or standardised mortality ratio) and a_j is the adjusted measurement for data point j , defined by:

$$a_j = e^{(-u_j - c_j)} y_j$$

where u_j is the total 'area effect' (i.e. the sum of the random effects at three levels of the cascade: super-region, region and country) and c_j is the total covariate effect (i.e. the mean combined fixed effects for sex, study level and country level covariates), defined by:

$$c_j = \sum_{k=0}^{K[I(j)]-1} \beta_{I(j),k} \hat{X}_{k,j}$$

with standard deviation

$$s_j = \sum_{l=0}^{L[I(j)]-1} \zeta_{I(j),l} \hat{Z}_{l,j}$$

where k denotes the mean value of each data point in relation to a covariate (also called x-covariate); $I(j)$ denotes a data point for a particular integrand, j ; $\beta_{I(j),k}$ is the multiplier of the k^{th} x-covariate for the I^{th} integrand; $\hat{X}_{k,j}$ is the covariate value corresponding to the data point j for covariate k ; l denotes the standard deviation of each data point in relation to a covariate (also called z-covariate); $\zeta_{I(j),l}$ is the multiplier of the l^{th} z-covariate for the I^{th} integrand; and δ_j is the standard deviation for adjusted measurement j , defined by:

$$\delta_j = \log[y_j + e^{(-u_j - c_j)} \eta_j + c_j] - \log[y_j + e^{(-u_j - c_j)} \eta_j]$$

Where m_j denotes the model for the j^{th} measurement, not counting effects or measurement noise and defined by:

$$m_j = \frac{1}{B(j) - A(j)} \int_{A(j)}^{B(j)} I_j(a) da$$

where $A(j)$ is the lower bound of the age range for a data point; $B(j)$ is the upper bound of the age range for a data point; and $I(j)$ denotes the function of age corresponding to the integrand for data point j .

The source code for DisMod-MR 2.1 as well as the wrapper code is available at the following link:

d.

A layman's description of DisMod MR 2.1

DisMod-MR 2.1 is an advanced tool developed for the Global Burden of Disease study, designed to enhance the estimation of the prevalence and incidence of diseases across different geographies over time. Given that available data on prevalence, incidence, and mortality may be incomplete or limited, it employs a statistical triangulation method to provide more robust estimates. This method ensures that incidence, prevalence, and mortality estimates are internally consistent, which means they logically fit together given that prevalence is a function of incidence, recovery, and death rates. The estimation process utilizes a hierarchical approach that starts with global estimates and then refines these based on more localized data to produce estimates for 204 countries and territories over different time periods.

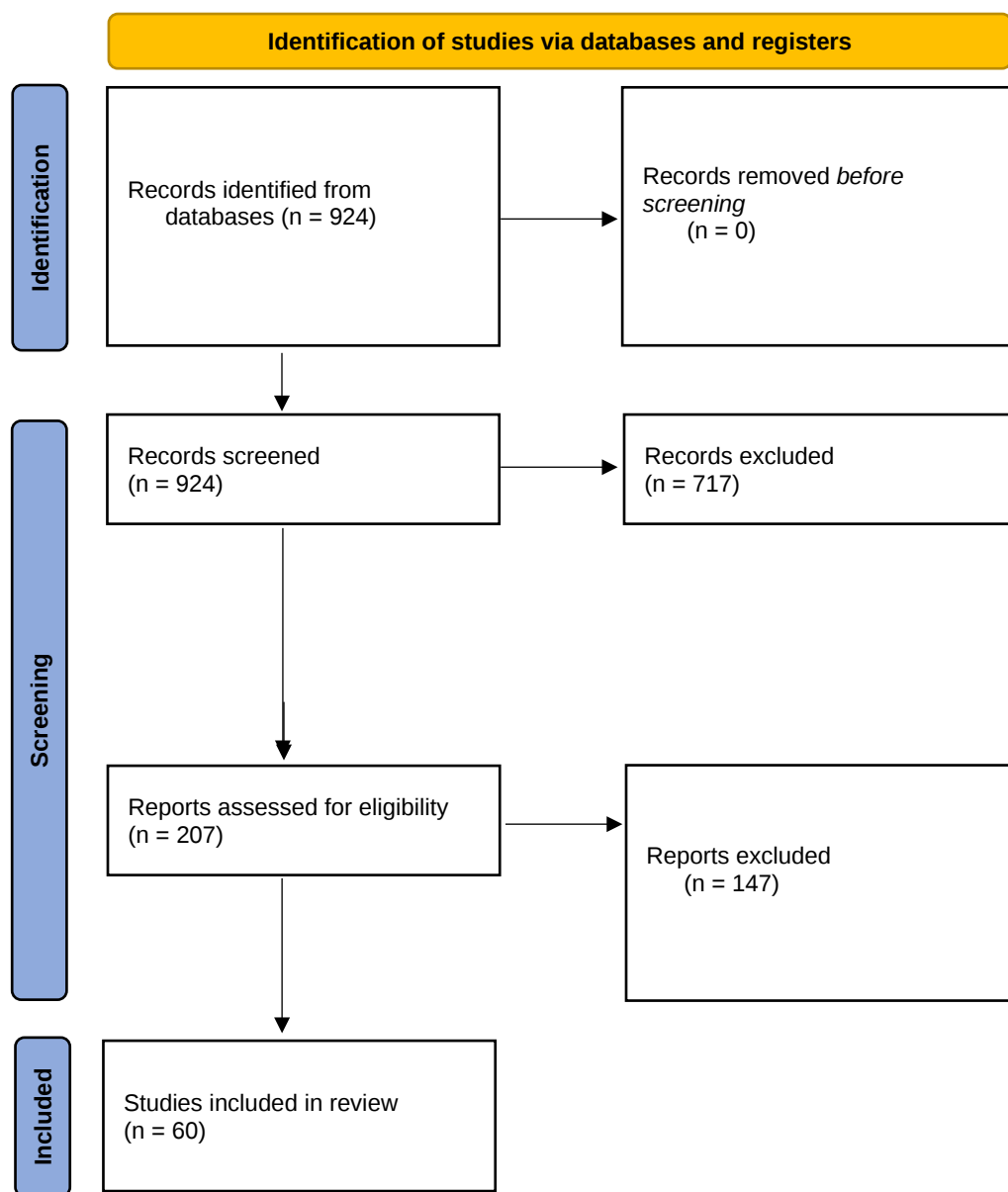
Diarrhoeal Aetiologies

There are 13 aetiologies in GBD 2021 for diarrhoea: adenovirus, *Aeromonas*, *Campylobacter*, *Vibrio cholerae*, *Clostridium difficile*, *Cryptosporidium*, *Entamoeba histolytica*, Enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-EPEC), typical Enteropathogenic *Escherichia coli* (tEPEC), norovirus, rotavirus, non-typhoidal *Salmonella*, and *Shigella*. The input data to inform the proportion of diarrhoea cases that tested positive for each pathogen for all aetiologies except *C. difficile* include data from published studies identified via systematic review and the Global Pediatric Diarrhoea Surveillance Network. We completed an updated systematic literature review covering the period February 2019 to December 2020. The inclusion criteria included studies reporting pathogen-specific data with a sample size of at least 100 and studies with at least one year of follow-up. Studies merging certain pathogens and reporting aggregated outcomes were ineligible for inclusion in our analysis. We also excluded studies that exclusively reported on diarrheal outbreaks and studies that combined acute gastroenteritis with and without diarrhoea. We searched articles using a PubMed search term that combined non-specific and aetiology-specific diarrhoea using the following search string:

(diarrhoea[title/abstract] OR diarrhea[title/abstract]) AND (2019/02/07:2020/12/31[PDat]) AND (incidence[title/abstract] OR prevalence[title/abstract] OR epidemiology[title/abstract] OR salmonella[title/abstract] OR aeromona[title/abstract] OR shigell*[title/abstract] OR enteropathogenic[title/abstract] OR enterotoxigenic[title/abstract] OR campylobacter[title/abstract] OR amoebiasis[title/abstract] OR entamoeb*[title/abstract] OR cryptosporid*[title/abstract] OR rotavirus[title/abstract] OR norovirus[title/abstract] OR adenovirus[title/abstract] OR etiology[title/abstract]) NOT (appendicitis[title/abstract] OR esophag*[title/abstract] OR surger*[title/abstract] OR gastritis[title/abstract] OR liver[title/abstract] OR case report[title] OR case-report[title] OR therapy[title] OR treatment[title] OR Crohn[title/abstract] OR "inflammatory bowel"[title/abstract] OR irritable[title/abstract] OR travel*[title] OR Outbreak[title] OR Review[ptyp] OR vomiting[title/abstract] NOT (animals[MeSH] NOT humans[MeSH]))*

We identified 924 studies, of which 60 met our inclusion criteria. We extracted data for location, sex, year, and age.

Figure 1. Diarrhoeal disease aetiology systematic review PRISMA diagram

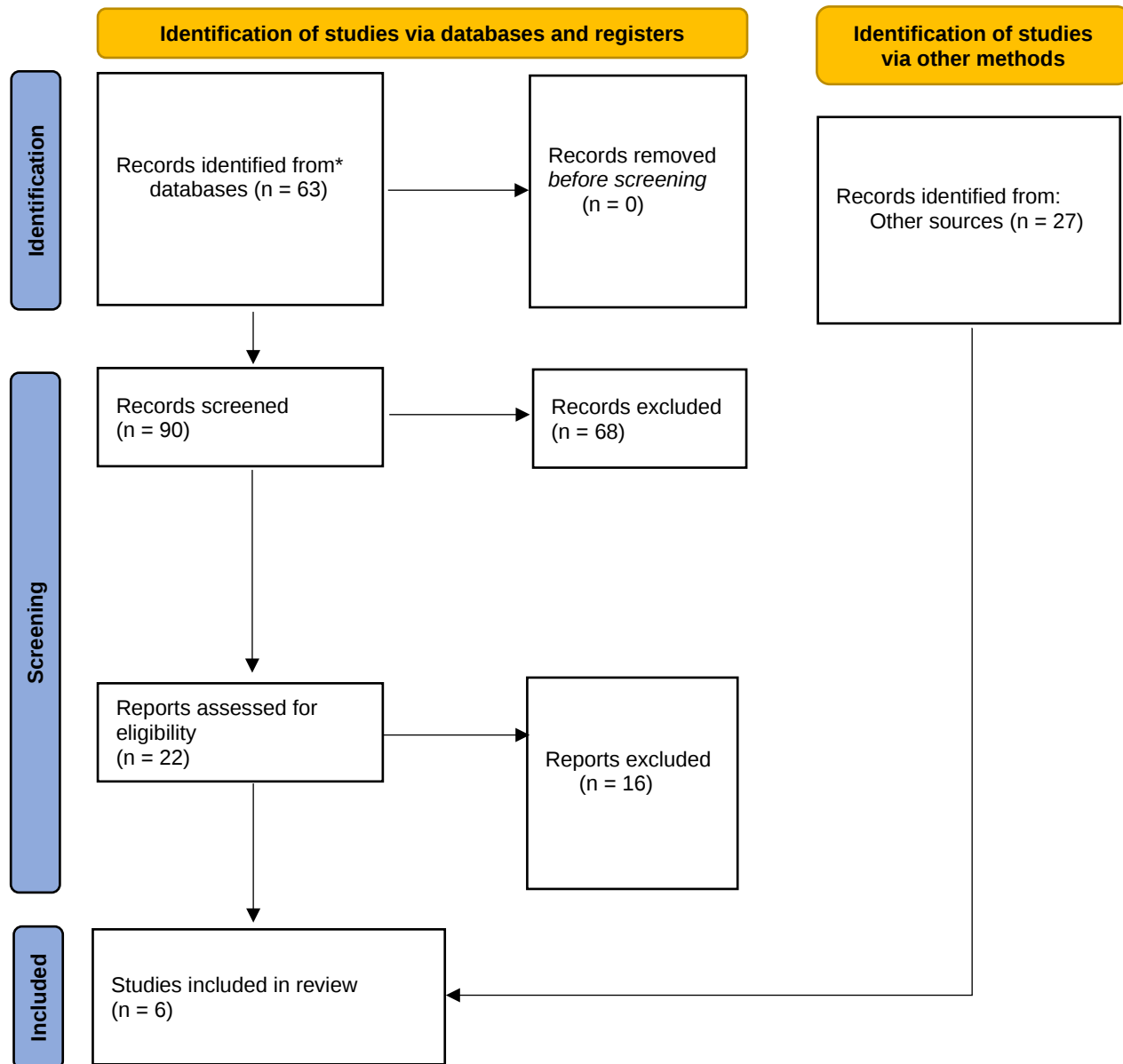


Additionally, we searched specifically for data sources detailing rotavirus coverage and vaccine efficacy using the following search string:

((rotavirus[title/abstract] AND vaccine[title/abstract] AND (efficacy[title/abstract] OR effectiveness[title/abstract]) AND (2019/02/07[PDAT] : 2020/12/31[PDAT]))) NOT Review[Publication Type] NOT (animals[MeSH] NOT humans[MeSH])

We identified 63 studies via PubMed and an additional 27 studies through manual reference search. Of the 90 studies identified, six met our inclusion criteria.

Figure 2. Rotavirus vaccine efficacy systematic review PRISMA diagram



We used the Global Enteric Multicenter Study (GEMS), a seven-site, case-control study of moderate-to-severe diarrhoea in children under 5 years,⁴ and the MAL-ED study,⁵ a multi-site birth cohort, to calculate odds ratios

for the diarrhoeal pathogens. We analysed raw data for a systematic reanalysis, representative of the distribution of cases and controls by age and site that were tested for the presence of pathogen using quantitative polymerase chain reaction (qPCR).⁶

Data that did not use qPCR for detection were adjusted for sensitivity and specificity prior to modelling in order to standardise data regardless of detection method. Adjusting these data prior to modelling allowed us to adjust only data that did not use qPCR, as well as better control for values at extreme bounds and capture uncertainty in modelling.

Case fatality rate (CFR) data for *Clostridium difficile* were collected from ICD-coded hospital records from Austria, Brazil, Canada, Italy, Mexico, New Zealand, and the USA. ICD codes A04.7 (ICD-10) and 008.45 (ICD-9) were used to identify intestinal infections with *Clostridium difficile*. Supplemental data for Romania collected as part of the International Nosocomial Infection Control Consortium (DOI: 10.1016/j.ajic.2016.01.005) were also included. We standardised age and sex across all datasets to the following most-detailed groups using the GBD causes of death age-sex splitting algorithm for age: 0–6, 7–27, and 28–364 days, and 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95+ years; and sex: male and female. This algorithm is based on the assumption that the age-sex pattern of the death or case rate for a given infectious syndrome or pathogen is inherent to the pathology of the disease and is therefore constant across location and year. Crude case-fatality rates were then estimated for the input data for each GBD age group and sex.

We estimated diarrhoeal disease aetiologies independently from overall diarrhoea envelope using a counterfactual strategy for enteric adenovirus, *Aeromonas*, *Entamoeba histolytica* (amoebiasis), *Campylobacter*, *Cryptosporidium*, enteropathogenic *Escherichia coli* (EPEC), enterotoxigenic *Escherichia coli* (ETEC), norovirus, non-typhoidal *Salmonella* infections, rotavirus, and *Shigella*. *Vibrio cholerae* and *C. difficile* were modelled separately.

Diarrhoeal aetiologies are attributed to diarrhoeal cases and deaths using a counterfactual approach. We calculated a population attributable fraction (PAF) from the proportion of diarrhoea cases that are positive for each aetiology. The PAF represents the relative reduction in diarrhoea burden if there was no exposure to a given aetiology. As diarrhoea can be caused by multiple pathogens and the pathogens may co-infect, PAFs can overlap and are not scaled to sum to 100%. We calculated the non-fatal PAF from the proportion of diarrhoea cases that are positive for each aetiology. We calculated the fatal PAF from the proportion of severe diarrhoea cases that are positive for each aetiology. We assumed that hospitalised diarrhoea cases are a proxy of severe and fatal cases. We used the following formula to estimate PAF:⁵

$$PAF = Proportion * (1 - \frac{1}{OR})$$

Where *Proportion* is the proportion of diarrhoea cases positive for an aetiology and *OR* is the odds ratio of diarrhoea given the presence of the pathogen.

We dichotomised the continuous qPCR test result using the value of the cycle threshold (Ct) that most accurately discriminated between cases and controls. The Ct values range from 0 to 35 cycles representing the relative concentration of the target gene in the stool sample. A low value indicates a higher concentration of the pathogen, while a value of 35 indicates the absence of the target in the sample. We used the lower Ct

value when we had multiple Ct values for the cut-point. The case definition for each pathogen is a Ct value that is below the established cutoff point.

In non-fatal modeling, we used a generalised linear mixed effects logistic regression model to calculate the odds ratio for under 1 year and 1–2 years old for each of our pathogens from the MAL-ED study. The MAL-ED study was used exclusively because the samples tested from that study are community-based samples, which we determined were more representative of non-fatal diarrhoea than the GEMS samples, which tested only moderate-to-severe diarrhoea. The odds ratio for 1–2 years was applied to all GBD age groups over 5 years. There were three pathogen-age odds ratios that were not statistically significant: *Aeromonas* and amoebiasis in under 1 year and *Campylobacter* in 1–2 years.

For fatal modeling, we used a mixed effects conditional logistic regression model to calculate the odds ratio for ages under 1 year and 1–4 years old for each of our pathogens. The stool samples from cases and controls in GEMS were used exclusively to calculate these odds ratios as we assumed that the association between pathogens and moderate-to-severe diarrhoea is a proxy for fatal outcomes. The odds ratio for ages 1–4 years was applied to all GBD age groups over 5 years. There were three pathogen-age odds ratios that were not statistically significant: *Aeromonas* and amoebiasis in under 1 year and *Campylobacter* in 1–4 years.

If the odds ratio was not statistically significant, we transformed the odds ratios only for those aetiologies in log-space such that exponentiated values could not be below 1. The transformation was:

$$\text{Odds ratio} = \exp(\log(\text{OR}) - 1) + 1$$

We modelled the proportion data using the Bayesian meta-regression tool DisMod-MR to estimate the proportion of positive diarrhoea cases for each separate aetiology by location/year/age/sex and to adjust for the covariates. To account for differences between studies, we also conducted a meta-regression of the ratio of reference to non-reference data using the meta-regression—Bayesian, regularised, trimmed (MR-BRT) tool. We adjusted inpatient data (Table 5) and single-pathogen data (Table 6).

Table 5. Inpatient to community crosswalk coefficients for diarrhoeal disease aetiologies, not including *Vibrio cholerae* or *C. difficile*

Aetiology	Data input	Reference or alternative case definition	Gamma	Crosswalk covariate	Beta coefficient, logit (95% UI)
All	community-based samples	ref	--	--	--
Adenovirus	Clinical, inpatient	alt	0.09	intercept	0.25 (0.08 to 0.43)
<i>Aeromonas</i>	Clinical, inpatient	alt	0.14	intercept	0.19 (–0.09 to 0.46)
Amoebiasis	Clinical, inpatient	alt	0.80	intercept	0.12 (–0.47 to 0.72)

<i>Campylobacter</i>	Clinical, inpatient	alt	0.26	intercept	−0.11 (−0.33 to 0.12)
<i>Cryptosporidium</i>	Clinical, inpatient	alt	0.05	intercept	0.24 (0.11 to 0.38)
EPEC	Clinical, inpatient	alt	0.02	intercept	0.03 (−0.10 to 0.16)
ETEC	Clinical, inpatient	alt	0.00	intercept	0.10 (−0.003 to 0.21)
Norovirus	Clinical, inpatient	alt	0.04	intercept	0.06 (−0.06 to 0.18)
Rotavirus	Clinical, inpatient	alt	0.35	intercept	0.70 (0.53 to 0.87)
<i>Salmonella</i>	Clinical, inpatient	alt	0.15	intercept	0.47 (0.19 to 0.74)
Shigellosis	Clinical, inpatient	alt	0.39	intercept	0.29 (0.02 to 0.57)

Table 6. Single to multi-pathogen study crosswalk coefficients for diarrhoeal disease aetiologies, not including *Vibrio cholerae* or *C. difficile*

Aetiology	Data input	Reference or alternative case definition	Gamma	Crosswalk covariate	Beta coefficient, logit (95% UI)
All	Multi-pathogen studies	ref	--	--	--
Adenovirus	Single pathogen	alt	0.00	intercept	1.06 (0.89 to 1.22)
<i>Aeromonas</i>	Single pathogen	alt	N/A	intercept	N/A
Amoebiasis	Single pathogen	alt	N/A	intercept	N/A
<i>Campylobacter</i>	Single pathogen	alt	N/A	intercept	N/A

<i>Cryptosporidium</i>	Single pathogen	alt	N/A	intercept	N/A
EPEC	Single pathogen	alt	N/A	intercept	N/A
ETEC	Single pathogen	alt	0.00	intercept	0.14 (−0.03 to 0.31)
Norovirus	Single pathogen	alt	N/A	intercept	N/A
Rotavirus	Single pathogen	alt	0.43	intercept	0.53 (0.23 to 0.84)
<i>Salmonella</i>	Single pathogen	alt	0.00	intercept	0.78 (0.50 to 1.07)
Shigellosis	Single pathogen	alt	0.00	intercept	0.72 (0.62 to 0.82)

We used the estimated sensitivity and specificity of the original laboratory diagnostic test results from the pooled GEMS and MAL-ED qPCR stool samples compared to the qPCR test result to adjust our proportion before we modelled the proportions:⁶

$$Proportion_{True} = \frac{(Proportion_{Observed} + Specificity - 1)}{(Sensitivity + Specificity - 1)}$$

We used this correction to account for the fact that the proportions we used are based on a new test that is not consistent with the laboratory-based case definition (qPCR versus GEMS conventional laboratory testing for pathogens).⁶ Because of differences in the type of PCR used in the original (non-reference qPCR diagnostic) between GEMS and MAL-ED in detecting norovirus, we combined the sensitivity and specificity results for norovirus such that 50% of the draws were coming from GEMS test results exclusively, and 50% of the draws were coming from MAL-ED test results exclusively. Additionally, because the original laboratory diagnostic technique used for *Campylobacter* in MAL-ED was one not commonly used, we only used GEMS to determine the sensitivity and specificity of bacterial culture compared to qPCR in detecting *Campylobacter*.⁸

In order to be consistent with the odds ratios that we obtained, we adjusted our proportion estimates of any EPEC to typical EPEC only. This adjustment was informed by all available data that reported both atypical and typical EPEC. We applied the same approach to differentiate between heat-stable toxin (ST) and heat-labile toxin-producing (LT) ETEC. This was based on work showing that ST-ETEC was much more pathogenic than LT-ETEC. As some of our proportion data were extracted for any ETEC, we determined a proportion of all ETEC that produced ST from all available data reporting both ETEC and ST-ETEC and applied that ratio to data representing all ETEC so that they represented ST-ETEC only.

For *Vibrio cholerae* (cholera), we used the literature review to estimate the expected number of cholera cases for each country-year using the incidence of diarrhoea (estimated using DisMod-MR) and the proportion of diarrhoea cases that are positive for cholera. We assigned cholera PAF using odds ratios from the qPCR results to estimate a number of cholera-attributable cases. We compared this expected number of cholera cases to the number reported to WHO at the country-year level.¹¹ We modelled the under-reporting fraction to correct the cholera case notification data for all countries using health system access and the diarrhoea SEV scalar to predict total cholera cases. We used the age-specific proportion of positive cholera samples in DisMod-MR and our incidence estimates to predict the number of cholera cases for each age/sex/year/location. Finally, we modelled the case fatality ratio of cholera using DisMod-MR to estimate the number of cholera deaths.

For *C. difficile*, we modelled incidence data identified via systematic review and excess mortality estimates in DisMod-MR 2.1. DisMod-MR uses a compartmental model to relate prevalence, incidence, remission, and mortality. We set remission in our model to 1 month. Excess mortality rates (EMRs) were computed based on case-fatality rates by age from hospital data and an assumed duration (1.0 month [0.3–1.7]) using the following equation:

$$EMR = -\ln(1 - CFR)/duration$$

C. difficile CFRs were calculated using MR-BRT, a meta-analytic mixed effects structure. The main model can be specified as follows:

$$\text{logit}(y_i) = X_i\beta + u_i1 + \epsilon_i, \quad \epsilon_i \sim N(0, \Sigma_i), \quad u_i \sim N(0, \gamma)$$

where

- y_i contains CFRs for data source i
- Design matrix X_i contains as columns the following covariates
 - HAQ Index
 - dummy-coded indicator for age group
 - neonatal–5 years, 5–50 years, 50–70 years, and 70 years and older
 - dummy-coded ICU indicator for data source
 - 1 if data source only compiles information on ICU patients, 0 if a mix between ICU/non-ICU patients
 - dummy-coded indicator for pathogen
- β are fixed effect multipliers
- ϵ_i are observation error terms with known variances
- u_i are data source-specific random intercepts with unknown covariance γ

We also implemented a prior on γ , the data source random effect. Many input data sources cover only a single country, leading to low variability in HAQ Index within each data source. Such collinearity adversely influenced the accuracy of the estimated effect of HAQ Index, which was instrumental in extrapolating trends from the input data to global results. To emphasise the contribution of HAQ Index over data source in the modelled estimates, we implemented a strong Gaussian prior (mean 0, standard error 0.001) on γ . Predictions for *Clostridium difficile* CFRs were generated for each country and age group as a function of each country's HAQ Index, assuming mixed ICU/non-ICU patients.

For rotavirus, we explicitly accounted for rotavirus vaccine efficacy when estimating attributable fraction, as in GBD 2019. The impact of the rotavirus vaccine is dependent on modelled vaccine coverage for a location-year and on the rotavirus vaccine efficacy (VE). Numerous studies demonstrate a difference in VE by national income and development.¹² We also determined via LASSO (least absolute shrinkage and selection operator) that Socio-demographic Index (SDI) was the best predictor of rotavirus VE. We used a meta-regression with SDI as covariate to predict the rotavirus VE by location and year.

Starting from GBD 2019, we explicitly incorporated the results from our analysis of VE to produce more robust estimates of the proportion of diarrhoea that has rotavirus over time and space. We assumed that the impact of the vaccine can be represented as 1 minus the product of the estimated vaccine coverage and VE.

$$Vaccine\ impact = 1 - vaccine\ coverage * vaccine\ efficacy$$

Both of these values vary in time and space but not by age. To avoid discontinuities in our DisMod model, we adjusted the input proportion data to remove the impact of the rotavirus vaccine by dividing the observed proportion by the vaccine impact.

$$Rotavirus\ proportion_{Adjusted} = \frac{Rotavirus\ proportion}{1 - Cov_{RotaV} * VE_{Modeled}}$$

The result from DisMod is the modelled proportion of diarrhoea positive for rotavirus in the absence of the vaccine. This modelled value is then multiplied by the impact of the rotavirus vaccine to determine the estimated proportion of diarrhoea positive for rotavirus in the presence of the vaccine. Our modified attributable fraction is then:

$$DisModPAF = Modeled\ Proportion\ (from\ DisMod) * \left(1 - \frac{1}{OR}\right)$$

The last step is to account for the expected impact of the rotavirus vaccine. We do this using the equation below:

$$PAF_{Rota} = DisModPAF * \frac{(1 - Cov_{RotaV} * VE_{Modeled})}{(1 - DisModPAF * Cov_{RotaV} * VE_{Modeled})}$$

Where the final attributable fraction for rotavirus is the product of the PAF estimated in DisMod-MR and the expected reduction in that PAF given modelled vaccine coverage and modelled VE by location-year, and this value is only applied to children 28 days to 5 years old. The product of the rotavirus attributable fraction and the number of deaths or cases of diarrhoea is the number of deaths and cases caused by rotavirus.

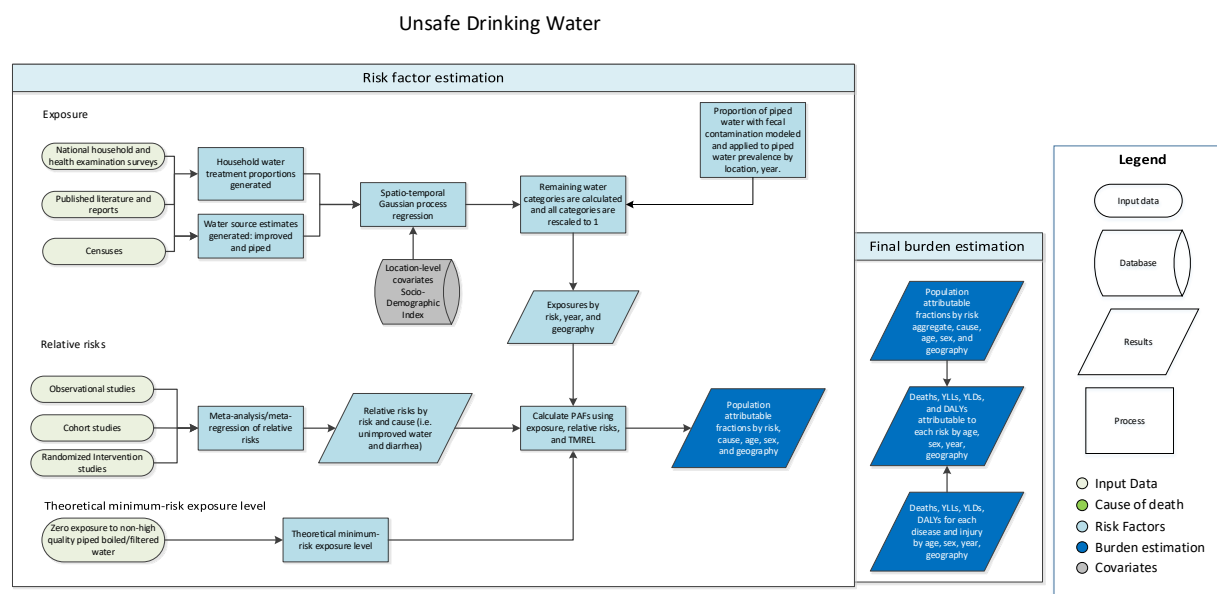
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Unsafe water

Flowchart



Input data and methodological summary

Exposure

Case definition

For the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021, exposure to unsafe water was defined based on (1) reported primary water source used by the household, and (2) use of household water treatment (HWT) to improve the quality of drinking water before consumption. Water sources were defined based on the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (JMP).¹ Examples of “improved” sources include boreholes, tube wells, protected wells, and packaged or delivered water. Piped water is also considered “improved” by the JMP but is placed into its own category for GBD purposes. Examples of “unimproved” sources include unprotected springs, unprotected wells, and surface water. Additionally, four different HWTs were determined to be effective point-of-use treatments based on effect sizes calculated from a network meta-analysis: solar treatment, chlorine treatment, boiling, and filtering. For modelling purposes, we grouped solar and chlorine treatment together, as well as boiling and filtering.

Input data

The search for usable data sources was conducted using the Global Health Data Exchange (GHDx) database. Water source input data came primarily from nationally representative surveys, such as the Demographic and Health Survey (DHS), the Multiple Indicator Cluster Surveys (MICS), the World Health Survey (WHS), and the DHS AIDS Indicator Survey (AIS). HWT input data were largely limited to the DHS and MICS due to data availability. Surveys that reported results at the household level were converted to the individual level using household size data to ensure that our models estimated the proportion of individuals, rather than households, exposed to a given indicator. For GBD 2021, we re-extracted nearly all of our sources from 2000 to present in an effort to standardise extraction outputs and fix past extraction errors. Additionally, we added 64 new sources for this cycle. After extraction, surveys and censuses were then tabulated to the water source

and water treatment categories of interest for each location. Table 1 provides a summary of the exposure input data.

Table 1: Exposure input data

Input data	Exposure
Source count (total)	1221
Number of countries with data	170

Modelling strategy

Water source data were modelled using an ordinal framework, with two distinct models: (1) proportion of the total population that uses piped water sources, and (2) proportion of the non-piped population that uses improved water sources. Both models were estimated for all ages and both sexes combined, and produced results for each unique location-year combination. This ordinal framework allowed estimating the category with the most data (piped water prevalence) and leveraging that estimate to anchor the estimates for the improved and unimproved water categories. The results of the improved proportion model were multiplied by 1 minus the piped water prevalence to calculate improved water prevalence. The sum of improved and piped water prevalence was then subtracted from 1 to yield unimproved water prevalence.

$$\begin{aligned}
 \textbf{Piped} &= \frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \\
 \textbf{Improved} &= \left(\frac{\# \text{ persons using improved water}}{\# \text{ persons without piped water}} \right) * (1 - \textbf{Piped}) \\
 \textbf{Unimproved} &= 1 - (\textbf{Piped} + \textbf{Improved})
 \end{aligned}$$

HWT categories were estimated in a similar ordinal framework. Its two models were (1) proportion of the total population that does not use any water treatment methods, and (2) proportion of the population that treat their water that use boiling or filtering as their primary HWT. Like the water source models, both HWT models were estimated for all ages and both sexes combined and produced results for each unique location-year combination. The proportion of individuals who boil/filter drinking water was calculated by multiplying the proportion who boil/filter modelled previously multiplied by the prevalence of any water treatment (estimated by subtracting the prevalence of no treatment from 1). The proportion of individuals who treat their water using solar/chlorine methods was estimated by subtracting from 1 the sum of prevalence of no treatment estimates and prevalence of filter/boil treatment.

$$\begin{aligned}
 \textbf{No HWT} &= \frac{\# \text{ persons who do not treat water}}{\# \text{ persons with nonmissing response}} \\
 \textbf{Boil or filter} &= \left(\frac{\# \text{ persons who treat water with boil or filter}}{\# \text{ persons who treat water with any method}} \right) * (1 - \textbf{No HWT}) \\
 \textbf{Chlorine or solar} &= 1 - (\textbf{No HWT} + \textbf{Boil or filter})
 \end{aligned}$$

Additionally, we modelled the microbiological quality of piped water sources primarily using data from a review by Bain et al 2014² that measured the proportion of piped water sources contaminated with faecal matter. We used the results from this model to split the prevalence of piped water into basic piped water and

high-quality piped water by location and year. High-quality piped water is piped water that enters the household free of contamination. Thus, HWT is irrelevant for this category, since treatment is only necessary if the water is contaminated.

$$\text{Faecal contamination} = \frac{\# \text{ contaminated piped water systems}}{\# \text{ piped water systems sampled}}$$

$$\text{Basic piped} = \text{Piped} * \text{Faecal contamination}$$

$$\text{HQ piped} = \text{Piped} - \text{Basic piped}$$

Each of the models described above was modelled using a three-step modelling scheme of mixed-effect linear regression followed by spatiotemporal Gaussian process regression (ST-GPR), which produced full time-series estimates for each GBD 2021 location. Socio-demographic Index (SDI), a composite measure of development combining education per capita, income per capita, and fertility, was set as a fixed effect in the linear regression since it proved to be a significant predictor. The proportion of individuals with access to piped water was also used as a covariate in the faecal matter model. Random effects were set at GBD 2021 region and super-region levels to fit the models but were not used in the predictions. The linear regression equations for each of the five ST-GPR models used for this risk factor are listed below.

Proportion using piped water: $\text{logit}(\text{data}) \sim \text{SDI} + (1|\text{level_1}) + (1|\text{level_2})$

Proportion of non-piped population using improved water: $\text{logit}(\text{data}) \sim \text{SDI} + (1|\text{level_1}) + (1|\text{level_2})$

Proportion using no HWT: $\text{logit}(\text{data}) \sim \text{SDI} + (1|\text{level_1}) + (1|\text{level_2})$

Proportion of HWT-using population that boils/filters: $\text{logit}(\text{data}) \sim \text{SDI} + (1|\text{level_1}) + (1|\text{level_2})$

Proportion of piped water systems contaminated with faecal matter: $\text{logit}(\text{data}) \sim \text{SDI} + \text{piped water access} + (1|\text{level_1}) + (1|\text{level_2})$

Piped water access = proportion of individuals with access to piped water
(1|level_1) = super-region-level random effects
(2|level_2) = region-level random effects

The process of vetting and validating models was accomplished primarily through an examination of ST-GPR scatter plots by GBD 2021 location from 1990 to 2021. Any poorly fitting datapoints were re-inspected for error at the level of extraction and survey implementation. If errors in data extraction were found, the study in question was re-extracted. In addition to SDI, a number of different potential fixed effects were considered, including lag-distributed income and urbanicity, but SDI proved to be the strongest predictor of the unsafe water categories. Uncertainty in the estimates was initially formed based on standard deviation by survey, then propagated through ST-GPR modelling by means of confidence intervals around each datapoint that reflected the point-estimate-specific variance. A datapoint with high variance, for example, would contribute relatively less influence to the model than a datapoint with lower variance.

Once models were vetted, full time-series outputs from ST-GPR modelling were then rescaled to form ten mutually exclusive categories that summed to 1 for each location-year combination. Table 2 provides the final result of this rescaling and also includes the formulas for each category.

Table 2: Exposure categories, definitions, and formulas

Exposure category	Definition	Formula
Unimproved, no HWT	Proportion of individuals who primarily use unimproved source and <i>do not</i> use any HWT to purify their drinking water.	$[1 - (Piped + Improved)] * \left[\frac{\# \text{ persons who do not treat water}}{\# \text{ persons with nonmissing response}} \right]$
Unimproved, chlorine/solar	Proportion of individuals who primarily use unimproved source, and who use solar or chlorine treatment to purify their drinking water.	$[1 - (Piped + Improved)] * [1 - (No HWT + Boil or filter)]$
Unimproved, boil/filter	Proportion of individuals who primarily use unimproved source and who boil or filter to purify their drinking water.	$[1 - (Piped + Improved)] * \left[\left(\frac{\# \text{ persons who treat water with boil or filter}}{\# \text{ persons who treat water with any method}} \right) * (1 - No HWT) \right]$
Improved water except piped, no HWT	Proportion of individuals who primarily use improved sources other than piped water supply and <i>do not</i> use any HWT to purify their drinking water.	$\left[\left(\frac{\# \text{ persons using improved water}}{\# \text{ persons without piped water}} \right) * \left[\frac{\# \text{ persons who do not treat water}}{\# \text{ persons with nonmissing response}} \right] \right]$
Improved water except piped, chlorine/solar	Proportion of individuals who primarily use improved sources other than piped water supply, and who use solar or chlorine treatment to purify their drinking water.	$\left[\left(\frac{\# \text{ persons using improved water}}{\# \text{ persons without piped water}} \right) * [1 - (No HWT + Boil or filter)] \right]$
Improved water except piped, boil/filter	Proportion of individuals who primarily use improved sources other than piped water supply and who boil/filter their drinking water.	$\left[\left(\frac{\# \text{ persons using improved water}}{\# \text{ persons without piped water}} \right) * \left[\left(\frac{\# \text{ persons who treat water with boil or filter}}{\# \text{ persons who treat water with any method}} \right) * (1 - No HWT) \right] \right]$
Basic piped water, no HWT	Proportion of individuals who primarily use basic piped water supply and <i>do not</i> use any HWT to purify their drinking water.	$\left[\left[\frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \right] * \left[\frac{\# \text{ contaminated piped water systems}}{\# \text{ piped water systems sampled}} \right] * \left[\frac{\# \text{ persons who do not treat water}}{\# \text{ persons with nonmissing response}} \right] \right]$
Basic piped water, chlorine/solar	Proportion of individuals who primarily use basic piped water supply, and who use solar or chlorine water treatment, to purify their drinking water.	$\left[\left[\frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \right] * \left[\frac{\# \text{ contaminated piped water systems}}{\# \text{ piped water systems sampled}} \right] * [1 - (No HWT + Boil or filter)] \right]$
Basic piped water, boil/filter	Proportion of individuals who primarily use basic piped water supply and who boil or filter to purify their drinking water.	$\left[\left[\frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \right] * \left[\frac{\# \text{ contaminated piped water systems}}{\# \text{ piped water systems sampled}} \right] * \left[\left(\frac{\# \text{ persons who treat water with boil or filter}}{\# \text{ persons who treat water with any method}} \right) * (1 - No HWT) \right] \right]$
High-quality piped water	Proportion of individuals who primarily use high-quality piped water.	$\left[\frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \right] - \left[\left[\frac{\# \text{ persons using piped water}}{\# \text{ persons with nonmissing response}} \right] * \left[\frac{\# \text{ contaminated piped water systems}}{\# \text{ piped water systems sampled}} \right] \right]$

Theoretical minimum-risk exposure level

The theoretical minimum-risk exposure level for unsafe water is defined as having access to high-quality piped water.

Relative risks

Input data

For GBD 2021, unsafe water was paired with one outcome – diarrhoeal diseases – given evidence provided by relative risk studies. Input data included in the GBD 2021 unsafe water relative risk analysis are as follows:

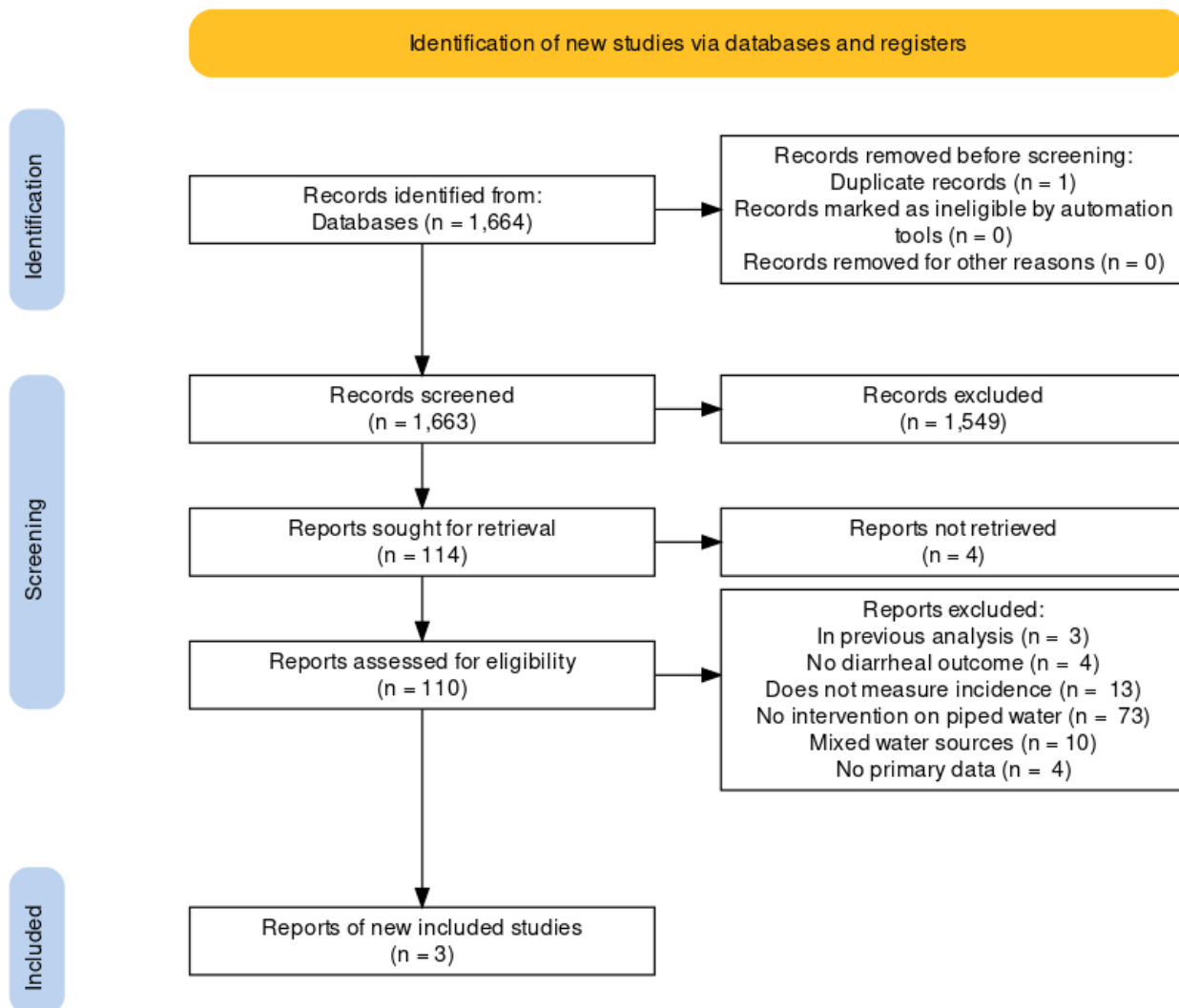
Table 3: Relative risk input data

Input data	Relative risk
Source count (total)	73
Number of countries with data	36

Two meta-analyses (Wolf et al 2014 and Wolf et al 2018) were used to identify relative risk studies, including years 1970-2016.^{3,4} Additionally, a literature review on the relationship between high-quality piped water and diarrhoea was conducted for GBD 2021, which yielded three new studies (Figure 1). We searched PubMed for relevant literature published from January 1, 1970 to July 2, 2020 (date of search), using the search string below:

("Drinking Water"[Mesh] OR "Water Quality"[Mesh] OR "Water Supply"[Mesh] OR "Piped water"[TIAB] OR "Tap water"[TIAB] OR "Potable water"[TIAB]) AND ("Diarrhea"[Mesh] OR Diarrh*[TIAB] OR "Diarrhea incidence"[TIAB] OR "Bacteriological"[TIAB] OR "Microbial water quality"[TIAB]) AND (1970[PDAT] : 3000[PDAT] NOT (animals[MeSH] NOT humans[MeSH]))

Figure 1: PRISMA diagram for systematic review of high-quality piped water and diarrheal disease



Modelling strategy

In GBD 2021, relative risk values were calculated using a network meta-analysis approach with a tool called meta-regression—Bayesian, regularised, trimmed (MR-BRT). One study-level covariate – whether conformity with the study interventions was self-reported or confirmed by the researchers – was included in the network meta-analysis. Several other covariates (whether exposure was captured at the individual level or population level; whether or not the study was randomised; whether or not the study adjusted for all major known confounders; and what the study’s follow-up percentage was) were considered but ultimately were not statistically significant and so were not included in the analysis. No priors were used. The risk of developing diarrhoea relative to using an unimproved water source was calculated for each of the following categories: boil or filter, solar or chlorine, improved, piped, and high-quality piped (Table 4). These model results were then combined and rescaled to match with our exposure definitions (Table 5). The combined effects of source interventions (ie, improved, piped, high-quality piped) and point-of-use interventions (ie, boil/filter, solar/chlorine) were assumed to be multiplicative. Additionally, we assumed that the lowest possible risk level is using the best source type (high-quality piped water) combined with the best point-of-use treatment (boil/filter).

Table 4: MR-BRT network meta-analysis results (reference: unimproved water source)

Intervention	Relative risk (95% UI)
Boil/filter water treatment	0.57 (0.37–0.87)
Chlorine/solar water treatment	0.77 (0.51–1.15)
Improved water source	0.84 (0.54–1.28)
Piped water source	0.67 (0.44–1.03)
High-quality piped water source	0.29 (0.12–0.70)

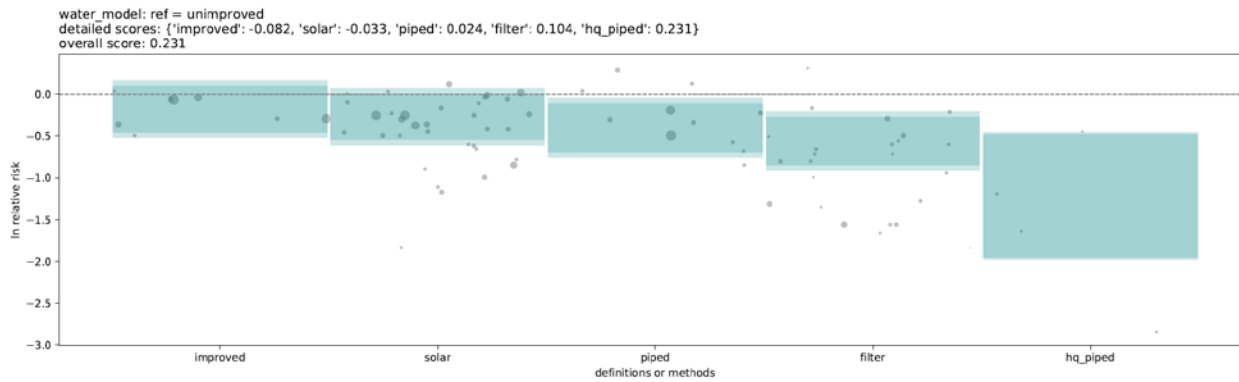
Table 5: Relative risks for each exposure category (reference: high-quality piped water)

Exposure category	Relative risk (95% UI)
Unimproved, no HWT	6.93 (2.20–17.54)
Unimproved, chlorine/solar	5.41 (1.59–14.02)
Unimproved, boil/filter	3.87 (1.42–8.66)
Improved water except piped, no HWT	5.97 (1.77–16.16)
Improved water except piped, chlorine/solar	4.67 (1.25–13.20)
Improved water except piped, boil/filter	3.33 (1.13–8.20)
Basic piped water, no HWT	4.73 (1.33–12.59)
Basic piped water, chlorine/solar	3.69 (1.01–10.14)
Basic piped water, boil/filter	2.64 (0.86–6.34)
High-quality piped water	1 (reference)

Figure 2 shows the results of the MR-BRT analysis in graphical form, along with the associated “risk-outcome scores” for each category, which is a measure of how good the evidence is for that particular relative risk estimate. Prior to generating an risk-outcome score, we conducted an additional post-analysis step to detect and flag publication bias in the input data. This approach is based on the classic Egger’s regression strategy, which is applied to the residuals in our model. In the current implementation, we do not correct for publication bias, but flag the risk–outcome pairs where the risk for publication bias is significant.

We did not detect publication bias based on the association between observation residuals and their standard errors (p-value = 0.195, Egger mean = –0.101, Egger SD = 0.118). The overall risk-outcome score for this risk factor is 0.231, which is the maximum of the individual category scores.

Figure 2: Risk-outcome scores

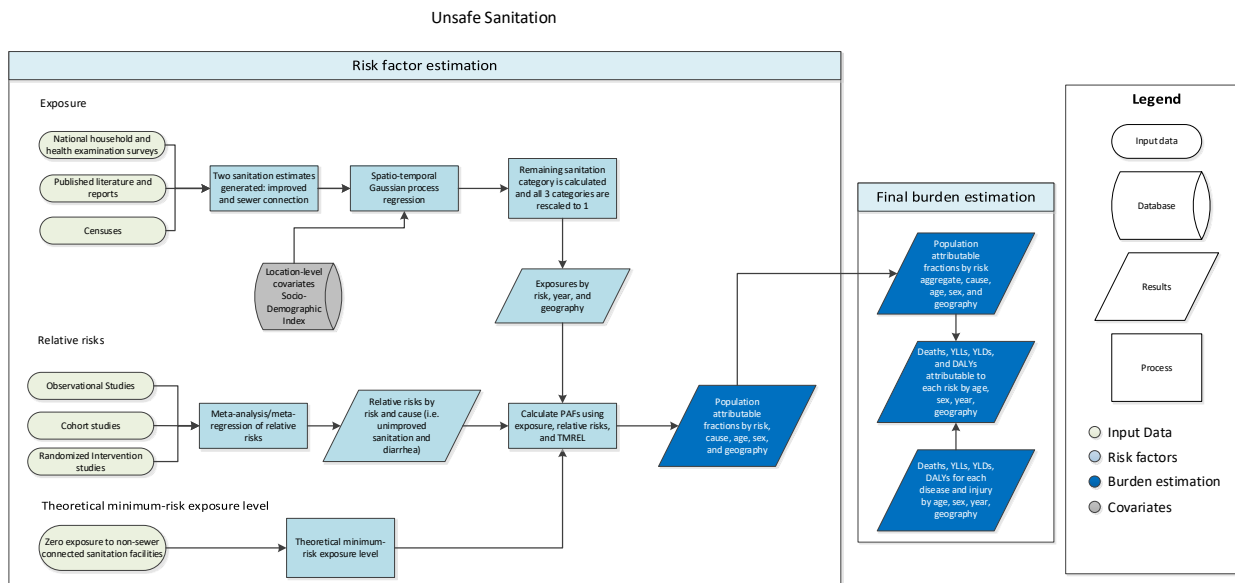


Unsafe Water References

1. WHO/UNICEF Joint Monitoring Programme: Drinking water. <https://washdata.org/monitoring/drinking-water> (accessed Oct 31, 2019).
2. Bain R, Cronk R, Wright J, Yang H, Slaymaker T, Bartram J. Fecal Contamination of Drinking-Water in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *PLOS Medicine* 2014; **11**: e1001644.
3. Wolf J, Pruss-Ustun A, Cumming O, *et al.* Assessing the impact of drinking water and sanitation on diarrhoeal disease in low- and middle-income settings: systematic review and meta-regression. *Tropical Medicine and International Health* 2014; **19**: 928–42.
4. Wolf J, Hunter PR, Freeman MC, *et al.* Impact of drinking water, sanitation and handwashing with soap on childhood diarrhoeal disease: updated meta-analysis and meta-regression. *Tropical Medicine and International Health* 2018; **23**: 508–25.

Unsafe sanitation

Flowchart



Input data and methodological summary

Exposure

Case definition

Exposure to unsafe sanitation is defined based on the primary toilet type used by households. For the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021, we modelled three different categories of sanitation: unimproved, improved, and facilities with a sewer connection or septic tank. These categories were defined according to the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (JMP).¹ Examples of “improved” sanitation facilities include ventilated improved pit latrines, composting toilets, and pit latrines with slabs. Examples of “unimproved” facilities include open pit latrines, open defecation, and toilets that flush into creeks or open fields. Sewer connection toilets include flush toilets or any toilet with connection to the sewer or septic tank.

Input data

The search for usable data sources was conducted using the Global Health Data Exchange (GHDx) database. Input data came primarily from nationally representative surveys, such as the Demographic and Health Survey (DHS), the Multiple Indicator Cluster Surveys (MICS), the World Health Survey (WHS), and the DHS AIDS Indicator Survey (AIS). Surveys that reported results at the household level were converted to the individual level using household size data, to ensure that our models estimated the proportion of individuals, rather than households, exposed to a given indicator. Surveys and censuses were then tabulated to two sanitation categories, sewer connection and improved sanitation, for each location. Table 1 provides a summary of the input data used.

Table 1: Exposure input data

Input data	Exposure
Source count (total)	1153
Number of countries with data	159

Modelling

For GBD 2021, sanitation was modelled in an ordinal framework. Two distinct indicators were estimated: (1) the proportion of the total population using sewer connection or septic tank facilities, and (2) the proportion of individuals using improved sanitation within the population not connected to a sewer or septic tank. This ordinal framework allows us to estimate the category with the most data (sewer connection/septic tank prevalence) and leverage that estimate to anchor the estimates for the improved and unimproved sanitation categories. The results of the improved-proportion model are multiplied by one minus the sewer connection/septic tank prevalence to calculate improved sanitation prevalence. The sum of improved and sewer connection/septic tank prevalence are subtracted from 1 to yield unimproved sanitation prevalence.

$$\begin{aligned} \text{Sewer} &= \frac{\# \text{ persons with sewer or septic connection}}{\# \text{ persons with nonmissing response}} \\ \text{Improved} &= \left(\frac{\# \text{ persons using improved facilities}}{\# \text{ persons without sewer or septic connection}} \right) * (1 - \text{Sewer}) \\ \text{Unimproved} &= 1 - (\text{Sewer} + \text{Improved}) \end{aligned}$$

The two indicators were each modelled using a three-step modelling scheme of mixed effect linear regression followed by spatiotemporal Gaussian process regression (ST-GPR), which produced full time-series estimates for each GBD 2021 location. Socio-demographic Index (SDI), a composite metric combining education per capita, income per capita, and fertility, was set as a fixed effect in the linear regression since it proved to be a significant predictor. Random effects were set at GBD 2021 region and super-region levels to fit the models but were not used in the predictions. The same linear regression equation was used for both ST-GPR models (see below).

$$\text{logit}(\text{data}) \sim \text{sdi} + (1|\text{level}_1) + (1|\text{level}_2)$$

SDI = Socio-demographic Index

(1|level_1) = super-region-level random effects

(2|level_2) = region-level random effects

The process of vetting and validating models was accomplished primarily through an examination of ST-GPR scatterplots by GBD 2021 location from 1990 to 2021. Any poorly fitting datapoints were re-inspected for error at the level of extraction and survey implementation. If errors in data extraction were found, the study in question was re-extracted. In addition to SDI, a number of different potential fixed effects were considered, including lag-distributed income and urbanicity, but SDI proved to be the strongest predictor of unsafe sanitation in terms of magnitude of the coefficient. Uncertainty in the estimates was initially constructed based on standard deviation around each survey mean, then propagated through ST-GPR modelling by incorporating the variance of each datapoint in the Gaussian process regression step. A datapoint with high variance, for example, would contribute relatively less influence to the model than a datapoint with lower variance.

Once models are vetted, full time-series outputs from ST-GPR modelling are then rescaled using the above equations to form three mutually exclusive categories that sum up to 1 for each location-year combination. Table 2 provides the final result of this rescaling.

Table 2: Exposure categories and definitions

Category	Definition
Unimproved sanitation	Proportion of individuals that use unimproved sanitation facilities.
Improved sanitation	Proportion of individuals that use improved sanitation facilities, excluding sewer connection or septic tank.
Sanitation facilities with sewer connection or septic tank	Proportion of individuals that use toilet facilities with sewer connection or septic tank.

Theoretical minimum-risk exposure level

The theoretical minimum-risk exposure level for unsafe sanitation was defined as having access to a sanitation facility with sewer connection or septic tank.

Relative risks

For GBD 2021, unsafe sanitation was paired with one outcome, diarrhoeal diseases. Two meta-analyses, by Wolf et al 2014 and Wolf et al 2018, along with a literature review that used the same search terms as Wolf et al 2014, were used to identify relative risk studies.^{2,3} Table 3 provides a summary of the relative risk data used.

Table 3: Relative risk input data

Input data	Relative risk
Source count (total)	16
Number of countries with data	13

In GBD 2021, relative risk values were calculated using a network meta-analysis approach with a tool called meta-egression—Bayesian, regularised, trimmed (MR-BRT). One study-level covariate – whether or not the study was generalisable to the general population – was included in the network meta-analysis. Several other covariates (whether exposure was captured at the individual level or population level; whether conformity with the study interventions was self-reported or confirmed by the researchers; whether or not the study was randomised; whether or not the study adjusted for all major known confounders; and what the study’s follow-up percentage was) were considered but ultimately were not statistically significant and so were not used in analysis. No priors were used. We calculated the risk of developing diarrhoea for those using improved sanitation facilities and sewer or septic facilities, relative to the reference category of those using unimproved facilities. Those model results were then rescaled so that the relative risk for using sewer or septic facilities was the reference category, in order to match with our exposure definition. Table 4 shows the results of the MR-BRT analyses. Table 5 shows the relative risks that were ultimately used for modelling.

Table 4: MR-BRT network meta-analysis results (reference: unimproved sanitation)

Intervention	Relative risk (95% CI)
Improved sanitation	0.795 (0.739–0.856)
Sanitation facilities with sewer connection or septic tank	0.310 (0.274–0.352)

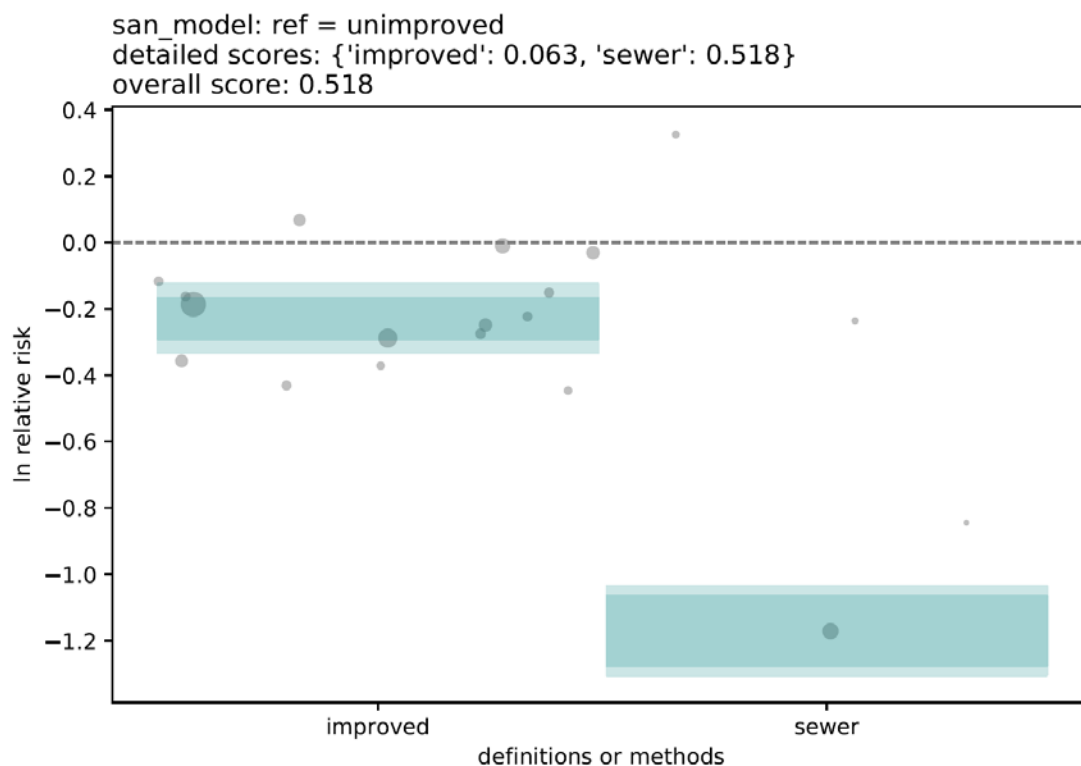
Table 5: Relative risks for each exposure category (reference: sewer or septic facilities)

Exposure category	Relative risk (95% CI)
Unimproved sanitation	3.22 (2.74–3.76)
Improved sanitation	2.57 (2.08–3.12)
Sanitation facilities with sewer connection or septic tank	1 (reference)

Figure 1 shows the results of the MR-BRT analysis in graphical form, along with the associated “risk-outcome scores” for each category, which is a measure of how good the evidence is for that particular relative risk estimate. Prior to generating an risk-outcome score, we conducted an additional post-analysis step to detect and flag publication bias in the input data. This approach is based on the classic Egger’s regression strategy, which is applied to the residuals in our model. In the current implementation, we do not correct for publication bias, but flag the risk–outcome pairs where the risk for publication bias is significant.

We did not detect publication bias based on the association between observation residuals and their standard errors (p-value = 0.337, Egger mean = -0.102, Egger SD = 0.243). The overall risk-outcome score for unsafe sanitation is 0.518, which is the maximum of the individual category scores.

Figure 1: Risk-outcome scores



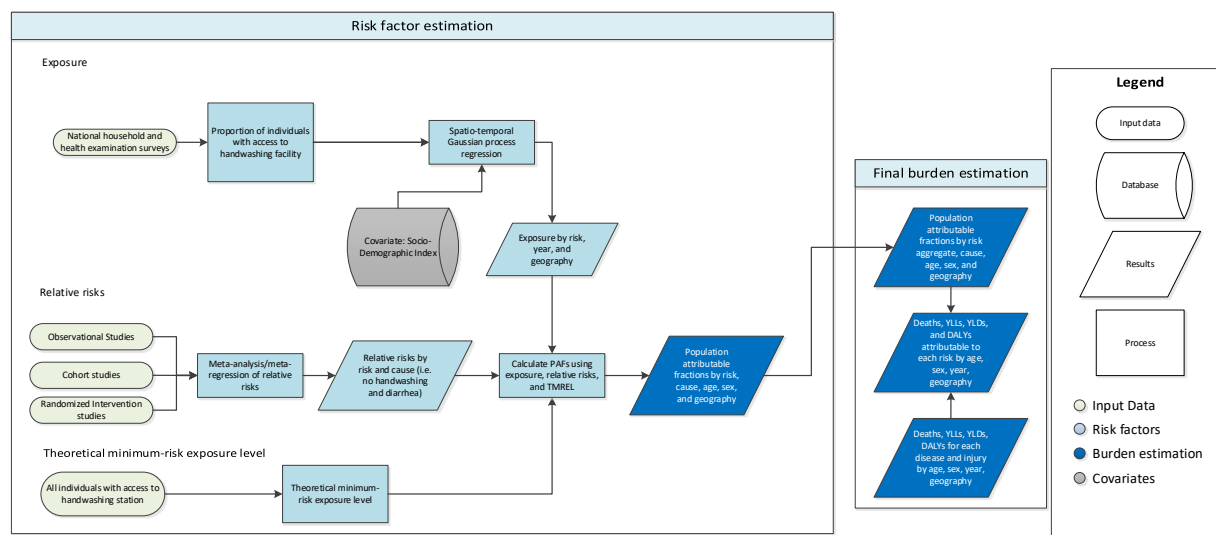
Unsafe Sanitation References

1. WHO/UNICEF Joint Monitoring Programme: Sanitation. <https://washdata.org/monitoring/sanitation> (accessed Oct 31, 2019).
2. Wolf J, Pruss-Ustun A, Cumming O, *et al.* Assessing the impact of drinking water and sanitation on diarrhoeal disease in low- and middle-income settings: systematic review and meta-regression. *Tropical Medicine and International Health* 2014; **19**: 928–42.
3. Wolf J, Hunter PR, Freeman MC, *et al.* Impact of drinking water, sanitation and handwashing with soap on childhood diarrhoeal disease: updated meta-analysis and meta-regression. *Tropical Medicine and International Health* 2018; **23**: 508–25.

No access to handwashing facility

Flowchart

Unsafe Handwashing



Input data and methodological summary

Exposure

Case definition

This risk is defined as the proportion of the population without access to a handwashing facility with soap (bar, liquid, or powder/detergent), water, and wash station (either permanent or mobile).¹ If any of these is missing, then the individual is counted as not having access.

Input data

Input data came primarily from geographically representative household surveys, including the Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS), and Performance Monitoring and Accountability 2020 (PMA2020) surveys. For the GBD 2021 study, a large number of new data sources were added, nearly doubling the total number of sources from 98 in GBD 2019 to 177 in GBD 2021. We also re-extracted all sources previously used to ensure that we were capturing individual-level exposure, in an effort to align with the WHO/UNICEF Joint Monitoring Programme's methodology.¹ As a result of this effort, we excluded several studies used in previous GBD rounds that included ash, sand, or soil in their definition of "soap." Table 1 provides a summary of the exposure input data.

Table 1: Exposure input data

Input data	Exposure
Source count (total)	177
Number of countries with data	89

Modelling strategy

We modelled exposure to this risk using a three-step modelling scheme of mixed effect linear regression followed by spatiotemporal Gaussian process regression (ST-GPR), which outputs full time-series estimates for

each GBD 2021 location. Two covariates were used as fixed effects in the linear regression: Socio-demographic Index (SDI), which is a composite measure of development that includes income per capita, education, and fertility, and proportion of individuals with access to piped water (see below for model equation). Random effects were set at GBD 2021 region and super-region levels to fit the model but were not used in the predictions.

$$\text{logit}(\text{data}) \sim \text{sdi} + \text{piped water access} + (1|\text{level}_1) + (1|\text{level}_2)$$

SDI = Socio-demographic Index
Piped water access = proportion of individuals with access to piped water
(1|level_1) = super-region-level random effects
(2|level_2) = region-level random effects

The process of vetting and validating models was accomplished primarily through an examination of ST-GPR scatterplots by GBD 2021 location from 1990 to 2021. Any poorly fitting datapoints were re-inspected for error at the level of extraction and survey implementation. If errors in data extraction were found, the study in question was re-extracted. In addition to SDI, a number of different potential fixed effects were considered, including lag-distributed income and urbanicity. However, SDI proved to be the strongest predictor.

Theoretical minimum-risk exposure level

The theoretical minimum-risk exposure level for unsafe hygiene is defined as having access to a handwashing facility with soap (bar, liquid, or powder/detergent), water, and wash station (either permanent or mobile).

Relative risks

Input data

Input data included in the GBD 2021 hygiene relative risk analysis are as follows:

Table 2: Relative risk input data

Input data	Relative risk
Source count (total)	41
Number of countries with data	22

For GBD 2021, unsafe hygiene was paired with two outcomes: diarrhoeal diseases and lower respiratory infections (LRI). A meta-analysis by Cairncross and colleagues 2010² provided relative risk values describing the relationship between lack of facility access and diarrhoeal diseases. A meta-analysis by Rabie & Curtis 2006³ provided relative risk evidence for the relationship between lack of facility access and LRI, including the years 1997-2004.

Modelling strategy

In GBD 2021, relative risk values were calculated using a tool called meta-regression—Bayesian, regularised, trimmed (MR-BRT). For the both the diarrhoea model and the LRI model, two study-level covariates were included – whether or not the study was randomised and whether or not the percentage of the study

population lost to follow-up was greater than 15%. No priors were used. Table 3 shows the results of the relative risk analyses.

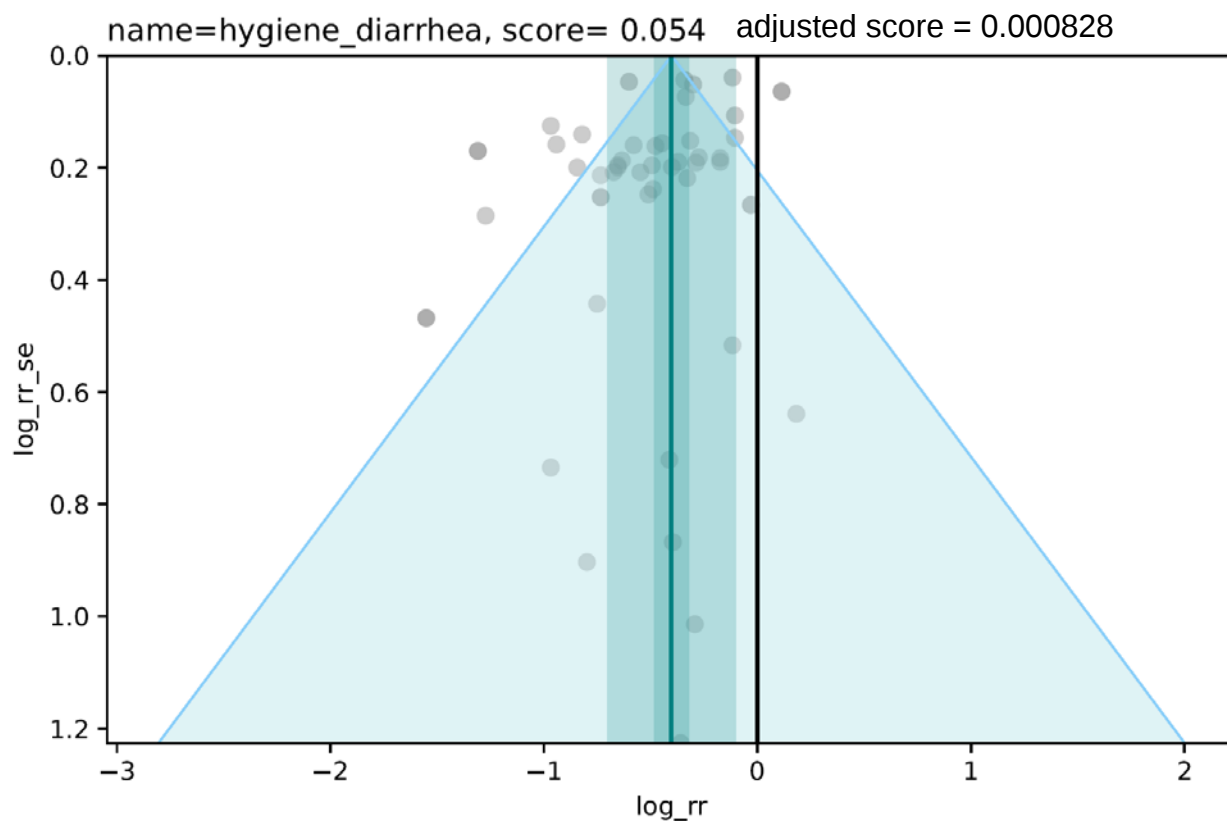
Table 3: Relative risks (reference: access to handwashing facility)

Outcome	Relative risk (95% CI)
Diarrhoeal diseases	1.52 (1.06–2.12)
Lower respiratory infections	1.43 (0.82–2.30)

Figures 2 and 3 show the funnel plots for each MR-BRT analysis, along with the associated “risk-outcome scores,” which measure how good the evidence is for that particular relative risk estimate. Prior to generating a risk-outcome score, we conducted an additional post-analysis step to detect and flag publication bias in the input data. This approach is based on the classic Egger’s regression strategy, which is applied to the residuals in our model. In the current implementation, we do not correct for publication bias, but flag the risk–outcome pairs where the risk for publication bias is significant.

For hygiene and diarrhoea, we detected publication bias based on the association between observation residuals and their standard errors (p-value = 0.0265, Egger mean = -0.302, Egger SD = 0.156). The risk-outcome score was 0.000828.

Figure 2: Hygiene–diarrhoea funnel plot and risk-outcome score

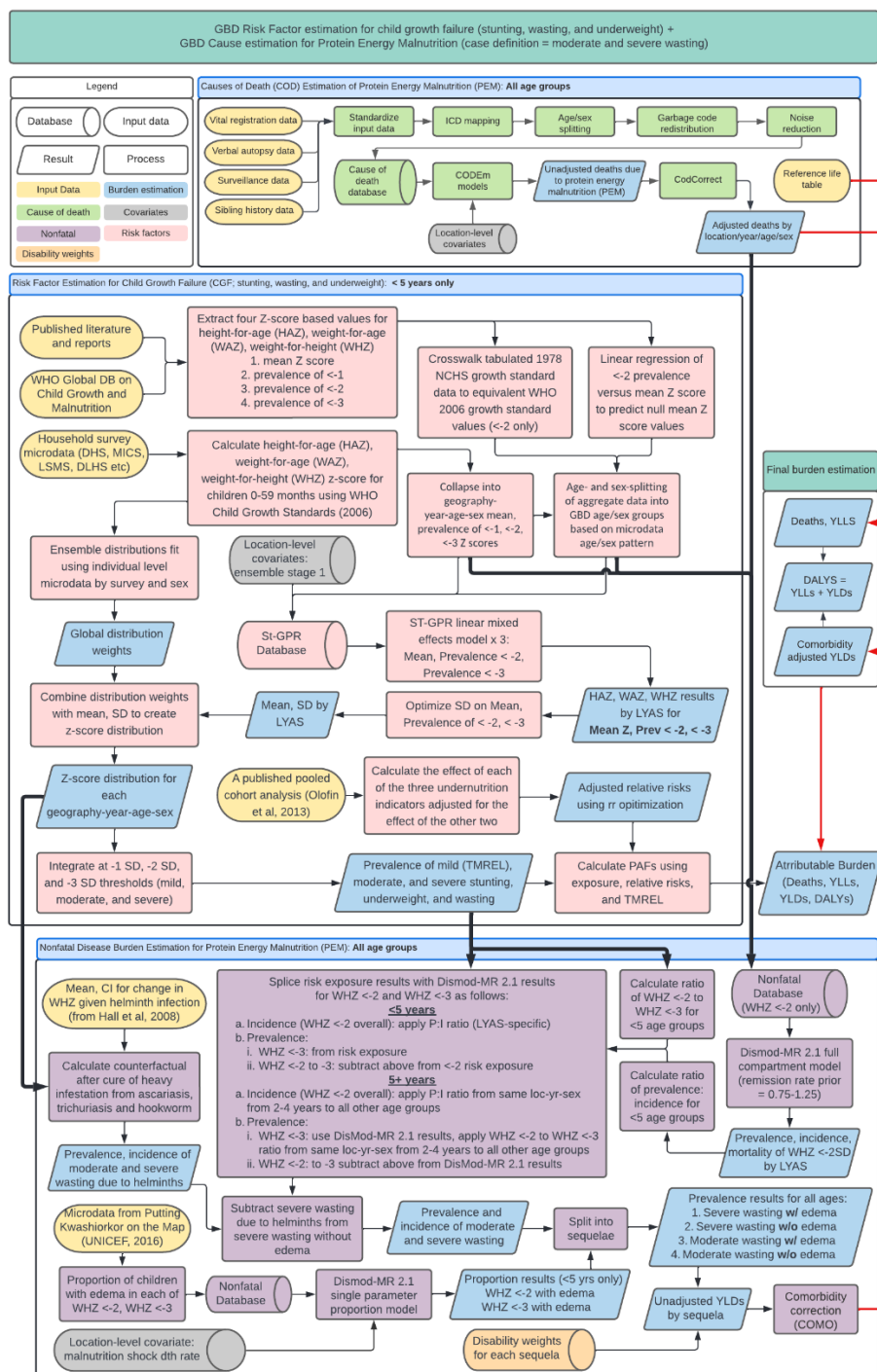


No access to handwashing facility References

1. WHO/UNICEF. JMP Methodology: 2017 update and SDG baselines. 2018.
2. Cairncross S, Hunt C, Boisson S, *et al.* Water, sanitation and hygiene for the prevention of diarrhoea. *International Journal of Epidemiology* 2010; **39**: i193–205.
3. Rabie T, Curtis V. Handwashing and risk of respiratory infections: a quantitative systematic review. *Tropical Medicine and International Health* 2006; **11**: 258–67.
4. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Jones MA, Thorning S, Beller EM, Clark J, Hoffmann TC, Glasziou PP, Conly JM. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database of Systematic Reviews* 2020, Issue 11. Art. No.: CD006207. DOI: 10.1002/14651858.CD006207.pub5. Accessed 13 April 2022.

Child growth failure

Combined Flowchart for Child Growth Failure and Protein Energy Malnutrition



Input data and methodological summary

Exposure

Case definition

Child growth failure (CGF) is estimated using three indicators (stunting, wasting, and underweight), all of which are based on categorical definitions using the WHO 2006 growth standards for children 0-59 months. Definitions are based on Z scores from the growth standards, which were derived from an international reference population. Mild (<-1 to -2 Z score), moderate (<-2 to -3 Z score), and severe (<-3 Z score) categorical prevalences were estimated for each of the three indicators.

Input data

There are three main inputs for the GBD child growth failure models: microdata from population surveys, tabulated data from reports and published literature, and the WHO Global Database on Child Growth and Malnutrition.¹⁵ The primary data additions in GBD 2021 for child growth failure were from population surveys that include anthropometry. Population surveys include a variety of multi-country and country-specific survey series such as Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS), Living Standards Measurement Surveys (LSMS), and the China Health and Nutrition Survey (CHNS), as well as other one-time country-specific surveys such as the Indonesia Family Life Survey and the Brazil National Demographic and Health Survey of Children and Women. These microdata contain information about each individual child's age (from which age in weeks and age in months are calculated), as well as height and/or weight. From that information, a height-for-age z-score (HAZ), weight-for-age z-score (WAZ), and weight-for-height z-score (WHZ) are calculated using the WHO 2006 Child Growth Standards and the LMS method.¹⁶ Data that did not meet the following three criteria were dropped: 1) non-sex-specific data, 2) data with invalid Z-scores (HAZ, WAZ, WHZ, or BMI above 6 SD or below -6 SD), and 3) data with impossible values (negative height, weight, or age).

All available data from the WHO Global Database on Child Growth and Malnutrition were extracted in GBD 2016 – much of which are from published studies. Exclusions included examination date prior to 1985, non-population-representative studies, and those based on self-report. A systematic literature review was last completed in GBD 2010. We looked for four metrics from all sources with tabulated data: mean Z score, prevalence <-1 Z score, prevalence <-2 Z score, and prevalence <-3 Z score. All data for each metric were extracted for each of stunting (height-for-age Z score; HAZ), wasting (weight-for-height Z score; WHZ), and underweight (weight-for-age Z score; WAZ).

Table 1: Input data counts for Child wasting exposure models

Input data	Exposure
Source count (total)	1908
Number of countries with data	159

Table 2: Input data counts for Child underweight exposure models

Input data	Exposure
Source count (total)	1897
Number of countries with data	160

Table 3: Input data counts for Child stunting exposure models

Input data	Exposure
Source count (total)	1897
Number of countries with data	160

Data processing

To maximise internal consistency and comprehensiveness of the modelling dataset, we performed three data transformations. First, any data that were reported using the National Center for Health Statistics (NCHS) 1978 growth standards were crosswalked to corresponding values on the WHO 2006 Growth Standards curves based on a study that evaluated growth standard concordance.¹⁷ Crosswalks from 1978 to 2006 growth standards were performed using OLS linear regression only on <-2 (ie, moderate) prevalence data, as that is where the concordance was most consistent. Second, for any study that lacked a measure of mean Z score for any of stunting, wasting, or underweight, we predicted a mean value for that study based on an ordinary-least-squares regression of mean Z score versus <-2 prevalence for that metric from all sources where both were available. Third, for any data that were presented as both sexes combined or for 0-59 months combined, we used the age and sex pattern from all data sources that included that detail to split into corresponding and age- and sex-specific data.

Modelling strategy

Exposure estimation

The following four-step modelling process was applied in parallel to each of stunting, wasting, and underweight.

First, all microdata were fit using an ensemble modelling. A series of 10 individual distributions (normal, log-normal, log-logistic, exponential, gamma, mirror gamma, inverse gamma, gumbel, mirror gumbel, and Weibull) were fit simultaneously to each microdata source in the dataset. All component distributions that were used to derive weights were parameterised using “method of moments,” meaning that each corresponding probability density function (PDF) could be described as a function of the mean and variance of the quantity of interest. From these distribution families, an ensemble distribution was parameterised using an updated methodology for GBD 2021, which has 2 main advantages over GBD 2019 methodology. Those advantages are described below.

The new ensemble modeling strategy is considered an advancement, in part, because the models were specifically fit on the portions of the distributions that constitute mild, moderate, and severe CGF. While

previous methods aimed to minimise predictive error across the entire distribution, the new GBD 2021 method aimed to minimise absolute prediction error in highly relevant areas of the curve.

The second advancement is that the optimisation process considers the fit across all microdata sources simultaneously. Therefore, the algorithm targets the set of ensemble weights that minimises the predictive error across all microdata sources collectively, as opposed to finding one set of weights for each individual microdata source and averaging those sets of weights together.

After ensemble distributions have been parameterised, the second modeling step begins. Models were developed for mean Z scores and prevalence of moderate and severe growth failure. Individual-level microdata were collapsed to calculate three metrics: mean z-score, moderate prevalence, and severe prevalence. These data were combined with those derived from literature, GHDx review, and the WHO Global Database on Child Growth and Malnutrition. Each of the three metrics was then modelled using spatiotemporal Gaussian process regression (ST-GPR), a common modelling framework used across GBD, generating estimates for each age group, sex, year, and location. Location-level covariates used in all models included Socio-demographic Index (SDI) and logit-transformed proportion of households with improved sanitation.

Third, we combined estimates of mean, prevalence (moderate and severe) with ensemble weights in an optimisation framework in order to derive the variance that would best correspond to the predicted mean and prevalence. This variance was then paired with the mean and, using the method of moments equation for each of the component distributions of the ensemble, PDF of the distribution of Z-scores were calculated for each location, year, age group, and sex.

Fourth, PDFs were integrated to determine the prevalence between -1 and -2 Z scores (mild), between -2 and -3 Z scores (moderate), and below -3 Z scores (severe). These were categorical exposures used for subsequent attributable risk analysis.

Theoretical minimum-risk exposure level

Theoretical minimum risk exposure level (TMREL) for underweight, stunting, and wasting was assigned to be greater than or equal to -1 SD of the WHO 2006 standard weight-for-age, height-for-age, and weight-for-height curves, respectively. This has not changed since GBD 2010.

Relative risks

The final list of outcomes paired with child growth failure risks included mortality and morbidity for lower respiratory infections (LRI), diarrhoea, malaria, measles, and protein-energy malnutrition (PEM), as shown in Table 6. These were derived from a Burden of Proof analysis that incorporated both a pooled analysis of ten prospective cohort studies by Olofin and colleagues⁵ as well as relative risk estimates from Knowledge Integration (KI) studies (Table 5). For the KI studies, aggregated relative risks of disease or cause-specific mortality were calculated for 1-unit z-score bins for stunting, wasting, and underweight (e.g., relative risk of diarrhea-attributable death in children 1 to 2 years of age and with a HAZ score between -4 and -3). The burden of proof analysis uses all available relative risks with corresponding uncertainty to create continuous relative risk curves for each outcome/risk pair. These continuous risk curves are then combined with the global exposure curves for HAZ, WAZ, and WHZ, to calculate exposure-weighted relative risks for severe, moderate, and mild stunting, wasting, and underweight with uncertainty.

Table 4: Input data counts for Child growth failure relative risk models

Input data	Risk
Source count (total)	53

There is a high degree of correlation between stunting, wasting, and underweight. Failing to account for their covariance and assuming independence would overestimate the total burden significantly and misrepresent the attributable burden of individual CGF indicators. Inability to address these correlations is the main reason that GBD 2010 only included childhood underweight.

In order to account for the high degree of correlation between CGF indicators, GBD uses a constrained optimisation method to adjust the observed univariate RRs that come out of the Burden of Proof analysis. First we created a joint distribution of stunting, underweight, and wasting from a population of children. Second, we generated one thousand RR draws for each univariate indicator and severity based from the Burden of Proof analysis. Third, we altered these univariate RRs for the four causes (diarrhoea, LRI, malaria, and measles) and the two outcomes (mortality and morbidity) based upon interactions among the CGF indicators. An interaction occurs when the effect of one CGF indicator variable (eg, stunting) has a different effect on the outcome depending on the value of another CGF indicator variable (eg, underweight). Interaction terms alter the risk of the outcome among children with more than one indicator of CGF. These interaction terms were extracted from a pooled cohort analysis of all-cause mortality published by McDonald et al.¹⁸ Lastly, we optimised the adjusted relative risks by minimising the error between the observed RRs (generated from Olofin et al.) and the altered RRs derived from the joint distribution and accounting for the interaction terms while ensuring that no alteration resulted in a previously identified increase in relative risk becoming protective.

For GBD 2021, we made several changes to improve the four main steps of RR adjustment. From GBD 2013 to GBD 2019, a simulated joint distribution of stunting, underweight, and wasting measures was created from the Olofin et al. meta-analysis. Sources in this meta-analysis were cross-sectional Demographic and Health Surveys (DHS). In GBD 2021, we created age-specific joint distributions of stunting, underweight, and wasting measures from 15 longitudinal studies (from 26 locations) in the Bill and Melinda Gates Foundation's Knowledge Integration (Ki) database⁶. (Study details are provided in Table 5). The RR adjustment method was strengthened in GBD 2021 by constraining optimisation in two ways. Optimisation was only permitted to alter the RR for an indicator/severity in draws where the observed RR was greater than 1, and constraints were placed on the error that penalise larger alterations to the RR. These changes enabled the estimation and utilisation of age-specific adjusted RRs for GBD 2021 burden estimation. The largest changes for GBD 2021 was conducting Burden of Proof Analyses for each cause/outcome/risk triplet using both data from Olofin et al as well as KI data. These changes result in identifying large differences in the relationship between CGF and mortality versus morbidity as well as identifying some impact of CGF on malaria.

Table 5: Bill and Melinda Gates Foundation Knowledge Integration (KI) database study details

Study name	Country	Sample Size	Years conducted
Zimbabwe Vitamin A for Mothers and Babies Trial	ZWE	14,110	1997-2001
CMC Vellore Birth Cohort Study	IND	373	2002-2006
International Lipid-Based Nutrient Supplements Project	MWI	1,206	2011-2014
Malnutrition and Enteric Disease Study	BGD	265	2009-2017
Malnutrition and Enteric Disease Study	IND	251	2009-2017
Malnutrition and Enteric Disease Study	NEP	240	2009-2017
Malnutrition and Enteric Disease Study	PER	303	2009-2017
Malnutrition and Enteric Disease Study	BRA	233	2009-2017
Malnutrition and Enteric Disease Study	ZAF	314	2009-2017
Malnutrition and Enteric Disease Study	TZA	262	2009-2017
Medical Research Council Keneba	GMB	2,867	-
Performance of Rotavirus and Oral Polio Vaccines In Developing Countries	BGD	700	2011-2014
Community-based Intervention Trial to Compare the Impact of Preventive and Therapeutic Zinc Supplementation Programs Among Young Children in Burkina Faso	BFA	7,634	2010-2012
WASH Benefits Bangladesh	BGD	4,423	2011-2014
WASH Benefits Kenya	KEN	5,649	2012-2016
Promotion of Breastfeeding Intervention Trial	BLR	16,897	1996-1998
Childhood Malnutrition and Infection Network	BGD	477	1993-1996
Childhood Malnutrition and Infection Network	BRA	119	1989-1998
Childhood Malnutrition and Infection Network	GNB	350	1987-1990
Childhood Malnutrition and Infection Network	GNB	885	1996-1997
Childhood Malnutrition and Infection Network	PER	210	1989-1991
Childhood Malnutrition and Infection Network	PER	224	1995-1998
Delhi Infant Vitamin D Study	IND	2,100	2007-2010
Characterization of Respiratory pathogens endemic to Pakistan in pregnant women and newborns in urban settings	PAK	380	2012-2013
Impact of Zinc Supplementation in Low Birth Weight Infants on Severe Morbidity, Mortality and Zinc Status: A Randomized Controlled Trial	IND	2,052	2005-2007
A Trial of Zinc and Micronutrients in Tanzanian Children	TZA	2,400	2007-2012

Table 6: Age-Specific Adjusted RRs for each risk-outcome pair for child growth failure

1 to 5 months		Incidence			Mortality		
Cause		<-3	-3,-2	-2,-1	<-3	-3,-2	-2,-1
Diarrhoea	HAZ	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.1 (0.9, 1.5)	3.6 (2.1, 4.4)	2.1 (1.6, 2.6)	1.4 (1.2, 1.6)
	WAZ	1.6 (0.9, 2.7)	1.6 (0.9, 2.6)	1.5 (0.9, 2.4)	6.7 (4.4, 9.3)	3.4 (2.2, 4.7)	1.8 (1.3, 2.2)
	WHZ	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	40.8 (0.8, 224.7)	12.8 (0.8, 51.5)	4.1 (0.9, 10.6)
6 to 11 months		Incidence			Mortality		
Cause		<-3	-3,-2	-2,-1	<-3	-3,-2	-2,-1
Diarrhoea	HAZ	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.1 (0.9, 1.5)	3.1 (2.2, 3.9)	1.9 (1.5, 2.4)	1.3 (1.2, 1.6)
	WAZ	1.6 (0.9, 2.7)	1.6 (0.9, 2.6)	1.5 (0.9, 2.4)	5.9 (3.7, 8.9)	3.1 (2.0, 4.5)	1.7 (1.3, 2.2)
	WHZ	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	40.7 (0.8, 224.7)	12.7 (0.8, 51.5)	4.1 (0.9, 10.6)

12 to 23 months		Incidence			Mortality		
Cause		<-3	-3,-2	-2,-1	<-3	-3,-2	-2,-1
Diarrhea	HAZ	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.1 (0.9, 1.5)	2.7 (2.2, 3.4)	1.7 (1.4, 2.2)	1.3 (1.1, 1.5)
	WAZ	1.6 (0.9, 2.7)	1.6 (0.9, 2.6)	1.5 (0.9, 2.4)	5.4 (3.7, 8.4)	2.9 (2.0, 4.4)	1.6 (1.3, 2.1)
	WHZ	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	40.7 (0.8, 225.5)	12.7 (0.8, 51.7)	4.0 (0.9, 10.6)

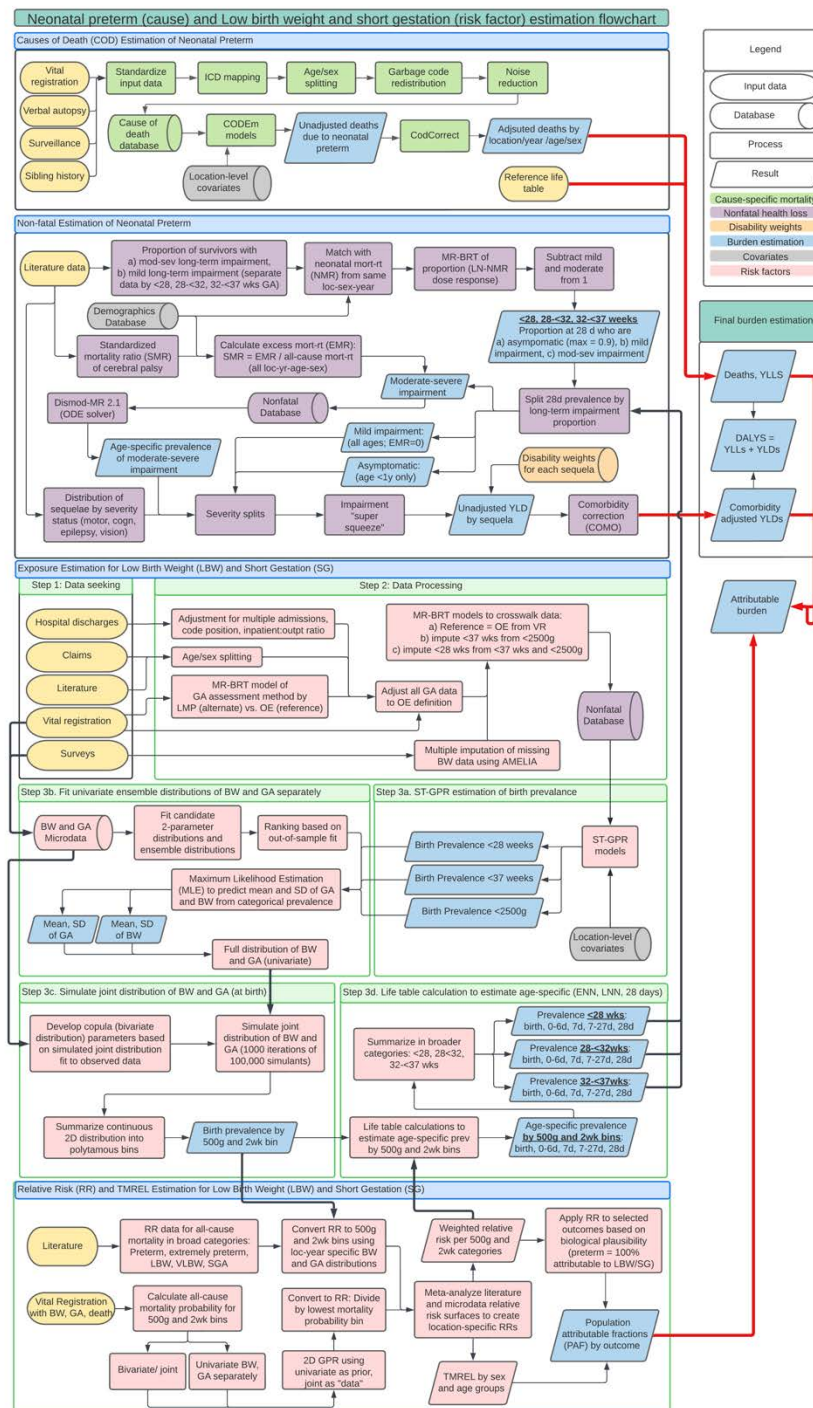
2 to 4 years		Incidence			Mortality		
Cause		<-3	-3,-2	-2,-1	<-3	-3,-2	-2,-1
Diarrhoea	HAZ	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.1 (0.9, 1.5)	2.8 (2.1, 3.4)	1.8 (1.5, 2.2)	1.3 (1.2, 1.5)
	WAZ	1.6 (0.9, 2.7)	1.6 (0.9, 2.6)	1.5 (0.9, 2.4)	5.6 (4.0, 8.3)	2.9 (2.1, 4.3)	1.6 (1.3, 2.1)
	WHZ	1.3 (0.8, 1.8)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	41.3 (0.8, 229.9)	12.8 (0.8, 52.4)	4.0 (0.9, 10.7)

Child Growth Failure References

6 Jumbe NL, Murray JC, Kern S. Data Sharing and Inductive Learning – Toward Healthy Birth, Growth, and Development. N Engl J Med. 2016 Jun 23;374(25):2415-7. doi: 10.1056/NEJMp1605441. Epub 2016 May 11. PMID: 27168111.

Low birthweight and short gestation

Flowchart



Input data and methodological summary

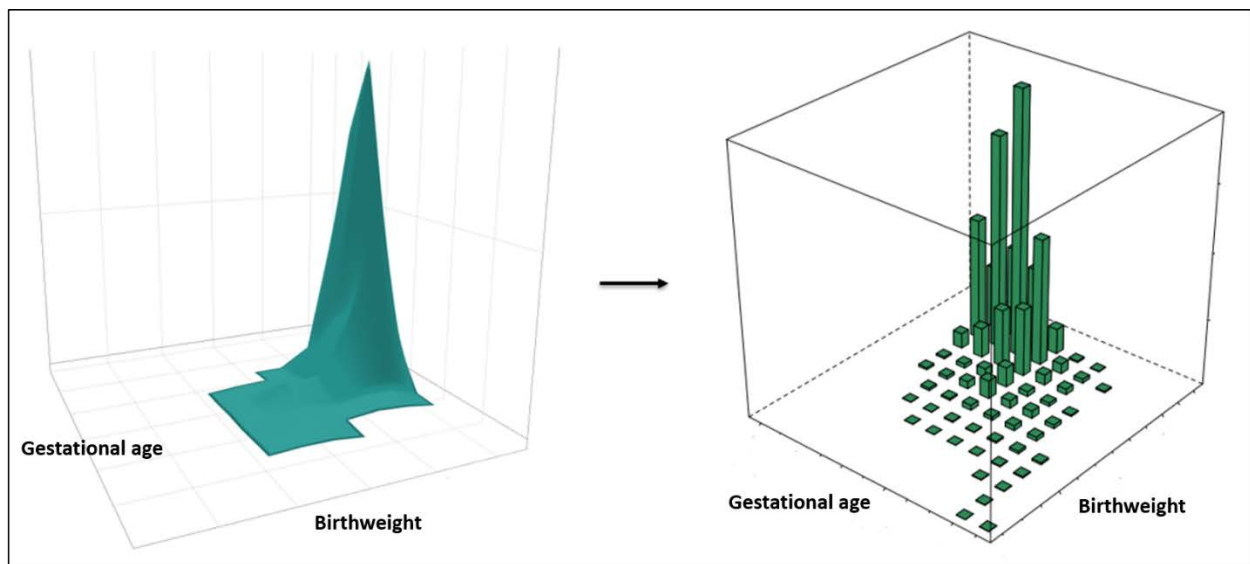
Short gestational age and low birthweight are highly correlated risk factors associated with poor child health outcomes. The “low birthweight and short gestation” (LBWSG) risk factor quantifies the burden of disease attributable to increased risk of death and disability due to 1) less than ideal birthweight (“low birthweight”) and 2) shorter than ideal length of gestation (“short gestation”).

Within GBD, attributable burden is generally estimated separately for each individual risk factor, but the combined burden attributable to multiple risk factors is of general interest. In GBD, attributable burden due to multiple risk factors is typically estimated through a “mediation analysis” that is applied after independent estimation of each risk factor’s exposure, relative risk, theoretical minimum risk exposure level (TMREL), and population attributable fraction (PAF). In the mediation analysis, a “mediation factor” adjusts the PAF of each risk factor by the amount of attributable burden mediated through the other GBD risk factors. While mediation may be common, direct quantification of the joint exposure, relative risk, and PAF of the combined risk factors is conceptually more straightforward.

In GBD 2016, LBWSG became the first (and, as of GBD 2021, only) group of GBD risk factors in which combined attributable burden is quantified by direct estimation of the joint exposure, relative risk, TMREL, and PAF of multiple risk factors. After first directly estimating the joint exposure, relative risk, TMREL, and PAF of birthweight and gestational age together, we then separate out the independent PAFs due to birthweight only or gestational age only. Because of this modelling strategy, the joint GBD risk factor quantifying the burden of disease due to both less than ideal birthweight (“low birthweight”) and shorter than ideal gestational age (“short gestation”) is grouped into a single “parent” risk factor termed “low birthweight and short gestation”. LBWSG is disaggregated into two “child” risk factors: “low birthweight for gestation” and “short gestation for birthweight”. Low birthweight for gestation quantifies the burden of disease attributable to less than ideal birthweight, after adjusting for the influence of gestational age. Likewise, short gestation for birthweight quantifies the burden of disease attributable to shortened gestational age, after adjusting for the influence of birthweight.

Ideally, the model for joint exposure and joint relative risk would be fully continuous. To simplify the computation for the analysis, a grid of 500-gram and 2-week units (“bins”) is used as the LBWSG dimensions and to approximate a fully continuous joint distribution model (see Figure 1).

Figure 3: Fully continuous analysis of joint gestational age and birthweight (left) is approximated with a grid of birthweight and gestational age with 500-gram and 2-week “bins” (right)



Case definition

“Low birthweight” has historically referred to any birthweight less than 2500 grams, dichotomising birthweight into two categories: “normal” and “low”. In the context of the GBD LBWSG risk factor, low birthweight refers to any birthweight less than the birthweight TMREL (the birthweight that minimises risk at the population level). Because LBWSG is estimated in a grid of 500-gram and 2-week bins, any 500-gram birthweight unit less than the TMREL, which was determined as [38, 40) weeks and [3500, 4000) g for the LBWSG parent risk factor, is considered “low birthweight”. This includes, for example, birthweight of [2500, 3000) grams, which the traditional, dichotomous definition of “low birthweight” would not include.

Like birthweight, gestational age is typically classified into broad categories. “Preterm” is used to describe any newborn baby born less than 37 completed weeks of gestation. In the GBD context, “short gestation” is used to refer to all gestational ages below the gestational age TMREL.

Exposure

In LBWSG, exposure refers to the portion of the joint distribution of gestational age and birthweight less than the TMREL, by location/year/sex (l/y/s), from birth to the end of the neonatal period. Modelling LBWSG exposure can be summarised in three steps:

- A. Model univariate gestational age and birthweight distributions at birth, by l/y/s
- B. Model joint distributions of gestational age and birthweight at birth, by l/y/s
- C. Model joint distributions from birth to the end of the neonatal period, by l/y/s

Table 1: Analytic steps in estimation of YLDs due to preterm birth

	Summary of exposure modelling strategy
Step A Model univariate distributions at birth	1. Model mean gestational age, prevalence of gestational age <28 weeks, and prevalence of gestational age <37 weeks, by l/y/s 2. Model mean birthweight and prevalence of birthweight <2500 grams, by l/y/s 3. Model univariate gestational age and birthweight distributions separately at birth, by l/y/s
Step B Model joint distributions at birth	1. Use copulae to model the correlation structure of the joint distribution of gestational age and birthweight, globally 2. Model the joint distribution of gestational age and birthweight, by location/year/sex at birth, by applying the globally modelled correlation structure to the location/year/sex-specific univariate models of gestational age and birthweight distributions
Step C Model joint distributions from birth to 28 days	1. Model all-cause mortality rates by gestational age and birthweight 2. Model gestational age and birthweight distributions of surviving neonates for all l/y/s from birth to end of the neonatal period, using all-cause mortality rates by gestational age and birthweight

Input data and data processing

Input data needed to model univariate gestational age and birthweight distributions at birth (Step A):

- Prevalence of preterm birth (<37 weeks), by l/y/s
- Prevalence of preterm birth (<28 weeks), by l/y/s
- Mean gestational age, by l/y/s
- Gestational age microdata
- Prevalence of low birthweight (<2500 grams), by l/y/s
- Mean birthweight, by l/y/s
- Birthweight microdata

To model joint distributions of gestational age and birthweight (Step B), joint microdata of gestational age and birthweight are also required. Additional inputs to modelling joint distributions from birth to 28 days (Step C) are all-cause mortality by l/y/s and joint birthweight and gestational age microdata linked to mortality outcomes.

Prevalence of extremely preterm birth (<28 weeks) and preterm birth (<37 weeks) were modelled using vital registration, survey, and clinical data. For the preterm models, only inpatient and insurance claims data were included from clinical informatics datasets; outpatient data were excluded because they were more likely to capture repeated visits by the same child rather than unique visits. Prevalence of low birthweight (<2500 grams) was modelled using only vital registration and survey data.

Literature review

Before GBD 2016, available preterm birth data were sourced by a technical working group. In GBD 2016 and GBD 2017, we conducted systematic reviews to identify additional sources beyond the data already used in the models. The PubMed database was searched using the following search string:

```
((("Infant, Premature"[Mesh] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR ("preterm"[All Fields] AND "infant"[All Fields]) OR "preterm infant"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR ("newborn"[All Fields] AND "infant"[All Fields])) AND (premature[All Fields] OR preterm[All Fields]) OR "premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR ("preterm"[All Fields] AND "birth"[All Fields]) OR "preterm birth"[All Fields]) ((("Infant, Premature"[Mesh] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR ("preterm"[All Fields] AND "infant"[All Fields]) OR "preterm infant"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR ("newborn"[All Fields] AND "infant"[All Fields])) AND (premature[All Fields] OR preterm[All Fields]) OR "premature birth"[MeSH Terms] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR ("preterm"[All Fields] AND "birth"[All Fields]) OR "preterm birth"[All Fields]) AND ("1985"[PDAT] : "3000"[PDAT]) AND "humans"[MeSH Terms].
```

The exclusion criteria were: studies that did not provide primary data on epidemiological parameters, non-representative studies (eg, only high-risk pregnancies), and reviews. Table 3 shows the search hits, number of full-texts reviewed, and number of extracted sources.

Table 3. LBWSG search hits, full-text review, extracted sources

Search	Hits	Full-text review	Extracted	Search date
GBD 2017	16,174	2200	154	6/6/2017

Table 4. Input data for exposure models

Input data	Exposure
Source count (total)	2233
Number of countries with data	176

Data processing

Any data that didn't fit a GBD age groups was split into age groups using a model that was run using only age-specific data. Starting in GBD 2019, as was the case with all other non-fatal analyses, we applied empirical age and sex ratios from previous models to disaggregate observations that did not entirely fit in one GBD age category or sex. Ratios were determined by dividing the result for a specific age and sex by the result for the aggregate age and sex specified in a given observation.

Low birthweight (<2500 grams) data were extracted from literature, vital registration systems, and surveys. Survey data (most commonly from DHS and MICS) were observed to have high missingness of birthweight responses. We evaluated the patterns of missingness and found a number of distinct patterns that suggested non-random omission of birthweight observations. We therefore imputed

missing birthweight values using the Amelia II (Version 1.7.6) package in R. Birthweight was predicted using the following variables also in the DHS surveys: urbanicity, sex, birthweight recorded on card, birth order, maternal education, paternal education, child age, child weight, child height, mother's age at birth, mother's weight, shared toilet facility, and household water treated.

After imputation, we completed a number of additional steps to standardize the dataset by applying a series of crosswalks. "Crosswalking" is a process of reducing non-random bias by adjusting non-standard data to the likely value had the data been collected using a reference definition, technique, or sample. Three crosswalks were applied for birthweight and gestational age data, all of the statistical models for which were developed using meta-regression – regularized, Bayesian, trimmed (MR-BRT).

First was a crosswalk for method of gestational age assessment that included three separate models. All microdata that reported GA and both obstetric estimate (OE) and last menstrual period were crosswalked to OE using the relationship derived from USA GA microdata (Figure 2). This crosswalk was developed with a spline on LMP in order to reliably match on the data that needed to be crosswalked.

Next, for all data that were only categorical, we adjusted all gestational age data to a reference definition of obstetric estimate (OE), which also included tabulations of the crosswalked microdata above. Two alternate definitions regularly appeared and both were crosswalked separately. These were Last Menstrual Period (LMP) for each of <37 weeks and <28 weeks gestation (Tables 5 and 6) and other measure of gestation age (Table 7 and 8).

The second set of crosswalks adjusted data derived from clinical administrative sources (ie. Hospital discharges and insurance claims) to matched vital registration data using OE (Tables 9 and 10).

The third set of crosswalks served to "square the input dataset" to ensure that every location-year with data had an observation for each of <2500g (birthweight), <37 weeks, and <28 weeks. This process utilized relationships between input data types to maximize the volume of data later input to models. Low birthweight data (<2500g) were crosswalked to preterm (<37 weeks) data (Table 11), preterm to extremely preterm (Table 12), and extremely preterm to preterm (Table 13).

Figure 2. MR-BRT OE-LMP crosswalk adjustment factor by LMP-reported gestational age

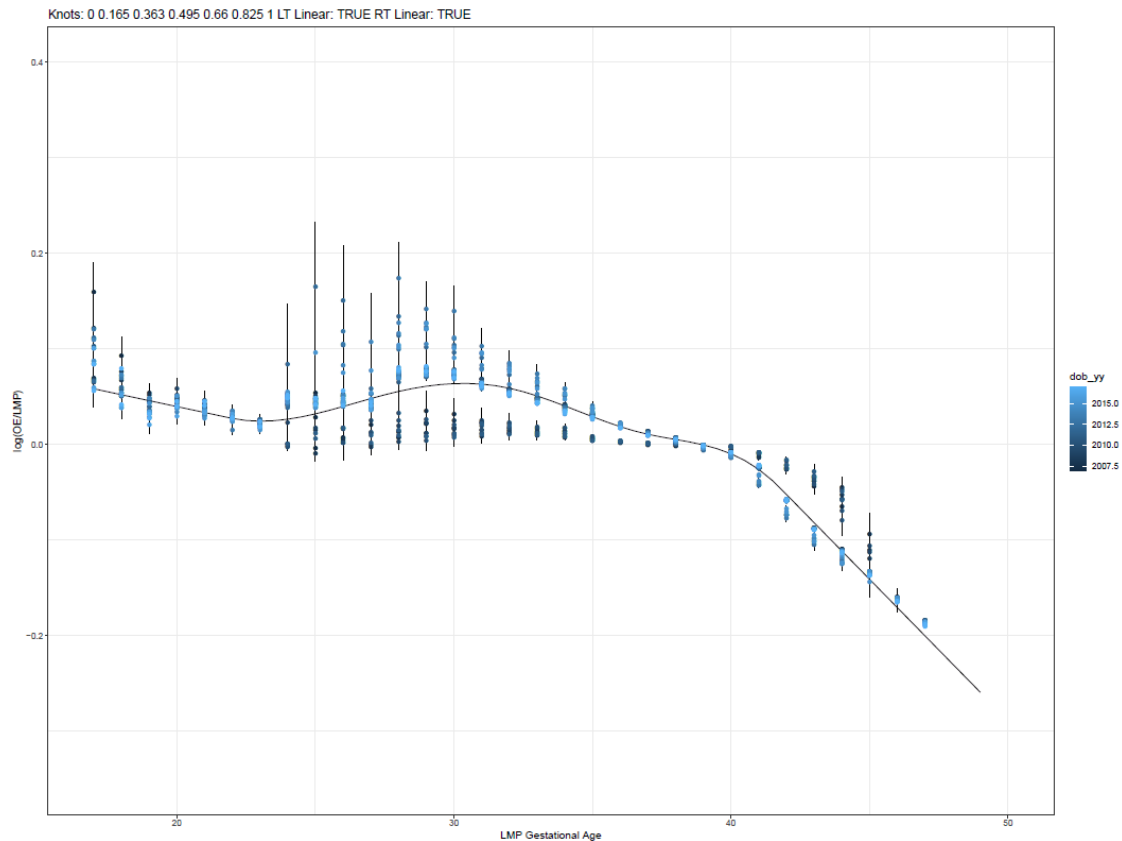


Table 5. MR-BRT OE-LMP crosswalk adjustment factor for preterm birth (<37 weeks of gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Obstetric estimate	Reference	0.01	---	---
Last menstrual period	Alternative		0.187 (0.142,0.231)	1.205 (1.153, 1.260)

Table 6. MR-BRT OE-LMP crosswalk adjustment factor for extremely preterm (<28 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Obstetric estimate	Reference	0.00	---	---
Last menstrual period	Alternative		0.0284 (0.268,0.300)	1.328 (1.308, 1.349)

Table 7. MR-BRT OE-other measure crosswalk adjustment factor for preterm birth (<37 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Obstetric estimate	Reference	0.10	---	---
Other measurement	Alternative		-0.243 (-0.494, 0.009)	0.785 (0.610, 1.01)

Table 8. MR-BRT OE-other measure crosswalk adjustment factor for extremely preterm birth (<28 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Obstetric estimate	Reference	0.37	---	---
Other measurement	Alternative		0.154 (-0.486, 0.793)	1.166 (0.615, 2.210)

Table 9. MR-BRT VR-claims crosswalk adjustment factor for preterm birth (<37 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Vital registration	Reference	0.07	---	---
Insurance claims	Alternative		-0.712 (-0.909, -0.515)	0.491 (0.403, 0.597)

Table 10. MR-BRT VR-insurance claims crosswalk adjustment factor for extremely preterm birth (<28 weeks of gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Vital registration	Reference	0.02	---	---
Insurance claims	Alternative		-1.258 (-1.447, -1.07)	0.284 (0.235, 0.344)

Table 11. MR-BRT low birthweight to preterm birth (<37 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
Preterm birth	Reference	0.08	---	---
Low birthweight	Alternative		-0.479 (-0.518, -0.440)	0.620 (0.596, 0.644)

Table 12. MR-BRT preterm (<37 weeks gestation) to extremely preterm (<28 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
28 weeks	Reference	0.06	---	---
37 weeks	Alternative		3.221 (3.161, 3.281)	25.053 (23.600, 26.604)

Table 13. MR-BRT extremely preterm (<28 weeks gestation) to preterm (<37 weeks gestation)

Data input	Reference or alternative case definition	Gamma	Beta coefficient, log (95% CI)	Adjustment factor*
37 weeks	Reference	0.05	---	---
28 weeks	Alternative		-3.208 (-3.266, -3.150)	0.0404 (0.0381, 0.0428)

*MR-BRT crosswalk adjustments can be interpreted as the factor the alternative case definition is adjusted by to reflect what it would have been had it been measured using the reference case definition. If the log/logit beta coefficient is negative, then the alternative is adjusted up to the reference. If the log/logit beta coefficient is positive, then the alternative is adjusted down to the reference.

**The adjustment factor column is the exponentiated beta coefficient. For log beta coefficients, this is the relative rate between the two case definitions. For logit beta coefficients, this is the relative odds between the two case definitions.

These data adjustments had the effect of dramatically increasing the size of each of the modelling datasets and are primarily responsible for most changes in preterm estimates between GBD 2019 and GBD 2021. After all crosswalks, we performed a deduplication step on GA models. Namely, if low birthweight data in countries that were 1) categorised as “data-rich” locations in cause-of-death modelling or had at least 10 consecutive years of vital registration data recording gestational age, and 2) had both preterm birth and low birthweight data, then crosswalked low birthweight data were outliered so that the model was informed only by the gestational age data.

Modelling strategy

Step A: Model univariate birthweight and gestational age distributions at birth, by I/y/s

Microdata are the ideal data source for modelling distributions; however, microdata are not widely available for birthweight and are scarcer for gestational age. Categorical prevalence data are more readily available from a wider range of locations and years for low birthweight (<2500g), extremely preterm (<28 weeks of gestation), and preterm birth (<37 weeks of gestation). Because categorical prevalence has wider availability than microdata, we use prevalence data to assist in modelling birthweight and gestational age ensemble distributions.

Ensemble distribution models can be constructed with three pieces of information: mean of the distribution, variance of the distribution, and the weights of the distributions being used in the ensemble. To model mean and variance for all I/y/s for birthweight and gestational age, we first used spatiotemporal Gaussian process regression (ST-GPR) models to model prevalence of low birthweight, extremely preterm, and preterm birth for all I/y/s at birth. To model mean birthweight for all I/y/s, OLS linear regression was used to regress mean birthweight on log-transformed low birthweight prevalence. This model was then used to predict mean birthweight for all I/y/s, using the prevalence of low birthweight (<2500 grams) modelled for all I/y/s in ST-GPR. Similarly, to model gestational age mean for all I/y/s, OLS linear regression model was used to regress mean gestational age on log-transformed preterm prevalence. Mean gestational age for all I/y/s was predicted using the preterm birth (<37 weeks) estimated modelled in ST-GPR.

Global ensemble weights for gestational age were derived by using all available gestational age and birthweight microdata in Table 14 to select the ensemble weights. The distribution families

included in the optimization process were exponential, gamma, gumbel, Weibull, log-normal, normal, mirrored gamma, and mirrored gumbel. As an advancement in GBD 2021, ensemble weights were fit that specifically targeted the fit at 28 weeks and 37 weeks for gestational age and 1500 grams and 2500 grams for low birthweight. In previous GBD cycles the fit of these models had been optimized to reduce error across the entire distribution. Additionally, as an improvement in GBD 2021, this ensemble weight fitting strategy optimized on all microdata sources simultaneously, as opposed to separately.

For each l/y/s, given the mean and ensemble weights, the variance was optimised to minimise error on the prevalence of preterm birth (<37 weeks) for the gestational age distribution and prevalence of low birthweight (<2500 grams) for the birthweight distribution.

Step B: Model joint birthweight and gestational age distributions at birth, by l/y/s

In order to model the joint distribution of gestational age and birthweight from separate distributions, information was needed about the correlation between the two distributions. Distributions of gestational age and birthweight are not independent; the Spearman correlation for each country where joint microdata were available (Table 14), pooling across all years of data available, ranged from 0.25 to 0.49. The overall Spearman correlation was 0.38, pooling across all countries in the dataset.

Table 14. Summary of microdata inputs

<i>Location</i>	<i>Years of data</i>	<i>Total births*</i>	<i>Format of data</i>	<i>Spearman correlation</i>	<i>Used in ensemble weight selection</i>	<i>Used in copula parameter selection</i>	<i>Used in relative risk models</i>
<i>BRA</i>	2016	2,854,380	Microdata	0.37	Yes	Yes	No
<i>ECU</i>	2003–2015	2,473,039	Microdata	0.34	Yes	Yes	No
<i>ESP</i>	1990–2014	8,537,220	Microdata	0.42	Yes	Yes	No
<i>JPN</i>	1995–2015	23,644,506	Tabulations	0.41	No	No	Yes
<i>MEX</i>	2008–2012	10,256,117	Microdata	0.35	Yes	Yes	No
<i>NOR</i>	1990–2014	1,489,210	Microdata	0.44	Yes	Yes	Yes
<i>NZL</i>	1990–2016	1,600,501	Microdata	0.25	Yes	Yes	Yes
<i>SGP</i>	1993–2015	972,775	Tabulations	0.41	No	No	Yes
<i>TWN</i>	1998–2002	1,331,760	Tabulations	0.38	No	No	Yes
<i>URY</i>	1996–2014	698,622	Microdata	0.49	Yes	Yes	No
<i>USA</i>	1990–2014	81,929,879	Microdata	0.38	Yes	Yes	Yes

** Pooled across all years and sexes, excluding data missing year of birth, gestational age, or birthweight*

Joint distributions between the birthweight and gestational age marginal distributions were modelled with copulae. The Copula and VineCopula packages in R were used to select the optimal copula family and copula parameters to model the joint distribution, using joint microdata from the country-years in Table 14. The copula family selected from the microdata was “Survival BB8”, with theta parameter set to 1.75 and delta parameter set to 1.

The joint distribution of birthweight and gestational age per location-year-sex was modelled using the global copula family and parameters selected and the location-year-sex gestational

age and birthweight distributions. The joint distribution was simulated 100 times to capture uncertainty. Each simulation consisted of 10,000 simulated joint birthweight and gestational age datapoints. Each joint distribution was divided into 500g by 2-week bins to match the categorical bins of the relative risk surface. Birth prevalence was then calculated for each 500g by 2-week bin.

Step C: Model joint distributions from birth to the end of the neonatal period, by l/y/s

Early neonatal prevalence and late neonatal prevalence were estimated using life table approaches for each 500g and 2-week bin. Using the all-cause early neonatal mortality rate for each location-year-sex, births per location-year-sex-bin, and the relative risks for each location-year-sex-bin in the early neonatal period, the all-cause early neonatal mortality rate was calculated for each location-year-sex-bin. The early neonatal mortality rate per bin was used to calculate the number of survivors at seven days and prevalence in the early neonatal period. Using the same process, the all-cause late neonatal mortality rate for each location-year-sex was paired with the number of survivors at seven days and late neonatal relative risks per bin to calculate late neonatal prevalence and survivors at 28 days.

Relative risks and theoretical minimum risk exposure level

LBWSG is paired with the outcomes listed in Table 15 and is only attributed to burden in the early and late neonatal period.

Table 15: Cause list of outcomes for low birthweight and short gestation

Cause name
Diarrhoeal diseases
Lower respiratory infections
Upper respiratory infections
Otitis media
Pneumococcal meningitis
<i>H influenzae</i> type B meningitis
Meningococcal meningitis
Other meningitis
Encephalitis
Neonatal preterm birth complications
Neonatal encephalopathy due to birth asphyxia and trauma
Neonatal sepsis and other neonatal infections
Haemolytic disease and other neonatal jaundice
Other neonatal disorders
Sudden infant death syndrome

Causes

The available data for deriving relative risk was only for all-cause mortality. The exception was the USA linked infant birth-death cohort data, which contained three-digit ICD causes of death,

but also had nearly 30% of deaths coded to causes that are ill-defined, or intermediate, in the GBD cause classification system. We analysed the relative risk of all-cause mortality across all available sources and selected outcomes based on criteria of biological plausibility. Some causes, most notably congenital birth defects, haemoglobinopathies, malaria, and HIV/AIDS, were excluded based on the criteria that reverse causality could not be excluded.

Input data

In the Norway, New Zealand, and USA Linked Birth/Death Cohort microdata datasets, livebirths are reported with gestational age, birthweight, and an indicator of death at 7 days and 28 days. For this analysis, gestational age was grouped into two-week categories, and birthweight was grouped into 500-gram categories. The Taiwan, Japan, and Singapore datasets were prepared in tabulations of joint 500-gram and two-week categories. A pooled country analysis of mortality risk in the early neonatal period and late neonatal period by “small-for-gestational-age” category in developing countries in Asia and sub-Saharan Africa were also used to inform the relative risk analysis.

Table 16: Input data for relative risk models

Input data	Relative risk
Source count (total)	113
Number of countries with data	6

Modelling strategy

For each location, data were pooled across years, and the risk of all-cause mortality at the early neonatal period and late neonatal period at joint birthweight and gestational age combinations was calculated. In all datasets except for the USA, sex-specific data were combined to maximise sample size. The USA analyses were sex-specific. To calculate relative risk at each 500-gram and two-week combination, logistic regression was first used to calculate mortality odds for each joint two-week gestational age and 500-gram birthweight category. Mortality odds were smoothed with Gaussian process regression, with the independent distributions of mortality odds by birthweight and mortality odds by gestational age serving as priors in the regression.

A pooled country analysis of mortality risk in the early neonatal period and late neonatal period by SGA category in developing countries in Asia and sub-Saharan Africa were also converted into 500-gram and two-week bin mortality odds surfaces. The relative risk surfaces produced from microdata and the Asia and Africa surfaces produced from the pooled country analysis were meta-analysed, resulting in a meta-analysed mortality odds surface for each location. The meta-analysed mortality odds surface for each location was smoothed using Gaussian process regression and then converted into mortality risk. To calculate mortality relative risks, the risk of each joint two-week gestational age and 500-gram birthweight category were divided by the

risk of mortality in the joint gestational age and birthweight category with the lowest mortality risk.

For each of the country-derived relative risk surfaces, the 500-gram and two-week gestational age joint bin with the lowest risk was identified. This bin differed within each country dataset. To identify the universal 500-gram and two-week gestational age category that would serve as the universal TMREL for our analysis, we chose the bins that was identified to be the TMREL in each country dataset to contribute to the universal TMREL. Therefore, the joint categories that served as our universal TMREL for the LBWSG risk factor were “38–40 weeks of gestation and 3500–4000 grams”, “38–40 weeks of gestation and 4000–4500 grams”, and “40–42 weeks of gestation and 4000–4500 grams”. As the joint TMREL, all three categories were assigned to a relative risk equal to 1.

Population attributable fraction

The total PAF for the low birthweight and short gestation joint risk factor was calculated by summing the PAF calculated from each 500g x two-week category, with the lowest risk category among all the 500g x two-week categories serving as the TMREL. The equation for calculating PAF for each 500g x two-week category is:

$$PAF_{joasgt} = \frac{\sum_{x=1}^u RR_{joast}(x)P_{jasgt}(x) - RR_{joasg}(TMRE_{jas})}{\sum_{x=1}^u RR_{joas}(x)P_{jasgt}(x)}$$

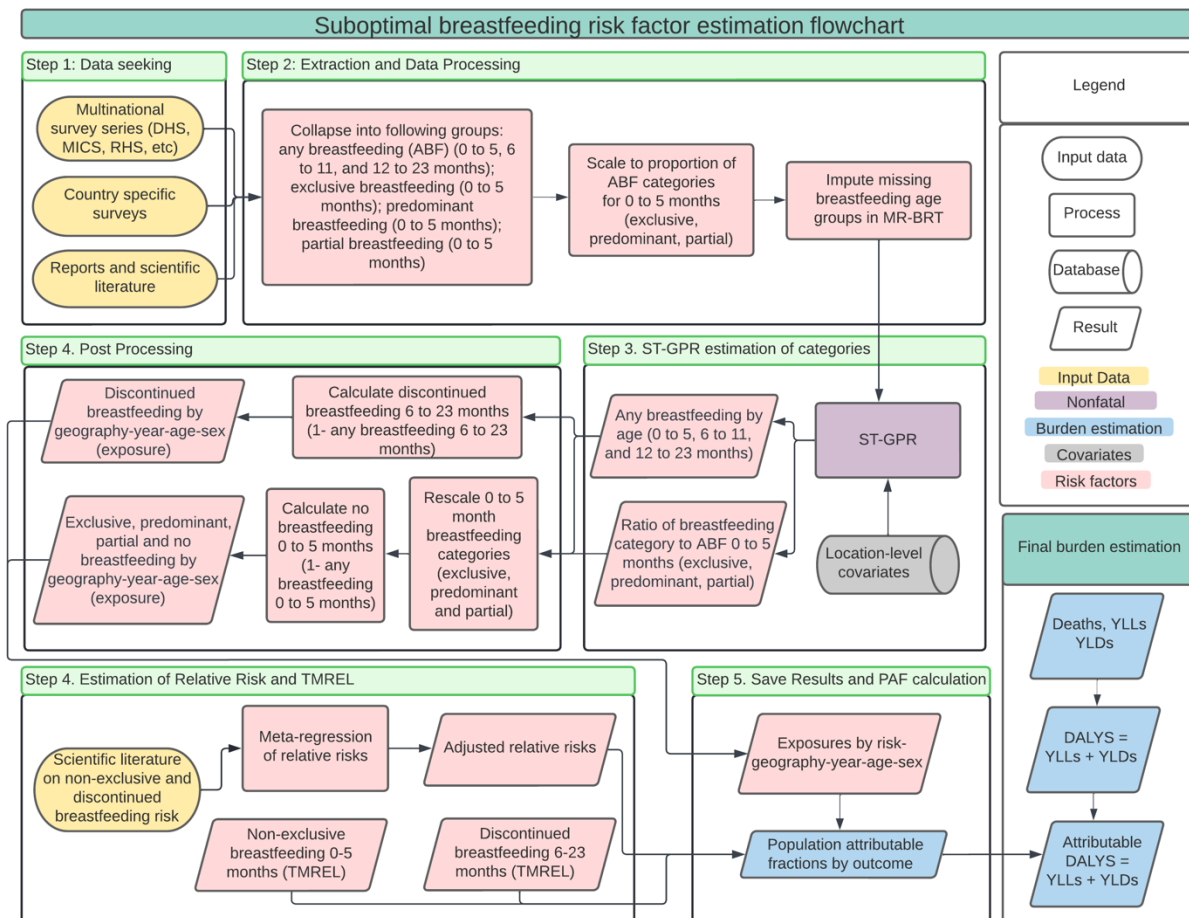
To calculate the PAFs for the univariate risks (‘short gestation for birthweight’ and ‘low birthweight for gestation’), relative risks are first weighted by global exposure in 2019, summed across one of the dimensions (gestational age or birthweight), and then rescaled by the maximum relative risk in the TMREL block (38–42 weeks of gestation and 3500–4500 grams). Any relative risk less than 1 was set to 1. Exposure was also summed across the same dimension, and the univariate PAF equalled the sum of the product of the weighted relative risks and exposures.

Low Birthweight and Short Gestation References

1. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *The Lancet*. 2013;382(9890):417–25.

Suboptimal breastfeeding

Flowchart



Input data and methodological summary

Definition

Exposure

Exposure to suboptimal breastfeeding is composed of two distinct categories: non-exclusive breastfeeding and discontinued breastfeeding.

Non-exclusive breastfeeding is defined as the proportion of children under 6 months of age who are not exclusively breastfed. We then parse those not exclusively breastfed into three categories – predominant, partial, and no breastfeeding. Exclusive breastfeeding is defined as the proportion of children who receive no other food or drink except breastmilk (allowing for ORS, drops, or syrups containing vitamins, minerals, or medicines). Predominant breastfeeding is the proportion of children whose predominant source of nourishment is breastmilk but also receive other liquids. Partial breastfeeding refers to those infants who receive breastmilk as

well as food and liquids, including non-human milk and formula. No breastfeeding refers to infants who do not receive breastmilk as a source of nourishment.

Discontinued breastfeeding is defined as the proportion of children between 6 and 23 months who receive no breastmilk as a source of nourishment.

Input data

Exposure

The data used in the analysis consist mostly of processed individual-level microdata from surveys; in the cases where microdata were unavailable, we used reported tabulated data from survey reports and scientific literature. Data used to categorise type of non-exclusive breastfeeding (predominant, partial, and none) come from surveys with 24-hour dietary logs based on maternal recall.

We updated our systematic review in GBD 2021 by searching the Global Health Data Exchange (GHDx) using the keyword “breastfeeding.” We prioritised extraction of surveys with microdata and new surveys from major survey series such as Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS).

Table 1. Input data counts – suboptimal breastfeeding exposure

	Countries with data	New sources	Total sources
Non-exclusive breastfeeding	169	49	737
Discontinued breastfeeding	162	50	679

To better ensure consistency in estimates across age groups, we identified location-years where we had data for “any breastfeeding 6–11 months” but no data for “any breastfeeding 12–23 months.” We then imputed data for “any breastfeeding 12–23 months” based on the observed 6–11 month datapoint in that location-year. We estimated the imputation adjustment by meta-analysing proportion ratios of matched pairs by source-location-year for any breastfeeding in these two age groups in meta-regression—Bayesian, regularised, trimmed (MR-BRT)¹, a Bayesian meta-analytic tool.

Table 2. MR-BRT adjustment factor for any breastfeeding 12–23 months imputation

Data input	Reference or alternative definition	Gamma	Beta coefficient, logit (95% UI)*	Adjustment factor**
Any breastfeeding 6–11 months	Ref	0.19	---	---

Any breastfeeding 12–23 months	Alt		-1.54 (-1.58 – -1.50)	0.21 (0.21–0.22)
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**MR-BRT crosswalk adjustments can be interpreted as the factor the alternative definition is adjusted by to reflect what it would have been had it been measured using the reference definition.*

***The adjustment factor column is the exponentiated beta coefficient. For logit beta coefficients, this is the relative odds between the two definitions.*

Relative risk

We included outcomes based on the strength of available evidence supporting a causal relationship. Studies evaluating the causal evidence for our risk-outcome pairs came primarily from studies compiled in a published review by the World Health Organization.² Non-exclusive breastfeeding was paired with diarrhoea and lower respiratory infection as diseases outcomes. Discontinued breastfeeding was paired with diarrhoea as an outcome.

Table 3. Input data counts – suboptimal breastfeeding relative risk

	Countries with data	New sources	Total sources
Relative risk	26	0	43

Modelling strategy

Exposure

Using the processed microdata and tabulated data from reports, we generated a complete time series from 1980 to 2022 for 1) any breastfeeding 0–5 months, 6–11 months, and 12–23 months, 2) ratio of exclusive breastfeeding to any breastfeeding 0–5 months, 3) ratio of predominant breastfeeding to any breastfeeding 0–5 months, and 4) ratio of partial breastfeeding to any breastfeeding 0–5 months using a three-step spatiotemporal Gaussian process regression. In previous GBD rounds, “any breastfeeding” was modelled separately for each of the estimated age groups. In GBD 2021 with the addition of new under-5 age groups that aligned with those ages we model, we incorporated the three age groups into a single model of “any breastfeeding.” This allowed us to borrow additional strength over space, age, and time by incorporating data from all sources in one model.

The first step of the ST-GPR process is an ensemble linear mixed-effects regression of our data on a set of potentially predictive covariates taken from the GBD Study covariates database. We tested every combination of these covariates in individual, sex-specific mixed-effects linear regressions with nested random effects at the super-region, region, and location levels. We then evaluated and ranked each of these sub-models by their out-of-sample root-mean-squared error. Finally, to produce initial estimates for every location, year, age, and sex in the analysis, we averaged the 50 top-performing models where the estimated coefficients were 1) statistically significant at $p < 0.05$ and 2) in the expected direction. We tested the following

covariates in the ensemble prior: Socio-demographic Index, SEV unsafe water, total fertility rate, maternal education, antenatal care (4+ visits), HIV mortality in women of reproductive age, high BMI in women of reproductive age, and underweight in women of reproductive age.

The second, spatiotemporal smoothing step of ST-GPR calculates the residual between our stage 1 regression estimate and each of our observed datapoints and then smooths this residual, drawing strength over space, age, and time and producing a revised stage 2 estimate of birth prevalence for every location, year, and sex. The third step of ST-GPR is a Gaussian process regression, using the stage 2 estimates as a prior and the observed datapoints and their variance to 1) further smooth the residual between the stage 2 predictions and observed data and produce a final mean estimate for each location, year, and sex, and 2) estimate uncertainty around this mean estimate, quantified by taking 1000 draws from the posterior Gaussian process. More detailed information on the ST-GPR modelling process can be found in the main text methods appendix.

To generate exposure categories for non-exclusive breastfeeding, we converted the modelled ratios of exclusive, predominant, and partial breastfeeding to the total category prevalence by multiplying each ratio by the estimates of any breastfeeding among infants aged 0–5 months. This ensured that these categories sum correctly to the “any breastfeeding 0–5 months” envelope. We calculated the proportion of infants receiving no breastmilk 0–5 months of age by subtracting the estimates of current breastfeeding from 1. We performed the same operation to estimate discontinued breastfeeding in the 6–11 months and 12–23 months categories.

Theoretical minimum-risk exposure level

For non-exclusive breastfeeding, those children that received no source of nourishment other than breastmilk (“exclusively breastfed”) were considered to be at the lowest risk of any of the disease outcomes. For discontinued breastfeeding, we assumed that children aged 6–23 months who received any breastmilk as a source of nourishment to be at the lowest risk of disease outcome.

Relative risk

We estimated relative risks for both non-exclusive and discontinued breastfeeding in a meta-analysis using the “metareg” package in Stata. For the 0–5 month age group we included diarrhoea and lower respiratory infection as outcomes, and for the 6–23 month age group we included diarrhoea as an outcome. We did not estimate separate relative risks for morbidity and mortality. The estimated relative risks are detailed in Table 4.

Table 4. Suboptimal breastfeeding relative risk estimates

Exposure category	Diarrhoea		Lower respiratory infection	
	Mortality	Morbidity	Mortality	Morbidity
0–5 months				
Exclusive breastfeeding	1.00	1.00	1.00	1.00

Predominant breastfeeding	2.35 (1.67–3.23)	2.35 (1.67–3.23)	1.37 (1.06–1.80)	1.37 (1.06–1.80)
Partial breastfeeding	2.63 (1.94–3.48)	2.63 (1.94–3.48)	1.48 (1.21–1.79)	1.48 (1.21–1.79)
No breastfeeding	3.60 (2.72–4.70)	3.60 (2.72–4.70)	1.74 (1.49–2.03)	1.74 (1.49–2.03)
6–23 months				
Any breastfeeding	1.00	1.00	--	--
Discontinued breastfeeding	1.31 (1.11–1.55)	1.31 (1.11–1.55)	--	--

Population attributable fraction

We used the standard GBD population attributable fraction (PAF) equation to calculate PAFs for non-exclusive breastfeeding and discontinued breastfeeding and each of their paired outcomes using exposure estimates, the theoretical minimum-risk exposure level, and relative risks.

Suboptimal Breastfeeding References

1. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; 396: 1204–22.
2. Horta, B., Vactora, C. (2013) Short-term effects of breastfeeding: a systematic review on the benefits of breastfeeding on diarrhoea and pneumonia mortality. The World Health Organization.

Justification for the counterfactual approach

There are two main approaches for the causal attribution of health outcomes: categorical attribution and counterfactual analysis. Categorical attribution assigns a single cause (e.g., a disease or a risk factor) or a group of causes to an event (e.g., death). Counterfactual analysis, on the other hand, estimates the impact of causes or risk factors by comparing the observed disease burden with what it would have been under an alternative hypothetical scenario, including scenarios where the risk factors are absent or reduced. This approach, which includes using a theoretical minimum risk exposure distribution to show potential health gains from reducing risk, can attribute the burden of disease to risk factors more comprehensively than categorical attribution, which might not account for the multifactorial nature of many diseases.

Counterfactual Approach References

1. Ezzati M, Hoorn SV, Lopez AD, et al. Comparative Quantification of Mortality and Burden of Disease Attributable to Selected Risk Factors. In: Lopez AD, Mathers CD, Ezzati M, et al., editors. Global Burden of Disease and Risk Factors. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 4. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK11813/> Co-published by Oxford University Press, New York.
2. Mathers, C. D., M. Ezzati, A. D. Lopez, C. J. L. Murray, and A. Rodgers. 2002. "Causal Decomposition of Summary Measures of Population Health." In Summary Measures of Population Health: Concepts, Ethics, Measurement, and Applications, ed. C. J. L. Murray, J. Salomon, C. D. Mathers, and A. D. Lopez. 273–290. Geneva: World Health Organization.

Estimation of population attributable fractions³

Risks are categorised on the basis of how exposure was measured: dichotomous, polytomous, and continuous. High low-density lipoprotein (LDL) cholesterol level is an example of a risk measured on a continuous scale. The PAF, which represents the proportion of risk that would be reduced in a given year if the exposure to a risk factor in the past were reduced to an ideal exposure scenario, is defined for a continuous risk factor as:¹⁹

$$PAF_{joasgt} = \frac{\int_{x=l}^u RR_{joasg}(x)P_{jasgt}(x)dx - RR_{joasg}(TMREL_{jas})}{\int_{x=l}^u RR_{joasg}(x)P_{jasgt}(x)dx}$$

Where PAF_{joasgt} is the PAF for cause o due to risk factor j for age group a , sex s , location g , and year t . $RR_{joasg}(x)$ is the RR as a function of exposure level x for risk factor j for cause o , age group a , sex s , and location g with the lowest level of observed exposure as l and the highest as u ; $P_{jasgt}(x)$ is the distribution of exposure at x for age group a , sex s , location g , and year t ; and $TMREL_{jas}$ is the TMREL for risk factor j , age group a , and sex s .

The PAF_{joasgt} for dichotomous and polytomous risk factors for every country is defined as:

$$PAF_{joasgt} = \frac{\sum_{x=l}^u RR_{joasg}(x)P_{jasgt}(x) - RR_{joasg}(TMREL_{jas})}{\sum_{x=l}^u RR_{joasg}(x)P_{jasgt}(x)}$$

where PAF_{joasgt} is the PAF for cause o due to risk factor j for age group a , sex s , location g , and year t . $RR_{joasg}(x)$ is the RR as a function of exposure level x for risk factor j for cause o , age group a , sex s , and location g on a plausible range of exposure levels from l to u ; $P_{jasgt}(x)$ is the proportion of the population in risk group (prevalence) for age group a , sex s , location g , and year t ; and $TMREL_{jas}$ is the TMREL for risk factor j , age group a , and sex s .

Calculating the burden of multiple risk factors³

A multiplicative aggregation of the PAFs of the individual risk factors was computed using the formula below:

$$PAF_{1..i} = 1 - \prod_{i=1}^n (1 - PAF_i)$$

where PAF is the population attributable fraction and i is each individual risk factor.

Risk factors and causal pathways leading to diarrhoeal diseases

Risk factor	Causal pathway that leads to diarrheal diseases
Unsafe water, unsafe sanitation, and no access to handwashing facility	Enteric pathogens enter the human gastrointestinal tract through contaminated drinking water, inadequate sanitation (e.g., unsafe disposal of human excreta), and poor hygiene practices (e.g., failing to wash one's hands after using the toilet). ¹ These pathogens can cause diarrhea by producing enterotoxins that induce increased secretion and by causing inflammation that decreases absorption in the intestines. ^{2,3}
Child growth failure (underweight, stunting, wasting)	Malnutrition can predispose the host to infections, including those caused by enteric pathogens, by impairing the body's defense mechanisms and enabling their colonization of the intestine. ⁴
Low birthweight and short gestation	The gastrointestinal tract's mucosal surfaces are underdeveloped, weakening the initial line of defense against enteric pathogens ⁵
Suboptimal breastfeeding	Suboptimal breastfeeding can increase the risk of diarrhea through the following mechanisms ⁶ : (1) human milk glycans, including oligosaccharides in their free and conjugated forms, are critical for the natural immune defense mechanism protecting breastfed infants from diarrheal diseases, and suboptimal breastfeeding can diminish this benefit; and (2) while breastfeeding reduces exposure to contaminated foods and fluids, suboptimal breastfeeding can increase exposure to them, thereby elevating the risk of developing diarrheal diseases in infants.
Vitamin A deficiency and zinc deficiency*	Vitamin A deficiency disrupts the integrity of the intestinal mucosa and alters immune responses, leading to increased susceptibility to infections and inflammation. ⁷ Similarly, zinc deficiency impairs the body's resistance to enteric pathogens and disrupts water and electrolyte absorption. ⁸
Particulate matter pollution*	Particulate matter pollution may alter the gut microbiome and immune function, impairing the intestinal barrier. ⁹

* The results for each individual risk factor are not displayed due to their small attribution; however, they are accessible for viewing at <https://vizhub.healthdata.org/gbd-compare/>.

Risk Factors and Causal Pathways: References

1. Baker KK, O'Reilly CE, Levine MM, et al. Sanitation and Hygiene-Specific Risk Factors for Moderate-to-Severe Diarrhea in Young Children in the Global Enteric Multicenter Study, 2007-2011: Case-Control Study. PLoS Med 2016; 13(5): e1002010.
2. Satchell KJ. Activation and suppression of the proinflammatory immune response by *Vibrio cholerae* toxins. Microbes Infect 2003; 5(13): 1241-7.

3. Hodges K, Gill R. Infectious diarrhea: Cellular and molecular mechanisms. Gut Microbes 2010; 1(1): 4-21.
4. Patwari AK. Diarrhoea and malnutrition interaction. Indian J Pediatr 1999; 66(1 Suppl): S124-34.
5. Ghattas H. INFECTION | Nutritional Interactions. In: Caballero B, ed. Encyclopedia of Human Nutrition (Second Edition). Oxford: Elsevier; 2005: 47-54.
6. Lamberti LM, Fischer Walker CL, Noiman A, Victora C, Black RE. Breastfeeding and the risk for diarrhea morbidity and mortality. BMC Public Health 2011; 11(3): S15.
7. Amimo JO, Michael H, Chepnengo J, Raev SA, Saif LJ, Vlasova AN. Immune Impairment Associated with Vitamin A Deficiency: Insights from Clinical Studies and Animal Model Research. Nutrients. 2022;14(23):5038.
8. Wapnir RA. Zinc deficiency, malnutrition and the gastrointestinal tract. The Journal of nutrition. 2000 May 1;130(5):1388S-92S.
9. Salim SY, Kaplan GG, Madsen KL. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut Microbes. 2014 Mar-Apr;5(2):215-9.

Statement of GATHER Compliance

Appendix Table 9. Checklist of information that should be included in reports of global health estimates, with description of compliance and location of information the current study

#	GATHER checklist item	Description of compliance	Reference
Objectives and funding			
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Narrative provided in paper and appendix describing indicators, definitions, populations, and time periods	Main text (Methods) and Appendix (Methods)
2	List the funding sources for the work.	Funding sources listed in paper	Summary (Funding)
Data Inputs			
<i>For all data inputs from multiple sources that are synthesized as part of the study:</i>			
3	Describe how the data were identified and how the data were accessed.	Narrative description of data seeking methods provided	Main text (Methods) and Appendix (Methods)
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Narrative about inclusion and exclusion criteria provided; ad hoc exclusions in appendix supplementary methods	Main text (Methods) and Appendix (Methods)
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	An interactive, online data source tool that provides metadata for data sources by component, geography, cause, risk, or impairment has been developed, and data source citations provided	Appendix (Methods) with additional information about these sources available at https://ghdx.healthdata.org/gbd-2021
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Summary of known biases included in appendix supplementary methods	Appendix (Methods)
<i>For data inputs that contribute to the analysis but were not synthesized as part of the study:</i>			

7	Describe and give sources for any other data inputs.	Included in online data source tool	Global Health Data Exchange https://ghdx.healthdata.org/gbd-2021
<i>For all data inputs:</i>			
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Downloads of input data available through online data tools; input data not available in tools will be made available upon request	Global Health Data Exchange https://ghdx.healthdata.org/gbd-2021
Data analysis			
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Flow diagram of methodological process provided, as well as narrative descriptions of modelling process	Main text (Methods) and Appendix (Methods)
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Flow diagram and detailed methods write-up covering all data extraction, processing, and modelling processes provided	Main text (Methods) and Appendix (Methods)
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Provided in methodological write-up	Appendix (Methods)
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Provided in methodological write-up	Appendix (Methods)
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Provided in main text methods narrative description and appendix methodological writeup	Main text (Methods) and Appendix (Methods)
14	State how analytic or statistical source code used to generate estimates can be accessed.	Remote code repository for access to analytic code provided	Remote code repository https://ghdx.healthdata.org/gbd-2021/code
Results and Discussion			
15	Provide published estimates in a file format from which data can be efficiently extracted.	Tables in appendices and online results tool	Appendix Results and https://ghdx.healthdata.org/gbd-2021
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Uncertainty provided with all results	Main text (Results), Appendix Results
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Discussion of results and methodological changes between GBD rounds provided in manuscript narrative and appendix	Main text (Methods, Results and Discussion) and Appendix (Methods)
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Discussion of limitations, including modelling assumptions and data limitations, included in manuscript narrative and appendix	Main text (Methods and Discussion) and Appendix (Methods)

Note: A full set of granular estimates can be found in the GBD Results Tool here, <https://vizhub.healthdata.org/gbd-results/>

Ethics Statement

The Global Burden of Diseases, Injuries, and Risk Factors Study used de-identified data, and the waiver of informed consent was reviewed and approved by the University of Washington Institutional Review Board (study number 9060).

Authorship Material

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