

# Global projections of temperature-attributable mortality due to enteric infections: a modelling study



Paul L C Chua, Veronika Huber, Chris Fook Sheng Ng, Xerxes T Seposo, Lina Madaniyazi, Simon Hales, Alistair Woodward, Masahiro Hashizume



## Summary

**Background** Mortality due to enteric infections is projected to increase because of global warming; however, the different temperature sensitivities of major enteric pathogens have not yet been considered in projections on a global scale. We aimed to project global temperature-attributable enteric infection mortality under various future scenarios of sociodemographic development and climate change.

**Methods** In this modelling study, we generated global projections in two stages. First, we forecasted baseline mortality from ten enteropathogens (non-typhoidal salmonella, *Shigella*, *Campylobacter*, cholera, enteropathogenic *Escherichia coli*, enterotoxigenic *E coli*, typhoid, rotavirus, norovirus, and *Cryptosporidium*) under several future sociodemographic development and health investment scenarios (ie, pessimistic, intermediate, and optimistic). We then estimated the mortality change from baseline attributable to global warming using the product of projected annual temperature anomalies and pathogen-specific temperature sensitivities.

**Findings** We estimated that in the period 2080–95, the global mean number of temperature-attributable deaths due to enteric infections could be as low as 6599 (95% empirical CI 5441–7757) under the optimistic sociodemographic development and climate change scenario, or as high as 83 888 (67 760–100 015) under the pessimistic scenario. Most of the projected temperature-attributable deaths were from shigellosis, cryptosporidiosis, and typhoid fever in sub-Saharan Africa and South Asia. Considerable reductions in the number of attributable deaths were from viral infections, such as rotaviral and noroviral enteritis, which resulted in net reductions in attributable enteric infection mortality under optimistic scenarios for Latin America and the Caribbean and East Asia and the Pacific.

**Interpretation** Temperature-attributable mortality could increase under warmer climate and unfavourable sociodemographic conditions. Mitigation policies for limiting global warming and sociodemographic development policies for low-income and middle-income countries might help reduce mortality from enteric infections in the future.

**Funding** Japan Society for the Promotion of Science, Japan Science and Technology Agency, and Spanish Ministry of Economy, Industry, and Competitiveness.

**Copyright** © 2021 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

## Introduction

Enteric infections cause a substantial burden of ill-health in low-income and middle-income countries (LMICs),<sup>1</sup> and they are likely to remain a public health risk under climate change, due to the increase in ambient temperature in particular.<sup>2</sup> This expectation can be explained by the influence of temperature on the growth and survival of enteropathogens, which cause enteric infections.<sup>3–5</sup> Some of them can grow, proliferate, and remain infective under warm temperatures in water, food, and other surfaces.<sup>6–8</sup> They can also accumulate under dry conditions, which very warm temperatures might contribute to.<sup>9</sup> High temperatures might also alter water availability, affecting access to clean and drinking water, as well as proper handwashing and hygiene.<sup>10–12</sup> Moreover, warmer temperatures were observed to increase pathogen loads in animal hosts and possibly prolong transmissions.<sup>13</sup>

Early global projections of enteric infections related to temperature change, based on a limited set of

exposure-response estimates, reported that risks were higher under future scenarios with high temperatures and in countries with low incomes.<sup>14</sup> Using this previous approach, the number of global temperature-related excess deaths was predicted to be in the range of 21 000–68 000 in 2030, but to slightly decrease to a value in the range of 15 000–49 000 by 2050.<sup>15</sup> Similarly, temperature-related infectious gastroenteritis cases in Japan were projected to decline by 0.8–9.1% in 2090–99, compared with the amount in 2010–19, with the greatest reduction occurring in a future with high radiative forcing (ie, a large change in global energy balance brought about by forcing agents like greenhouse gases that contribute to climate change).<sup>16</sup> This net reduction was attributed to a probable diminishing of cold-related morbidity that outweighed the heat-related increases.<sup>16</sup> The authors suggested that cold-related morbidity could be largely due to viral infections that have negative associations with ambient temperature.<sup>17,18</sup>

Because the previous projections did not have any tax-specific or pathogen-specific analyses, they could not

*Lancet Planet Health* 2021;  
5: e436–45

Department of Global Health, School of Tropical Medicine and Global Health (P L C Chua MSc, C F S Ng PhD, X T Seposo PhD, L Madaniyazi PhD) and Department of Pediatric Infectious Diseases, Institute of Tropical Medicine (L Madaniyazi), Nagasaki University, Nagasaki, Japan; Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (Prof M Hashizume PhD, P L C Chua); Department of Physical, Chemical and Natural Systems, Universidad Pablo de Olavide, Sevilla, Spain (V Huber PhD); Department of Public Health, University of Otago, Wellington, New Zealand (Prof S Hales PhD); Department of Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand (Prof A Woodward PhD)

Correspondence to:  
Paul L C Chua, Department of Global Health, School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki 852-8102, Japan  
paulcarloschua@gmail.com

### Research in context

#### Evidence before this study

We searched PubMed, Web of Science, Scopus, and Google Scholar for research articles published from Jan 1, 2000, to Dec 31, 2019. The search terms comprised “projection”, “temperature”, and “diarrhoea”. We also expanded the search in Google to consider non-research articles and unpublished materials. Projections of global temperature-attributable mortality due to enteric infections have been generated previously using all-cause infections; however, enteric infections have varying temperature sensitivities, depending on their cause. Studies generally found that bacterial pathogens have positive associations with ambient temperature, whereas viral pathogens have negative temperature associations. One study in Japan suggested that reductions in the number of temperature-related viral enteric infections could cause net reductions in the overall number of temperature-attributable enteric infections. Another study in an Indian city projected a net increase in excess temperature-attributable enteric infections despite reductions in rotavirus prevalence. Global-level projections of temperature-attributable enteric infection mortality might be improved if

various pathogens were considered separately according to their temperature sensitivities.

#### Added value of this study

This study showed that most temperature-attributable excess deaths due to enteric infections might be caused mainly by shigellosis, cryptosporidiosis, and typhoid fever. Reductions in temperature-attributable deaths might be from a decrease in cases of rotaviral and noroviral enteritis. Most global temperature-attributable excess enteric infection deaths are projected to occur in sub-Saharan Africa and South Asia across all sociodemographic and climate change scenarios. Net reductions might occur in Latin America and the Caribbean as well as East Asia and the Pacific under optimistic scenarios of sociodemographic development and effective climate change mitigation.

#### Implications of all the available evidence

Global temperature-attributable deaths in the future could be reduced by supporting climate change mitigation policies on a global level as well as socioeconomic development and health adaptation for low-income and middle-income countries.

account for the different temperature sensitivities of various enteropathogens. A 2016 study in children in an Indian city approached this issue by modelling all-cause diarrhoea cases categorised into three major pathogens.<sup>3</sup> With use of an agent-based modelling framework for pathogen ingestion via contaminated drinking water, the study reported that a temperature rise in the future would decrease the prevalence of rotavirus by 10·5% and would increase the prevalence of *Cryptosporidium* by 9·9% and *Escherichia coli* by 6·3% in 2080–99 relative to the 2011–30 baseline.<sup>3</sup> Aggregating the diarrhoea cases together resulted in a net increase of 6·4% per 1°C temperature rise because of a combined increase in the prevalence of cryptosporidiosis and *E coli* enteritis.<sup>3</sup> Although this finding is notable, there are additional important pathogens known to cause enteric infections, such as *Shigella*, typhoidal salmonella, *Vibrio cholerae*, and norovirus, which also have varying temperature sensitivities,<sup>19,20</sup> and are yet to be accounted for in projection studies.

In this Article, we aimed to use an extended pathogen-specific approach to undertake future projections of temperature-attributable mortality due to enteric infections. Our study is based on global mortality due to enteric infections from specific pathogens previously estimated by the Institute for Health Metrics and Evaluation-Global Burden of Diseases, Injuries, and Risk Factors Study (IHME-GBD).<sup>20</sup> We refined these estimates by considering the effects of temperature on enteric infection under future scenarios of climate change, sociodemographic development, and health investments. The additional dimensions considered in

our analysis could provide evidence underpinning the mitigation of greenhouse gas emissions at the global level and the promotion of adaptation strategies for health, particularly in LMICs.<sup>21</sup>

## Methods

### Study design

We projected global temperature-attributable mortality from enteric infections in two stages. First, we forecasted pathogen-specific mortality due to enteric infections according to sociodemographic and health drivers without considering temperature. Second, we estimated the temperature-attributable mortality per pathogen on the basis of projected temperature anomalies and pathogen-specific temperature sensitivities.

### Enteric infection mortality forecasting

We adopted Foreman and colleagues' method for forecasting pathogen-specific mortality using the socio-demographic index (SDI), trend, and scalar of risk factors.<sup>22</sup> A linear mixed model was used, with the SDI and trend as fixed effects, and the country, age, and pathogen as random effects:

$$\ln[E(D_{r,l,a,t})] = \alpha_{r,l,a} + \beta_0 SDI_{<0.8,l,t} + \beta_1 SDI_{\geq 0.8,l,t} + \theta_a t + \ln(S_{l,a,t})$$

where the logarithm of projected annual enteric infection mortality rate  $D$  is expressed as an additive relationship between the intercept  $\alpha$ , the  $SDI$  (as a piecewise-linear function with a cutoff value of 0·8), the year  $t$ , and a scalar of risk factors  $S$  (as an offset). The symbol  $r$  denotes the pathogen,  $l$  the country, and  $a$  the age group, and

$\beta_0$ ,  $\beta_1$ , and  $\theta$  denote the parameters of estimation. The model was fitted using data from 1990–2005 (appendix pp 3–4), and projections were generated for 2006–2100 (appendix pp 5–7).

We obtained the 1990–2005 pathogen-specific enteric infection mortality rates ( $D$ ) from the IHME-GBD, which we used as baseline values for  $D$ .<sup>23</sup> On the basis of existing evidence for their associations with ambient temperature, the following ten enteric pathogens were selected: non-typhoidal salmonella, *Shigella*, *Campylobacter*, cholera, enteropathogenic *E coli*, enterotoxigenic *E coli*, typhoid, rotavirus, norovirus, and *Cryptosporidium*.<sup>24</sup> The selected pathogens accounted for 85% of the overall enteric infections described in the IHME-GBD. The mortality rate data (expressed per 100 000 of population) were reported in five age groups and 179 countries. We grouped the countries by World Bank regions: sub-Saharan Africa, South Asia, East Asia and the Pacific, Latin America and the Caribbean, North America, Europe and Central Asia, and Middle East and North Africa.

The SDI was based on the gross domestic product per capita,<sup>25,26</sup> mean years of schooling per capita in the population aged 25 years and older, and total fertility rate per capita in the population aged 15–25 years,<sup>27,28</sup> which were projected according to shared socioeconomic pathways (SSPs) 1, 2, and 3 (appendix p 5). SSPs are scenarios that depict different narratives of future scenarios: SSP1 depicts a future of sustainability with low challenges in mitigation and adaptation; SSP2 is the middle of the road scenario, which generally follows historical trends; and SSP3 describes a divided and unstable future with high challenges in mitigation and adaptation.<sup>29</sup> Mitigation refers to actions related to reducing greenhouse gas emissions thereby limiting global warming and its related effects, while adaptation refers to adjustments in socioeconomic systems in response to expected effects of climate change.

The scalar of risk factors  $S$  was a combination of the non-pathogen-specific population-attributable fractions of unsafe sanitation, no access to handwashing facilities, underweight children, child wasting, child stunting, vitamin A deficiency, and zinc deficiency.<sup>30</sup> Projections of these scalars were based on the weighted annualised rate of change (AROC) by country and age group (appendix p 6).<sup>22</sup> Three scenarios were derived using pooled AROCs: (1) baseline health investment (BHI) was the reference AROC; (2) additional health investment (AHI) was based on the 85th percentile AROC; and (3) lowered health investment (LHI) was based on the 15th percentile AROC.<sup>22</sup> The AHI scenario depicts faster reductions of exposure to the risk factors, whereas the LHI scenario has slower reductions over time. The BHI scenario follows the historical trends of each country and age group. We paired the health investment scenarios according to the SSP narratives that they are aligned with.<sup>29</sup> The main scenario combinations were SSP1-AHI

(termed optimistic), SSP2-BHI (intermediate), and SSP3-LHI (pessimistic). We also ran all possible scenarios for comparison: SSP1-BHI, SSP2-AHI, SSP2-LHI, and SSP3-BHI. This process was to test the sensitivity of assuming different health investments under the same SSP scenario.

Mortality counts were quantified as 16-year means (1990–2005, 2020–35, 2050–65, and 2080–95) and are presented at global level and for each World Bank region. To derive alternative forecasts of baseline mortality rates, used in sensitivity analyses, we used the Mathers and Loncar model, which uses gross domestic product, mean years of schooling, and trend without any scalar of risk factors (appendix p 7).<sup>31</sup> We validated the models using the out-of-sample root mean squared error (appendix p 7).

#### Temperature-attributable enteric infection mortality estimation

We estimated the annual number of temperature-attributable enteric infection deaths from the baseline enteric infection mortality rates using the product of temperature anomalies and pathogen-specific temperature sensitivity as follows:<sup>15</sup>

$$\hat{d}_{r,l,t} = D_{r,l,a,t} \times P_{l,a,t} \times \frac{e^{\beta_r \times (T_{\text{projected}} - T_{\text{baseline}})} - 1}{\beta_r \times (T_{\text{projected}} - T_{\text{baseline}})}$$

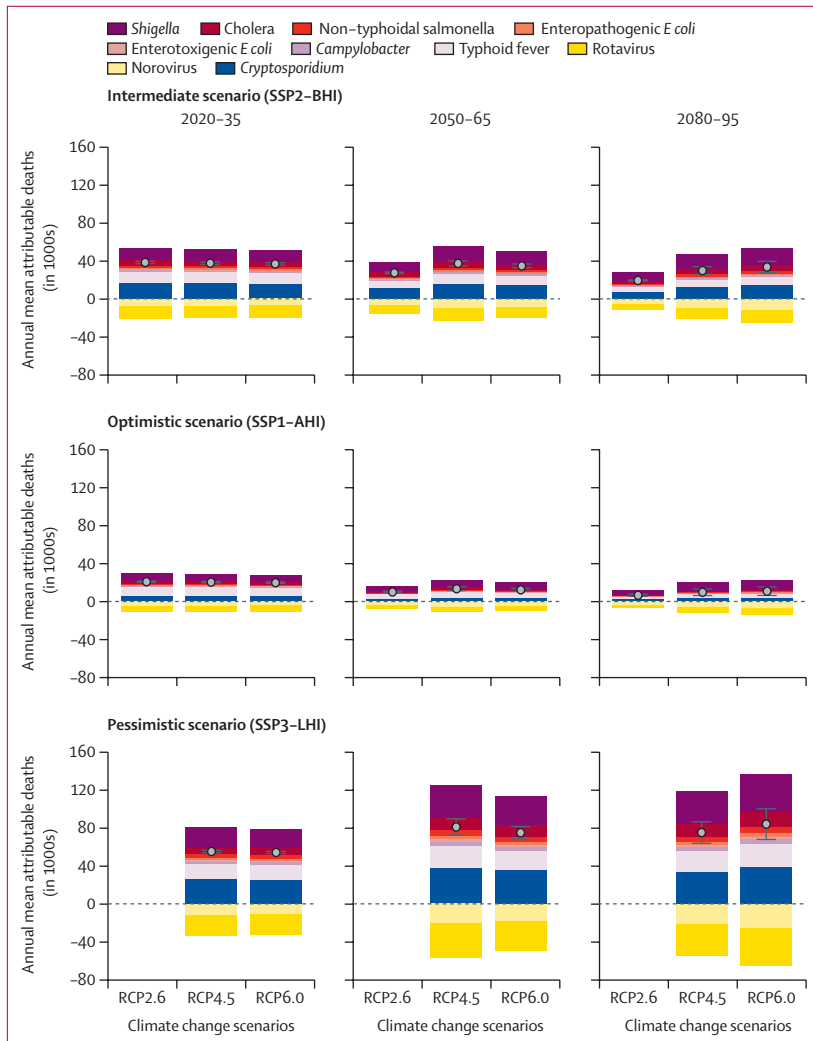
where  $d$  is the temperature-attributable enteric infection mortality,  $D$  is the baseline enteric infection mortality rates derived from the first stage,  $P$  is the population,  $\beta$  is the pathogen-specific mortality change per 1°C increase in temperature, and  $T$  is the annual mean temperature.

To convert the mortality rates into the numbers of deaths, we used population projections for SSPs 1, 2, and 3 from the Intersectoral Impact Model Inter-comparison Project 2b (ISIMIP2b),<sup>32</sup> which are related to the projections of several SDI components.<sup>27,33</sup> We assumed that the mortality rates applied to the whole country so we multiplied the rates with the population projection in the appropriate grid cells within each of the 179 country boundaries.

The  $\beta$  values were derived from a previous meta-analysis (appendix p 10).<sup>24</sup> We assumed that the short-term temperature-morbidity associations were applicable to annual-level mortality outcomes.<sup>15</sup>

The annual temperature anomaly was calculated by subtracting the mean near surface air temperature during 1976–2005 from the projected annual near surface air temperatures during 2006–99 with use of 0.5° × 0.5° grid cells. Near surface air temperature data were obtained from ISIMIP2b,<sup>32</sup> and they corresponded to the downscaled and bias-corrected Coupled Model Intercomparison Project phase 5 simulations from four global climate models (GCMs), namely GFDL-ESM2M, HadGEM2-ES, IPSL-CM5A-LR, and MIROC5.<sup>34</sup> They are modelled according to mitigation scenarios called representative concentration pathways (RCPs), which report radiative

See Online for appendix



**Figure 1: Global climate model-ensemble estimates of mean global temperature-attributable enteric infection deaths by pathogen and all-cause under various scenarios**  
 Filled circles indicate net change across all pathogens and whiskers show 95% empirical CIs. An additional figure with a varying y-axis range is shown in the appendix (p 35). *E coli*= *Escherichia coli*. SSP=shared socioeconomic pathway. BHI=baseline health investment. AHI=additional health investment. LHI=lowered health investment. RCP=representative concentration pathway.

For reproducible codes see <https://github.com/paulcarlos>

forcing in watt per square metre by 2100.<sup>35</sup> Since the pairings between RCPs and SSPs are based on the specific SSP narrative, which can theoretically produce the radiative forcing levels, we limited the analysis to only RCP2.6, 4.5, and 6.0. RCP2.6 represents high mitigation response, whereas RCP4.5 and 6.0 depict lesser mitigation and more reliance on non-renewable sources emitting more greenhouse gas emissions.

**Statistical analysis**

All RCPs were pairable with the optimistic (SSP1-AHI) and intermediate (SSP2-BHI) scenarios, whereas only RCPs 4.5 and 6.0 were paired with the pessimistic scenario (SSP3-LHI; appendix p 11).<sup>29</sup> We also ran all possible combinations of SSPs and health investment

scenarios for comparison. We presented the mean annual number of temperature-attributable enteric infection deaths by the selected 16-year periods (2020–35, 2050–65, and 2080–95).

We used a bootstrapping approach to account for the uncertainty related to different GCMs and  $\beta$  values. Specifically, we generated 1000 estimations of temperature-attributable enteric infection deaths per GCM, by drawing from the Gaussian distribution defined by the central  $\beta$  estimates and their SEs.<sup>36</sup> The 95% empirical CIs (eCIs) were determined from the 2.5th and 97.5th percentiles of the bootstrapped sample, pooling estimates across GCMs.

We also derived the temperature-attributable fractions by dividing the projected mean temperature-attributable deaths by the projected baseline mean deaths according to pathogen. The attributable fractions to temperature generally show the percentage change produced by the  $\beta$  values and temperature anomalies. To further explore the changes from the  $\beta$  values and temperature anomalies, we analysed no population change scenarios since the baseline year of 2005.

In addition to pathogen-specific results, we also derived attributable mortality estimates aggregated across taxa and across all pathogens (all-cause) using the pooled estimates of temperature sensitivity values from a 2020 meta-analysis.<sup>24</sup> This approach is to observe how different the pathogen-specific projections will be compared with simpler approaches of taxa-specific and all-cause.

All analyses were done using R programming, version 4.0.2.<sup>37</sup> We ran the model using lme4 package and derived the 95% eCIs with the fitdistrplus package.<sup>38,39</sup> Reproducible codes are available in the lead author’s GitHub and all outputs are available in the ISIMIP data archive.<sup>32</sup>

**Role of the funding source**

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

**Results**

We projected that across all scenarios the mean annual number of global deaths from enteric infections would decrease from the 1864 355 in 1990–2005 to 414871 under the intermediate scenario (SSP2-BHI), 196 296 under the optimistic scenario (SSP1-AHI), and 1051819 under the pessimistic scenario (SSP3-LHI) in 2080–95 (appendix pp 12–20). The change was greatest under the optimistic scenario and smallest under the pessimistic scenario. In terms of health investment scenarios, the number of deaths increased in LHI and decreased in AHI with BHI as a reference under all SSPs (appendix p 21). Rotaviral enteritis, shigellosis, and cryptosporidiosis were the three main pathogens predicted to contribute to the total number of global enteric infection deaths, accounting

for 60% of future enteric infection deaths in 2080–95 under the intermediate scenario. Non-typhoidal salmonellosis, enteropathogenic *E coli* enteritis, and enterotoxigenic *E coli* enteritis account for the three smallest proportions of enteric infection deaths over the years. Across all scenarios, the regions with the most deaths were sub-Saharan Africa and South Asia, whereas those with the lowest were Europe and Central Asia and North America.

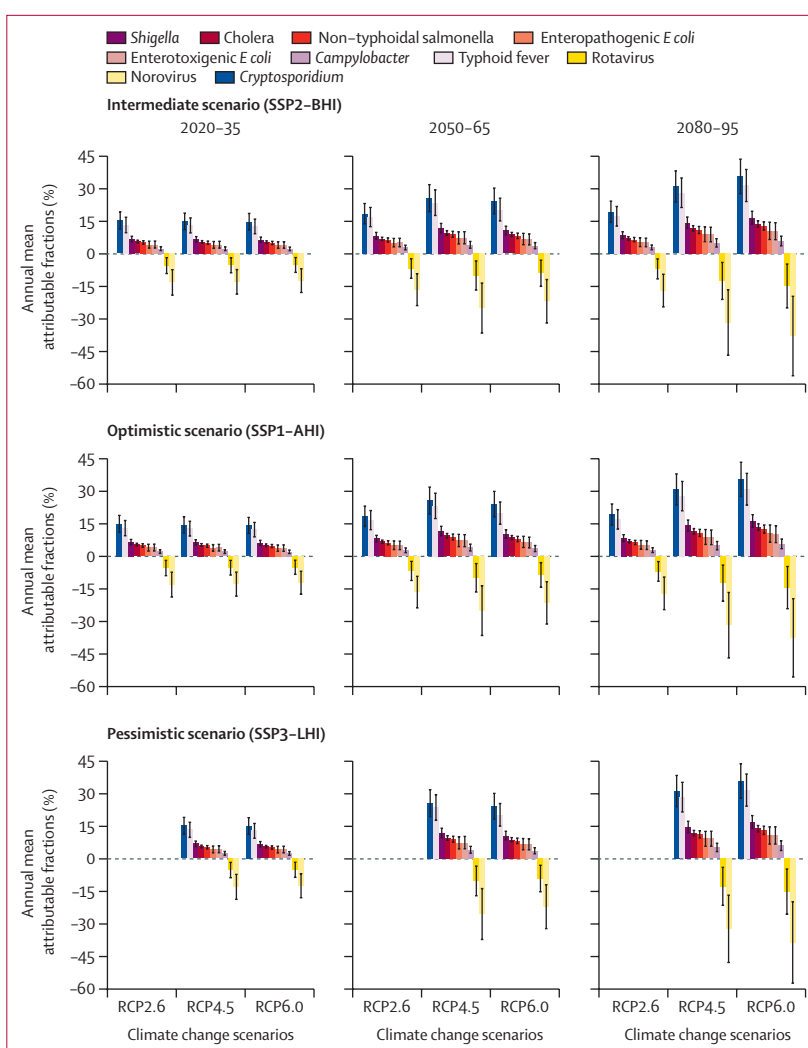
Mean annual global temperature anomalies were generally low in 2020–35. In 2050–65, the mean temperature anomalies were higher compared with 2020–35 and were highest under RCP4.5. By 2080–95, the mean temperature anomalies were increasing by radiative forcing at 1.85°C (range 1.10–2.45) under RCP2.6, at 3.04°C (1.84–4.17) under RCP4.5, and at 3.71°C (2.68–4.96) under RCP6.0. The Europe and Central Asia region was expected to have the largest positive temperature anomalies, whereas the smallest anomalies were expected in Latin America and the Caribbean (appendix p 22).

The mean number of global temperature-attributable deaths under the intermediate scenario is expected to decrease from 37 508 (95% eCI 36 266–38 751) in 2020–35 to 29 786 (25 666–33 906) in 2080–95 under RCP4.5 (figure 1, appendix pp 23–29). The temperature-attributable fractions, by contrast, will increase from 3.85% (95% eCI 3.72–3.98) in 2020–35 to 7.18% (6.19–8.17) in 2080–95 under RCP4.5 (figure 2). With no population change, the mean number of temperature-attributable deaths were generally lower with an estimated 15 694 deaths (95% eCI 14 744–16 644) under the intermediate scenario and RCP4.5 (appendix p 30).

Shigellosis, cryptosporidiosis, and typhoid were the pathogens with the most projected temperature-attributable excess deaths and temperature-attributable fractions. Under RCP4.5, in 2080–95, shigellosis will account for 15 978 (95% eCI 13 030–18 925), cryptosporidiosis for 12 955 (9935–15 976), and typhoid for 6897 (5217–8577) temperature-attributable enteric infection deaths. The least attributable deaths and fractions are expected from enteropathogenic *E coli* enteritis, enterotoxigenic *E coli* enteritis, and campylobacteriosis.

We observed reductions in the number of temperature-attributable deaths in 2080–95 of –11803 (95% eCI –3863 to –19743) for rotaviral enteritis and –9273 (–4871 to –13676) for noroviral enteritis under RCP4.5. The smallest temperature-attributable fractions were from noroviral enteritis. In general, the reductions showed a decreasing trend under RCP2.6 and an increasing trend under RCP6.0. Between 2080 and 2095, a higher number of temperature-attributable deaths and fractions can be expected as radiative forcing increases.

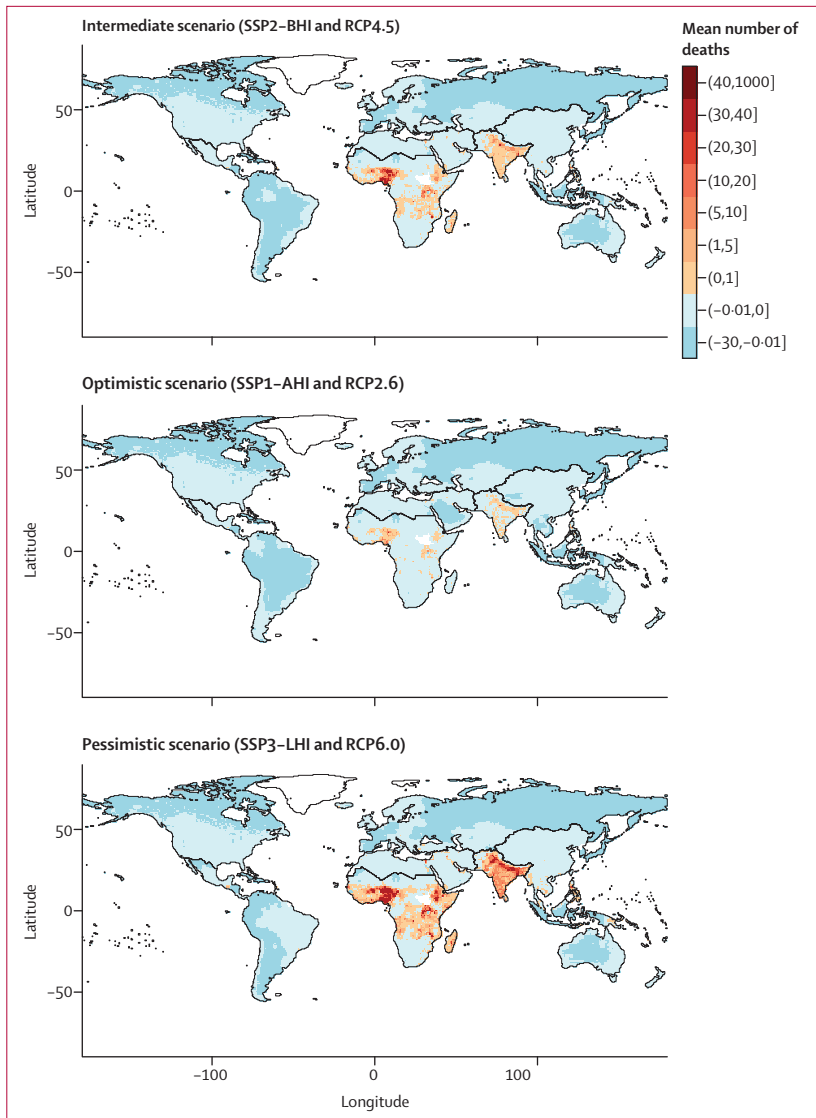
The number of temperature-attributable enteric infection deaths under the optimistic scenario was lower than that under the intermediate scenario, with the lowest estimates under RCP2.6 at 20 915 (95% eCI 20 157–21 674)



**Figure 2:** Global climate model-ensemble estimates of mean global temperature-attributable fractions of enteric infection deaths by pathogen under various scenarios

Whiskers show 95% empirical CIs. Alternate figures with a varying y-axis range are shown in the appendix (pp 36–38). *E coli*=*Escherichia coli*. SSP=shared socioeconomic pathway. BHI=baseline health investment. AHI=additional health investment. LHI=lowered health investment. RCP=representative concentration pathway.

in 2020–35, 10 023 (9178–10 867) in 2050–65, and 6599 (5441–7757) in 2080–95. This optimistic scenario also produces similar patterns for the pathogen composition under the intermediate scenario, with shigellosis contributing the most to excess deaths, and rotaviral enteritis having the largest reduction in temperature-attributable enteric infection deaths. Under the pessimistic scenario, more temperature-attributable enteric infection deaths are estimated than with the intermediate scenario. The pessimistic scenario also yields increasing numbers of temperature-attributable enteric infection deaths over time, unlike the optimistic and intermediate scenarios. The number of temperature-attributable enteric infection deaths were 54 081 (95% eCI 52 922–55 240) in 2020–35, 74 844 (68 409–81 280)



**Figure 3:** Global climate model-ensemble estimates of mean temperature-attributable enteric infection deaths under various scenarios in 2080–95 by 0.5° × 0.5° grids

*E. coli* = *Escherichia coli*. SSP=shared socioeconomic pathway. BHI=baseline health investment. AHI=additional health investment. LHI=lowered health investment. RCP=representative concentration pathway.

in 2050–2065, and 83 888 (67 760–100 015) in 2080–2095 under RCP6.0.

Most of the estimated global temperature-attributable deaths due to enteric infections are from the sub-Saharan Africa and South Asia regions (figure 3). Between 2080 and 2095, the mean number of temperature-attributable enteric infection deaths in sub-Saharan Africa could be as low as 4538 (95% eCI 4325–4751), as projected under the optimistic scenario and RCP2.6, or could be as high as 60 001 (52 224–67 778), as projected under the pessimistic scenario and RCP6.0. Under the intermediate scenario and RCP4.5, most temperature-attributable enteric infection deaths in sub-Saharan Africa in 2080–95 are projected to be from cryptosporidiosis (11 999

[95% eCI 9196–14 801]) and shigellosis (10 648 [8689–12 607]). The mean number of temperature-attributable enteric infection deaths in South Asia in 2080–95 is projected to be 1871 (95% eCI 1367–2375) under the optimistic scenario and RCP2.6 or 22 014 (16 861–27 168) under the pessimistic scenario and RCP6.0. Low numbers of temperature-attributable enteric infection deaths in 2080–95 were projected for the Europe and Central Asia and North America regions, especially under the optimistic scenario and RCP2.6 with 47 (95% eCI 21–73) for Europe and Central Asia and nine (1–19) for North America. The Middle East and North Africa was projected to have 1044 deaths (95% eCI 538–1551) under the pessimistic scenario and RCP6.0. Without population change, mean temperature-attributable deaths were lower than with population change especially in sub-Saharan Africa (appendix p 39).

Net reductions in the number of enteric infection deaths are projected in East Asia and the Pacific and Latin America and the Caribbean. East Asia and the Pacific showed reductions in 2080–95 under the optimistic scenario and RCP2.6 (–98 [95% eCI –630 to 433]) but not under the pessimistic scenario and RCP6.0 (949 [–903 to 2802]). Projections also suggested that Latin America and the Caribbean could see reductions in the number of enteric infection deaths in 2080–95 of up to –223 (95% eCI –961 to 514), as estimated under the pessimistic scenario and RCP6.0, or as little as –47 (–173 to 79), as estimated under the optimistic scenario and RCP2.6. The net reductions for both regions result from decreases in the numbers of rotaviral and noroviral enteritis deaths.

The estimated numbers of global temperature-attributable enteric infection deaths calculated by taxa-specific and all-cause temperature sensitivity are similar to the pathogen-specific estimates (figure 4). Under the intermediate scenario and RCP4.5, in 2080–95, the mean number of temperature-attributable enteric infection deaths estimated according to taxa-specific temperature sensitivity is 35 023 (95% eCI 32 572–37 474), and that estimated according to the all-cause approach is 31 391 (23 382–39 400), both of which are higher than the estimate based on the pathogen-specific approach. However, the region-specific estimates of temperature-attributable enteric infection death vary according to approach (appendix pp 40–46). The numbers of temperature-attributable enteric infection deaths derived using the Mathers and Loncar model were lower under SSP2 and SSP3, but were higher under SSP1 in comparison to those derived using Foreman and colleagues' model (appendix p 47).<sup>22</sup>

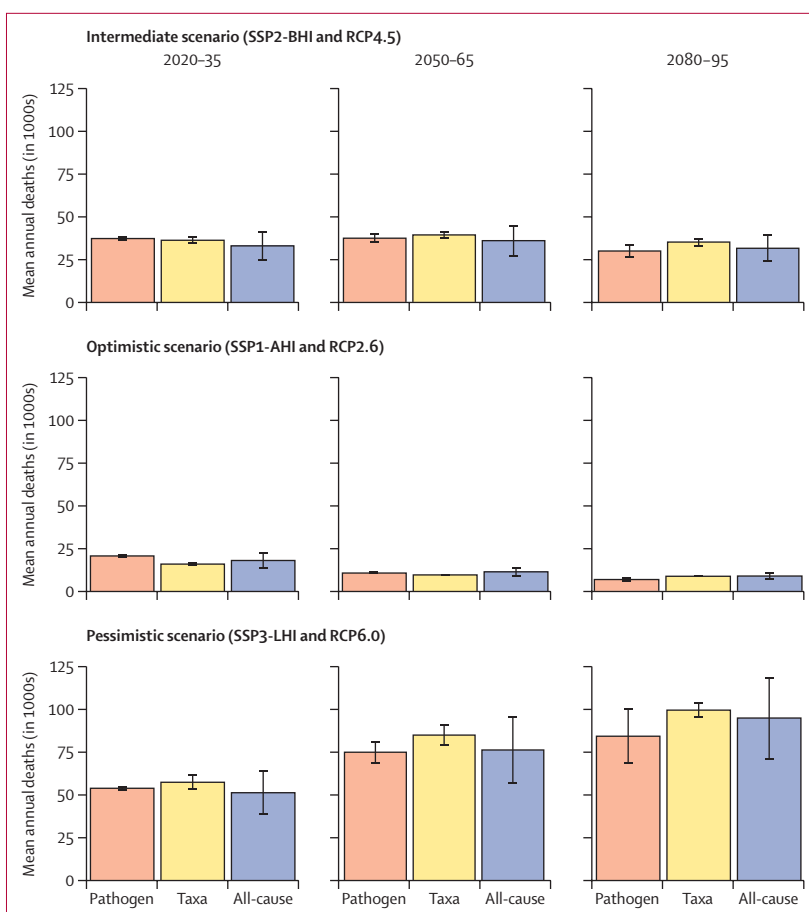
## Discussion

We estimated the global temperature-attributable mortality due to enteric infections under various sociodemographic and climate scenarios, up to 2099. For the first time to our knowledge, we considered the different effects of temperature on major enteric pathogens. Our findings

showed that the number of global temperature-related excess deaths due to enteric infections could increase under the pessimistic sociodemographic and health investment scenarios, despite considerable reductions in the number of deaths from viral pathogens. Conversely, fewer temperature-related excess deaths are predicted to occur under a future with optimistic sociodemographic growth and health investments. This result is consistent with the findings from previous global projections of diarrhoeal mortality in children in which poor socioeconomic growth was found to slow down the reductions.<sup>15</sup> We also found that a future with a warmer climate might have higher enteric infection mortality compared with a future in which there is less warming.<sup>40,41</sup>

Our projections suggest that temperature-related excess deaths will mainly be caused by *Shigella*, *Cryptosporidium*, and *Salmonella enterica* serovar Typhi. These enteropathogens are already a substantial burden in LMICs.<sup>42</sup> Shigellosis was estimated as the second leading cause and cryptosporidiosis was estimated as the fifth leading cause of diarrhoea mortality in 2016, which predominantly affects young children and older populations.<sup>43,44</sup> Similarly, typhoid fever was estimated to cause substantial mortality in young children in 2017.<sup>45</sup> These pathogens are generally transmitted person to person via the faecal–oral route.<sup>42</sup> The former two diseases are common causes of moderate to severe diarrhoea in young children, which can be fatal.<sup>46</sup> These pathogens are projected to cause excess deaths attributable to ambient temperature because their transmissions in the future could be exacerbated by warmer climate via extended bioavailability through environmental or animal reservoirs,<sup>13,47</sup> food spoilage,<sup>6,48</sup> or contaminated drinking water.<sup>2</sup> Sustaining the current approaches for water, sanitation, and hygiene as well as child nutrition, together with the possible development of vaccines, would help prevent infections and deaths from these pathogens.<sup>49,50</sup>

We projected that increasing global temperatures would lead to a reduction in deaths from rotavirus and norovirus. This finding diminished the overall attributable enteric infection deaths, especially in futures characterised by unfavourable sociodemographic development and warmer climate. In the Latin America and the Caribbean and East Asia and the Pacific regions, the reductions in the number of temperature-attributable enteric infection deaths from viral pathogens led to net reductions in the number of temperature-attributable enteric infection deaths from all-cause enteric infections. This result is in agreement with the findings of a projection study of infectious gastroenteritis done in Japan wherein net reductions were found to occur owing to a considerable decrease in cold-related morbidity, which might have been associated with viral pathogens.<sup>16</sup> Rotavirus is the leading cause of diarrhoea mortality in all age groups, but particularly in young children.<sup>20</sup> As with many enteropathogens, rotavirus and norovirus are primarily transmitted via the faecal–oral route or via



**Figure 4: Global climate model-ensemble estimates of global temperature-attributable enteric infection deaths by temperature-sensitivity approach**

Whiskers show 95% empirical CIs. SSP=shared socioeconomic pathway. BHI=baseline health investment. AHI=additional health investment. LHI=lowered health investment. RCP=representative concentration pathway.

contaminated food or water.<sup>42</sup> Unlike some bacteria, viral pathogens have lower survival in food, water, and other surfaces as the temperature increases,<sup>51,52</sup> explaining their future reductions in temperature-attributable deaths. However, reductions in the number of temperature-attributable deaths from rotavirus could be less important in futures with sustained rotavirus vaccination and the introduction of rotavirus vaccination to countries currently without, which could drastically reduce baseline mortality from rotavirus.<sup>22</sup>

Warmer temperatures might bring a more suitable environment for the growth and survival of some bacterial enteropathogens such as *Salmonella*, *Shigella*, *Campylobacter*, and *E coli*,<sup>53–56</sup> supporting the projected increase in deaths under futures with substantial warming. However, this is not the case for *Cryptosporidium*, which has reduced survival under warmer temperatures, especially beyond 15°C.<sup>57,58</sup> A possible explanation would be that milder winter temperatures could bring more suitable ambient temperatures for survival. Additionally, numerous pathways related to warmer temperatures can

explain the increase in *Cryptosporidium* cases. Ikiroma and Pollock suggested that changes in human activities such as swimming in untreated freshwater streams and lakes, increased demand for drinking water, and less conscientious hygiene might promote infections with *Cryptosporidium* during warmer temperatures.<sup>59</sup> Additionally, Lake and colleagues postulated that overflow from animal reservoirs might be responsible for the increased *Cryptosporidium* infections during early summer months.<sup>60</sup> The authors found associations between river flow and cryptosporidiosis during April to July, which might be explained by the release of large numbers of highly infectious newborn farm animals onto land from which their excrement could readily be washed into freshwater bodies.<sup>60,61</sup> Ultimately, the complex processes behind the biological, social, and environmental transmissions make the association for a specific pathway very difficult to pinpoint, not only for *Cryptosporidium* but for all enteropathogens.

The pathogen-specific approach showed that the regions of concern remain sub-Saharan Africa and South Asia, similar to the previous projection study.<sup>15</sup> Most of the global burden of enteric infections was still from these regions because there were more non-viral infections that were sensitive to temperature increases unlike the Latin America and the Caribbean or East Asia and the Pacific regions, which had more viral infections. Generally, a low number of deaths was found in other regions like the Middle East and North Africa, Europe and Central Asia, and North America. Results showing net reductions in some regions were not generated when all-cause or taxa-specific approaches in estimating temperature-attributable mortality were applied. The result could mean that this approach reveals smaller geographical locations that require more attention in terms of their medical management of enteric infections and other necessary means to control the transmission of enteropathogens.

This study has some major caveats. First, the pathogen-specific relative risks (RRs; mortality change per 1°C increase in temperature) that we used are subject to some assumptions and uncertainty. We assumed that daily or weekly temperature-enteric infection associations were applicable to annual-level mortality and that they remained constant over the years. However, the associations between annual temperature and annual mortality might be different and could change over time. We also assumed that a single RR per pathogen from the meta-analysis would capture the mean risk for all locations. This assumption might not be the case because various geographical areas have different physical characteristics like climate, urbanisation, population density, and altitude, among others that could affect pathogen distribution and transmission. It should also be noted that the pathogen-specific RRs derived from the studies found in a separate systematic review and meta-analysis had limitations.<sup>24</sup> For some of the pathogens like

typhoid, norovirus, and cryptosporidiosis, estimates were based on only a few studies. Moreover, the RR for shigellosis was derived mainly from studies in China, which might not be representative of other locations. Second, we were not able to incorporate the effect of vaccinations into the model. Vaccinations against rotavirus could further accelerate reductions in mortality from rotaviral enteritis, especially in countries where the rotavirus vaccine is not yet administered.<sup>62</sup> It is worth noting that this scenario could be captured to some extent in projections for sociodemographic development. Accelerated vaccination could change the proportions of pathogens that we assumed were constant. Third, although we accounted for uncertainties inherent in GCMs and RRs, we were not able to consider several other sources of uncertainty. These include uncertainties from the modelled pathogen-specific mortality data from IHME-GBD, the prediction of baseline mortality, and the projection of sociodemographic development and scalar of risk factors. Since we were not able to consider other sources of uncertainty, the projected estimates might have wider uncertainties than what were presented. Fourth, the projections of future scalar of risk factors for enteric infections were not based on SSPs. Modelling future scenarios of water, sanitation, and hygiene as well as nutrition within SSPs might help improve projections of health outcome and diseases like enteric infections. Lastly, given the empirical evidence currently available, we were only able to incorporate temperature as one pathway through which climate change might affect enteric infections. Humidity, rainfall, drought, flooding, and El Niño–Southern Oscillation affect the transmission of enteric infections but modelling them remains a challenge especially in large geographical areas. The results of this study should be interpreted as temperature-attributable mortality, which should be a part of the excess mortality due to climate change. Future projections of enteric infections should attempt to incorporate other factors.

In summary, shigellosis, cryptosporidiosis, and typhoid were projected to have the largest contributions to global temperature-attributable deaths due to enteric infections, outweighing projected reductions in the number of such deaths from viral pathogens. Net excess deaths due to enteric infections could increase under a future with a warmer climate and pessimistic sociodemographic development. It would be beneficial to support mitigation policies that limit global warming and to promote sociodemographic development for LMICs.

#### Contributors

PLCC and MH conceptualised the study. PLCC collected and processed the secondary data, ran the modelling, and drafted the manuscript. MH, VH, SH, and AW guided the methods, presentation of results, and discussion. CFSN, XTS, and LM guided the data analysis and R coding. PLCC, MH, and VH verified the projection outputs. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed and approved the manuscript.



**Declaration of interests**

We declare no competing interests.

**Data sharing**

The data inputs for mortality and scalar of risk factors, gross domestic product, education and fertility, and ambient temperature can be accessed online. The data outputs are freely accessible online or through the corresponding author.

**Acknowledgments**

We thank Kyle Foreman, Chun-Wei Yuan, and Simon Lloyd for giving ideas for the modelling approach. We also thank the ISIMIP health sector for their support. This work was supported by the Japan Society for the Promotion of Science grant-in-aid for scientific research (KAKENHI; grant number JP19H03900). PLCC is a recipient of the Japanese Government (Monbukagakusho) Scholarship from the Ministry of Education, Science, Sport, and Culture of Japan. VH received support from the Spanish Ministry of Economy, Industry and Competitiveness (grant number PCIN-2017-046). MH was supported by the Japan Science and Technology Agency as part of the Strategic International Collaborative Research Program (grant number JPMJSC20E4).

Editorial note: the *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

**References**

- Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health* 2012; **12**: 220.
- Levy K, Woster AP, Goldstein RS, Carlton EJ. Untangling the impacts of climate change on waterborne diseases: a systematic review of relationships between diarrheal diseases and temperature, rainfall, flooding, and drought. *Environ Sci Technol* 2016; **50**: 4905–22.
- Mellor J, Kumpel E, Ercumen A, Zimmerman J. Systems approach to climate, water, and diarrhea in Hubli-Dharwad, India. *Environ Sci Technol* 2016; **50**: 13042–51.
- Saha S, Halder M, Mookerjee S, Palit A. Seasonal influence, enteropathogenic microbial load and diarrhoeal enigma in the Gangetic Delta, India: present scenario and health implications. *J Infect Public Health* 2019; **12**: 540–48.
- Korajkic A, Wanjugi P, Brooks L, Cao Y, Harwood VJ. Persistence and decay of fecal microbiota in aquatic habitats. *Microbiol Mol Biol Rev* 2019; **83**: e00005-19.
- Tirado MC, Clarke R, Jaykus LA, McQuatters-Gollop A, Frank JM. Climate change and food safety: a review. *Food Res Int* 2010; **43**: 1745–65.
- Asadgol Z, Mohammadi H, Kermani M, Badirzadeh A, Gholami M. The effect of climate change on cholera disease: the road ahead using artificial neural network. *PLoS One* 2019; **14**: e0224813.
- Uyanik MH, Yazgi H, Ayyildiz A. Survival of *Salmonella typhi* and *Shigella flexneri* in different water samples and at different temperatures. *Turk J Med Sci* 2008; **38**: 307–10.
- Moors E, Singh T, Siderius C, Balakrishnan S, Mishra A. Climate change and waterborne diarrhoea in northern India: impacts and adaptation strategies. *Sci Total Environ* 2013; **468–69** (suppl): S139–51.
- Stanke C, Kerac M, Prudhomme C, Medlock J, Murray V. Health effects of drought: a systematic review of the evidence. *PLoS Curr* 2013; **5**: ecurrents.dis.7a2cee9e980f91ad7697b570bcc4b004.
- Besner MC, Prévost M, Regli S. Assessing the public health risk of microbial intrusion events in distribution systems: conceptual model, available data, and challenges. *Water Res* 2011; **45**: 961–79.
- Hunter PR, Zmirou-Navier D, Hartemann P. Estimating the impact on health of poor reliability of drinking water interventions in developing countries. *Sci Total Environ* 2009; **407**: 2621–24.
- Lal A, Hales S, French N, Baker MG. Seasonality in human zoonotic enteric diseases: a systematic review. *PLoS One* 2012; **7**: e31883.
- Patz JA, Githeko AK, McCarty JP, Hussein S, Confalonieri U, De Wet N. Climate change and infectious diseases. <https://www.who.int/globalchange/publications/climatechangechap6.pdf> (accessed June 14, 2021).
- Kovats S, Lloyd S. Diarrhoeal disease. In: Hales S, Kovats S, Lloyd S, Campbell-Lendrum D, eds. Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s. Geneva: World Health Organization, 2014: 37–50.
- Onozuka D, Gasparrini A, Sera F, Hashizume M, Honda Y. Modeling future projections of temperature-related excess morbidity due to infectious gastroenteritis under climate change conditions in Japan. *Environ Health Perspect* 2019; **127**: 77006.
- Levy K, Hubbard AE, Eisenberg JNS. Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis. *Int J Epidemiol* 2009; **38**: 1487–96.
- Jagai JS, Sarkar R, Castronovo D, et al. Seasonality of rotavirus in South Asia: a meta-analysis approach assessing associations with temperature, precipitation, and vegetation index. *PLoS One* 2012; **7**: e38168.
- Kotloff KL, Nasrin D, Blackwelder WC, et al. The incidence, aetiology, and adverse clinical consequences of less severe diarrhoeal episodes among infants and children residing in low-income and middle-income countries: a 12-month case-control study as a follow-on to the Global Enteric Multicenter Study (GEMS). *Lancet Glob Health* 2019; **7**: e568–84.
- Troeger C, Forouzanfar M, Rao PC, et al. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017; **17**: 909–48.
- Nissan H, Conway D. From advocacy to action: projecting the health impacts of climate change. *PLoS Med* 2018; **15**: e1002624.
- Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018; **392**: 2052–90.
- Institute for Health Metrics and Evaluation. Global Health Data Exchange. 2019. <http://ghdx.healthdata.org/gbd-results-tool> (accessed Jan 20, 2020).
- Chua PLC, Fook C, Ng S, Tobias A, Seposo XT, Hashizume M. Associations between ambient temperature and enteric infections by aetiology: a systematic review and meta-analysis. *SSRN* 2021; published online April 8. <http://dx.doi.org/10.2139/ssrn.3822570> (preprint).
- Dellink R, Chateau J, Lanzi E, Magné B. Long-term economic growth projections in the shared socioeconomic pathways. *Glob Environ Change* 2017; **42**: 200–14.
- International Institute for Applied Systems Analysis. SSP Database. Version 2. <https://tntcat.iiasa.ac.at/SspDb/dsd?Action=htmlpage&page=about#v2> (accessed Jan 20, 2020).
- Lutz W, Goujon A, KC S, Stonawski M, Stilianakis N. Demographic and human capital scenarios for the 21st century. 2018. <https://op.europa.eu/en/publication-detail/-/publication/e1853ba8-4444-11e8-a9f4-01aa75ed71a1/language-en> (accessed Jan 20, 2020).
- Wittgenstein Centre for Demography and Global Human Capital. Wittgenstein Centre Data Explorer Version 2.0 (Beta). 2018. <http://www.wittgensteincentre.org/dataexplorer> (accessed Jan 20, 2020).
- Riahi K, van Vuuren DP, Kriegler E, et al. The shared socioeconomic pathways and their energy, land use, and greenhouse gas emissions implications: an overview. *Glob Environ Change* 2017; **42**: 153–68.
- Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1923–94.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**: e442.
- ISIMIP. Inter-Sectoral Impact Model Intercomparison Project Database. 2019. <https://esg.pik-potsdam.de/search/isimip/> (accessed Jan 20, 2020).
- Samir KC, Lutz W. The human core of the shared socioeconomic pathways: population scenarios by age, sex and level of education for all countries to 2100. *Glob Environ Change* 2017; **42**: 181–92.
- Lange S. Earth2Observe, WFDEI and ERA-Interim data Merged and Bias-corrected for ISIMIP (EWEMBI). GFZ Data Serv. 2016. <https://doi.org/10.5880/pik.2016.004> (accessed Jan 20, 2020).

For mortality and scalar of risk factors see <http://ghdx.healthdata.org/gbd-results-tool>

For gross domestic product see <https://tntcat.iiasa.ac.at/SspDb/dsd?Action=htmlpage&page=10>

For education and fertility see <http://dataexplorer.wittgensteincentre.org/wcde-v2/>

For ambient temperature see <https://esg.pik-potsdam.de/search/isimip/>

For data outputs see <https://esg.pik-potsdam.de/search/isimip/>

- 35 van Vuuren DP, Edmonds J, Kainuma M, et al. The representative concentration pathways: an overview. *Clim Change* 2011; **109**: 5–31.
- 36 Wu J, Zhou Y, Gao Y, et al. Estimation and uncertainty analysis of impacts of future heat waves on mortality in the eastern United States. *Environ Health Perspect* 2014; **122**: 10–16.
- 37 R Core Team. R: a language and environment for statistical computing. 2020. <https://www.r-project.org/> (accessed Aug 11, 2020).
- 38 Bates D, Mächler M, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67**: 1.
- 39 Delignette-Muller ML, Dutang C. fitdistrplus: an R package for fitting distributions. *J Stat Softw* 2015; **64**: 4.
- 40 Gasparrini A, Guo Y, Sera F, et al. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet Health* 2017; **1**: e360–67.
- 41 Vicedo-Cabrera AM, Guo Y, Sera F, et al. Temperature-related mortality impacts under and beyond Paris Agreement climate change scenarios. *Clim Change* 2018; **150**: 391–402.
- 42 Kotloff KL. The burden and etiology of diarrheal illness in developing countries. *Pediatr Clin North Am* 2017; **64**: 799–814.
- 43 Khalil IA, Troeger C, Blacker BF, et al. Morbidity and mortality due to *Shigella* and enterotoxigenic *Escherichia coli* diarrhoea: the Global Burden of Disease Study 1990–2016. *Lancet Infect Dis* 2018; **18**: 1229–40.
- 44 Khalil IA, Troeger C, Rao PC, et al. Morbidity, mortality, and long-term consequences associated with diarrhoea from *Cryptosporidium* infection in children younger than 5 years: a meta-analysis study. *Lancet Glob Health* 2018; **6**: e758–68.
- 45 Stanaway JD, Reiner RC, Blacker BF, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2019; **19**: 369–81.
- 46 Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013; **382**: 209–22.
- 47 Kelly JJ, Minalt N, Culotti A, Pryor M, Packman A. Temporal variations in the abundance and composition of biofilm communities colonizing drinking water distribution pipes. *PLoS One* 2014; **9**: e98542.
- 48 Lake IR. Food-borne disease and climate change in the United Kingdom. *Environ Health* 2017; **16** (suppl 1): 117.
- 49 Hodges M, Belle JH, Carlton EJ, et al. Delays reducing waterborne and water-related infectious diseases in China under climate change. *Nat Clim Chang* 2014; **4**: 1109–15.
- 50 Riddle MS, Chen WH, Kirkwood CD, MacLennan CA. Update on vaccines for enteric pathogens. *Clin Microbiol Infect* 2018; **24**: 1039–45.
- 51 Kraay ANM, Brouwer AF, Lin N, Collender PA, Remais JV, Eisenberg JNS. Modeling environmentally mediated rotavirus transmission: the role of temperature and hydrologic factors. *Proc Natl Acad Sci USA* 2018; **115**: E2782–90.
- 52 Rzezutka A, Cook N. Survival of human enteric viruses in the environment and food. *FEMS Microbiol Rev* 2004; **28**: 441–53.
- 53 Bronikowski AM, Bennett AF, Lenski RE. Evolutionary adaptation to temperature. VIII. Effects of temperature on growth rate in natural isolates of *Escherichia coli* and *Salmonella enterica* from different thermal environments. *Evolution* 2001; **55**: 33–40.
- 54 Elgayar KE, El kholy IM, Abd Elmonem YM. Application of *Salmonella typhi*'s outer membrane (OMP) in diagnosis of typhoid. *Int J Curr Res* 2013; **5**: 2037–42.
- 55 Lampel KA, Sandlin R. Shigella. In: Encyclopedia of Food Sciences and Nutrition, 2nd edn. Oxford: Academic Press, 2003: 5261–68.
- 56 Duffy L, Dykes GA. Growth temperature of four *Campylobacter jejuni* strains influences their subsequent survival in food and water. *Lett Appl Microbiol* 2006; **43**: 596–601.
- 57 King BJ, Keegan AR, Monis PT, Saint CP. Environmental temperature controls *Cryptosporidium* oocyst metabolic rate and associated retention of infectivity. *Appl Environ Microbiol* 2005; **71**: 3848–57.
- 58 King BJ, Monis PT. Critical processes affecting *Cryptosporidium* oocyst survival in the environment. *Parasitology* 2007; **134**: 309–23.
- 59 Ikiroma IA, Pollock KG. Influence of weather and climate on cryptosporidiosis—a review. *Zoonoses Public Health* 2021; **68**: 285–98.
- 60 Lake IR, Bentham G, Kovats RS, Nichols GL. Effects of weather and river flow on cryptosporidiosis. *J Water Health* 2005; **3**: 469–74.
- 61 Lake IR, Pearce J, Savill M. The seasonality of human cryptosporidiosis in New Zealand. *Epidemiol Infect* 2008; **136**: 1383–87.
- 62 Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr* 2018; **172**: 958–65.