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Correspondence to: Dr Robert C Reiner Jr, Institute for Health Metrics and Evaluation, Department of Health Metrics Sciences, School of Medicine, University of Washington, Seattle, WA 98121, USA, bcreiner@uw.edu.

Local Burden of Disease Diarrhoea Collaborators

Robert C Reiner Jr, Kirsten E Wiens, Aniruddha Deshpande, Mathew M Baumann, Paulina A Lindstedt, Brigitte F Blacker, Christopher E Troeger, Lucas Earl, Sandra B Munro, Degu Abate, Hedayat Abbastabar, Foad Abd-Allah, Ahmed Abdelalim, Ibrahim Abdollahpour, Rizwan Suliankatchi Abdulkader, Getaneh Abebe, Kedir Hussein Abegaz, Lucas Guimarães Abreu, Michael R M Abrigo, Manfred Mario Kokou Accrombessi, Dilaram Acharya, Maryam Adabi, Oladimeji M Adebayo, Rufus Adesoji Adedoyin, Victor Adekanmbi, Olatunji O Adetokunboh, Davoud Adham, Beyene Meressa Adhena, Mohsen Afarideh, Keivan Ahmadi, Mehdi Ahmadi, Anwar E Ahmed, Muktar Beshir Ahmed, Rushdia Ahmed, Olufemi Ajumobi, Chalachew Genet Akal, Temesgen Yihunie Akalu, Ali S Akanda, Genet Melak Alamene, Turki M Alanzi, James R Albright, Jacqueline Elizabeth Alcalde Rabanal, Birhan Tamene Alemnew, Zewdie Aderaw Alemu, Beriwan Abdulqadir Ali, Muhammad Ali, Mehran Alijanzadeh, Vahid Alipour, Syed Mohamed Aljunied, Ali Almasi, Amir Almasi-Hashiani, Hesham M Al-Mekhlafi, Khalid Altirkawi, Nelson Alvis-Guzman, Nelson J Alvis-Zakzuk, Azmeraw T Amare, Saeed Amini, Arianna Maeve Loreche Amit, Catalina Liliana Andrei, Masresha Tessema Aneqago, Mina Anjomshoa, Fereshteh Ansari, Carl Abelardo T Antonio, Ernoiz Antriyandarti, Seth Christopher Yaw Appiah, Jalal Arabloo, Olatunde Aremu, Bahram Armoon, Krishna K Aryal, Afsaneh Arzani, Mohsen Asadi-Lari, Alebachew Fasil Ashagre, Hagos Tasew Atalay, Suleman Atique, Sachin R Atre, Marcel Ausloos, Leticia Avila-Burgos, Ashish Awasthi, Nefsu Awoke, Beatriz Paulina Ayala Quintanilla, Getinet Ayano, Martin Amogre Ayanore, Asnakew Achaw Ayele, Yared Asmare Aynalem, Samad Azari, Ebrahim Babaei, Alaa Badawi, Shankar M Bakkannavar, Senthilkumar Balakrishnan, Ayele Geleto Bali, Maciej Banach, Aleksandra Barac, Till Winfried Bärnighausen, Huda Basaleem, Quique Bassat, Mohsen Bayati, Neeraj Bedi, Masoud Behzadifar, Meysam Behzadifar, Yibeltal Alemu Bekele, Michelle L Bell, Derrick A Bennett, Dessalegn Ajema Berbada, Tina Beyranvand, Anusha Ganapati Bhat, Kritika Bhattacharyya, Suraj Bhattarai, Soumyadeep Bhauumik, Ali Bijani, Boris Bikbov, Raaj Kishore Biswas, Kassawmar Angaw Bogale, Somayeh Bohoulou, Oliver J Brady, Nicola Luigi Bragazzi, Andrey Nikolaevich Briko, Nikolay Ivanovich Briko, Sharath Burugina Nagaraja, Zahid A Butt, Ismael R Campos-Nonato, Julio Cesar Campuzano Rincon, Rosario Cárdenas, Félix Carvalho, Franz Castro, Collins Chansa, Pranab Chatterjee, Vijay Kumar Chattu, Bal Govind Chauhan, Ken Lee Chin, Devasahayam J Christopher, Dinh-Toi Chu, Rafael M Claro, Natalie M Cormier, Vera M Costa, Giovanni Damiani, Farah Daoud, Lalit Dandona, Rakhi Dandona, Amira Hamed Darwish, Ahmad Daryani, Jai K Das, Rajat Das Gupta, Tamirat Tesfaye Dasa, Claudio Alberto Davila, Nicole Davis Weaver, Dragos Virgil Davitoiu, Jan-Walter De Neve, Feleke Mekonnen Demeke, Asmamaw Bizuneh Demiss, Gebre Teklemariam Demoz, Edgar Denova-Gutiérrez, Kebede Deribe, Assefa Desalew, Getenet Ayalew Dessie, Samath Dhamminda Dharmaratne, Preeti Dhillon, Meghnath Dhimial, Govinda Prasad Dhungana, Daniel Diaz, Eric L Ding, Helen Derara Diro, Shirin Djalalinia, Huyen Phuc Do, David Teye Doku, Christiane Dolecek, Manisha Dubey, Eleonora Dubljanin, Bereket Duko Adema, Susanna J Dunachie, Andre R Durães, Senbagam Duraisamy, Andem Effiong, Aziz Eftekhari, Iman El Sayed, Maysaa El Sayed Zaki, Maha El Tantawi, Demelash Abewa Elemineh, Shaimaa I El-Jaafary, Hajer Elkout, Aisha Elsharkawy, Shymaa Enany, Aklilu Endalamaw, Daniel Adane Endalew, Sharareh Eskandarieh, Alireza Esteghamati, Arash Etemadi, Tamer H Farag, Emerito Jose A Faraon, Mohammad Fareed, Roghiyeh Faridnia, Andrea Farioli, Andre Faro, Hossein Farzam, Ali Akbar Fazaeli, Mehdi Fazlzadeh, Netsanet Fentahun, Seyed-Mohammad Fereshtehnejad, Eduarda Fernandes, Irina Filip, Florian Fischer, Masoud Foroutan, Joel Msafiri Francis, Richard Charles Franklin, Joseph Jon Frostad, Takeshi Fukumoto, Reta Tsegaye Gayesa, Kidane Tadesse Gebremariam, Ketema Bizuwork Gebremedhin, Gebreamlak Gebremedhn Gebremeskel, Getnet Azeze Gedefaw, Yilma Chisha Dea Geramo, Birhanu Geta, Kebede Embaye Gezae, Ahmad Ghashghae, Fariba Ghassemi, Paramjit Singh Gill, Ibrahim Abdelmageed Ginawi, Srinivas Goli, Nelson G M Gomes, Sameer Vali Gopalani, Bárbara Niegia Garcia Goulart, Ayman Grada, Harish Chander Gugnani, Davide Guido, Rafael Alves Guimarães, Yuming Guo, Rahul Gupta, Rajeev Gupta, Nima Hafezi-Nejad, Michael Tamene Hailu, Gesessew Bugssa Hailu, Arvin Haj-Mirzaian, Arya Haj-Mirzaian, Brian James Hall, Demelash Woldeyohannes Handiso, Hamidreza Haririan, Ninuk Hariyani, Ahmed I Hasaballah, Md. Mehedi Hasan, Amir Hasanzadeh, Hadi Hassankhani, Hamid Yimam Hassen, Desta Haftu Hayelom, Behnam Heidari, Nathaniel J Henry, Claudiu Herteliu, Fatemeh Heydarpour, Hagos D de Hidru, Chi Linh Hoang, Praveen Hoogar, Mojtaba Hoseini-Ghahfarokhi, Naznin Hossain, Mostafa Hosseini, Mehdi Hosseinzadeh, Mowafa Houssein, Guoqing Hu, Ayesha Humayun, Syed Ather Hussain, Segun Emmanuel Ibitoye, Olayinka Stephen Ilesanmi, Milena D Ilic, Leeberk Raja Inbaraj, Seyed Sina Naghibi Irvani, Sheikh Mohammed Shariful Islam, Chinwe Juliana Iwu, Anelisa Jaca, Nader Jafari Balalami, Nader Jahanmehr, Mihajlo Jakovljevic, Amir Jalali, Achala Upendra Jayatilleke, Ensiyeh Jenabi, Ravi Prakash Jha, Vivekanand Jha, John S Ji, Peng Jia, Kimberly B Johnson, Jost B Jonas, Jacek Jerzy Jó wiak, Ali Kabir, Zubair Kabir, Amaha Kahsay, Hamed Kalamani, Tanuj Kanchan, Behzad Karami Matin, André Karch, Surendra Karki, Amir Kasaeian, Gebremicheal Gebreslassie Kasahun, Gbenga A Kayode, Ali Kazemi Karyani, Peter Njenga Keiyor, Daniel Bekele Ketema, Yousef Saleh Khader, Morteza Abdullatif Khafaie, Nauman Khalid, Ali Talha Khalil, Ibrahim Khalil, Rovshan Khalilov, Md Nuruzzaman Khan, Ejaz Ahmad Khan, Gulfaraz Khan, Junaid Khan, Khaled Khatab, Amir Khater, Mona M Khater, Alireza Khatony, Maryam Khayamzadeh, Mohammad Khazaei, Salman Khazaei, Ehsan Khodamoradi, Mohammad Hossein Khosravi, Jagdish Khubchandani, Aliasghar A Kiadaliri, Yun Jin Kim, Ruth W Kimokoti, Adnan Kisa, Sezer Kisa, Niranjan Kisson, Shivakumar K M Kondlahalli, Margaret N Kosek, Ai Koyanagi, Moritz U G Kraemer, Kewal Krishan, Nuworza Kugbey, G Anil Kumar, Manasi Kumar, Pushpendra Kumar, Dian Kusuma, Carlo La Vecchia, Ben Lacey, Aparna Lal, Dharmesh Kumar Lal, Faris Hasan Lami, Van C Larsingh, Savita Lasrado, Paul H Lee, Mostafa Leili, Tsegay Lelaso Lenjebo, Aubrey J Levine, Sonia Lewycka, Shanshan Li, Shai Linn, Rakesh Lodha, Joshua Longbottom, Platon D Lopukhov, Sameh Magdeldin, Phetole Walter Mahasha, Narayan Bahadur Mahotra, Deborah Carvalho Malta, Abdullah A Mamun, Farzad Manafi, Navid Manafi, Ana-Laura Manda, Mohammad Ali Mansournia, Chabila Christopher Mapoma, Dadi Marami, Laurie B Marczak, Francisco Rogerlândia Martins-Melo, Winfried März, Anthony Masaka, Manu Raj Mathur, Pallab K Maulik, Benjamin K Mayala, Colm McAlinden, Man Mohan Mehndiratta, Ravi Mehrotra, Kala M Mehta, Gebrekiros Gebremichael Meles, Addisu Melese, Ziad A Memish, Alemayehu Toma Mena, Ritesh G Menezes, Melkamu Merid Mengesha, Desalegn Tadesse Mengistu, Getnet Mengistu, Tuomo J Meretoja, Bartosz Miazgowski, Kebabnew Mulatu M Mihretie, Molly K Miller-Petrie, Edward J Mills, Seyed Mostafa Mir, Parvaneh Mirabi, Erkin M Mirrakhimov, Amjad Mohammadi-Bolbanabad, Dara K Mohammad, Karzan Abdulmuhsin Mohammad, Yousef Mohammad, Aso Mohammad Darwesh, Naser Mohammad Gholi Mezerji, Noushin Mohammadifard, Ammas

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Siraj Mohammed, Jemal Abdu Mohammed, Shafiq Mohammed, Farnam Mohebi, Ali H Mokdad, Yohan Moodley, Ghobad Moradi, Mousavi, Miliya Mozaffar, Atalay Goshu Muluneh, Moses K Muriithi, Christopher J L Murray, GVS Murthy, Kamarul Imran Musa, Ghulam Mustafa, Saravanan Muthupandian, Mehdi Naderi, Ahmarshan Jayaraman Nagarajan, Mohsen Naghavi, Farid Najafi, Vinay Nangia, Javad Nazari, Duduzile Edith Ndwandwe, Ionut Negoii, Josephine W Ngunjiri, Cuong Tat Nguyen, QuynhAnh P Nguyen, Trang Huyen Nguyen, Dabere Nigatu, Dina Nur Anggraini Ningrum, Chukwudi A Nnaji, Marzieh Nojomi, Jean Jacques Noubiapi, In-Hwan Oh, Oluchi Okpala, Andrew T Olagunju, Ahmed Omar Bali, Obinna E Onwujekwe, Doris D V Ortega-Altamirano, Osayomwanbo Osarenotor, Frank B Osei, Mayowa Ojo Owolabi, Mahesh P A, Jagadish Rao Padubidri, Adrian Pana, Tahereh Pashaei, Sanghamitra Pati, Ajay Patle, George C Patton, Kebreab Paulos, Veincent Christian Filipino Pepito, Alexandre Pereira, Norberto Perico, Konrad Pesudovs, David M Pigott, Bakhtiar Piroozii, James A Platts-Mills, Mario Poljak, Maarten J Postma, Hadi Pourjafar, Farshad Pourmalek, Akram Pourshams, Hossein Poustchi, Sergio I Prada, Liliana Preotescu, Hedley Quintana, Mohammad Rabiee, Navid Rabiee, Amir Radfar, Alireza Rafiei, Fakher Rahim, Vafa Rahimi-Movaghar, Muhammad Aziz Rahman, Fatemeh Rajati, Kiana Ramezanzadeh, Saleem M Rana, Chhabi Lal Ranabhat, Davide Rasella, David Laith Rawaf, Salman Rawaf, Lal Rawal, Giuseppe Remuzzi, Vishnu Renjith, Andre M N Renzaho, Melese Abate Reta, Satar Rezaei, Ana Isabel Ribeiro, Jennifer Rickard, Carlos Miguel Rios González, Maria Jesus Rios-Blancas, Leonardo Roever, Luca Ronfani, Elias Merdassa Roro, Ali Rostami, Dietrich Rothenbacher, Enrico Rubagotti, Salvatore Rubino, Anas M Saad, Siamak Sabour, Ehsan Sadeghi, Saeed Safari, Mahdi Safdarian, Rajesh Sagar, Mohammad Ali Sahraian, S Mohammad Sajadi, Mohammad Reza Salahshoor, Nasir Salam, Farkhonde Salehi, Saleh Salehi Zahabi, Hosni Salem, Marwa R Rashad Salem, Yahya Salimi, Hamideh Salimzadeh, Evanson Zondani Sambala, Abdallah M Samy, Juan Sanabria, Itamar S Santos, Sivan Yegnanarayana Iyer Saraswathy, Abdur Razzaque Sarker, Benn Sartorius, Brijesh Sathian, Maheswar Satpathy, Alyssa N Sbarra, Lauren E Schaeffer, David C Schwebel, Anbissa Muleta Senbeta, Subramanian Senthilkumaran, Hosein Shabaninejad, Amira A Shaheen, Masood Ali Shaikh, Ali S Shalash, Seifadin Ahmed Shallo, Mehran Shams-Beyranvand, Mohammad Bagher Shamsi, Morteza Shamsizadeh, Mehdi Sharif, Muki Shehu Shey, Kenji Shibuya, Wondimeneh Shibabaw Shiferaw, Mika Shigematsu, Apurba Shil, Jae Il Shin, Rahman Shiri, Reza Shirkoohi, Si Si, Soraya Siabani, Jasvinder A Singh, Narinder Pal Singh, Dharendra Narain Sinha, Malede Mequanent Sisay, Eirini Skiadarezi, David L Smith, Mohammad Reza Sobhiyeh, Anton Sokhan, Moslem Soofi, Joan B Soriano, Muluken Bekele Sorrie, Ireneous N Soyiri, Chandrashekar T Sreeramareddy, Agus Sudaryanto, Mu'awiyah Babale Sufiyan, Hafiz Ansar Rasul Suleria, Bryan L Sykes, Koku Sisay Tamirat, Aberash Abay Tassew, Nuno Taveira, Bineyam Taye, Arash Tehrani-Banihashemi, Mohamad-Hani Temsah, Berhe Etsay Tesfay, Fisaha Haile Tesfay, Zemenu Tadesse Tessema, Kavumpurathu Raman Thankappan, Sathish Thirunavukkarasu, Nihal Thomas, Kenean Getaneh Tlaye, Boikhutso Tlou, Marcos Roberto Tovani-Palone, Eugenio Traini, Khanh Bao Tran, Indang Trihandini, Irfan Ullah, Bhaskaran Unnikrishnan, Sahel Valadan Tahbaz, Pascual R Valdez, Santosh Varughese, Yousef Veisani, Francesco S Violante, Sebastian Vollmer, Theo Vos, Fiseha Wadilo Wada, Yasir Waheed, Yafeng Wang, Yuan-Pang Wang, Girmay Teklay Welde Samuel, Catherine A Welgan, Ronny Westerman, Taweewat Wiangkham, Tissa Wijeratne, Charles Shey Wiysonge, Haileab Fekadu Wolde, Dawit Zewdu Wondafrash, Tewodros Eshete Wonde, Ai-Min Wu, Gelin Xu, Ali Yadollahpour, Seyed Hossein Yahyazadeh Jabbari, Tomohide Yamada, Mehdi Yaseri, Muluken Azage Yenesew, Alex Yeshaneh, Mekdes Tigistu Yilma, Ebrahim M Yimer, Paul Yip, Aberash Desalegn Yirsaw, Engida Yisma, Naohiro Yonemoto, Mustafa Z Younis, Hebat-Allah Salah A Yousof, Chuanhua Yu, Hasan Yusefzadeh, Mohammad Zamani, Carlos Zambrana-Torrel, Hamed Zandian, Ayalew Jejaw Zeleke, Nejimu Biza Zepro, Taye Abuhay Zewale, Dongyu Zhang, Yunquan Zhang, Xiu-Ju Zhao, Arash Ziapour, Sanjay Zodpey, and Simon I Hay.

Affiliations

Institute for Health Metrics and Evaluation (R C Reiner Jr PhD, K E Wiens PhD, A Deshpande MPH, M M Baumann BS, P A Lindstedt MPH, B Blacker MPH, C E Troeger MPH, L Earl, S B Munro PhD, J R Albright BS, N M Cormier MPSA, F Daoud BS, Prof L Dandona MD, Prof R Dandona PhD, N Davis Weaver MPH, S D Dharmaratne MD, T Farag PhD, J J Frostad MPH, N J Henry BS, K B Johnson MS, A J Levine MSPH, L B Marczak PhD, B K Mayala PhD, M K Miller-Petrie MSc, Prof A H Mokdad PhD, Prof C J L Murray DPhil, Prof M Naghavi MD, Q P Nguyen BS, D M Pigott DPhil, A N Sbarra MPH, L E Schaeffer MS, Prof D L Smith PhD, Prof T Vos PhD, C A Welgan BS, Prof S I Hay FMedSci), Department of Global Health (I Khalil MD), Department of Health Metrics Sciences, School of Medicine (R C Reiner Jr PhD, Prof L Dandona, Prof A H Mokdad PhD, Prof C J L Murray DPhil, Prof M Naghavi MD, D M Pigott DPhil, Prof B Sartorius PhD, Prof D L Smith PhD, Prof T Vos PhD, Prof S I Hay FMedSci), University of Washington, Seattle, WA, USA; College of Health and Medical Sciences (H D Diro BS), Department of Epidemiology and Biostatistics (M Mengesha MPH), Department of Medical Laboratory Sciences (D Abate MSc, S Balakrishnan PhD, D Marami MSc), School of Nursing and Midwifery (T T Dasa MSc, A Desalew MS), School of Pharmacy (A S Mohammed BA, G Mengistu MS), School of Public Health (A G Bali MPH), Haramaya University, Harar, Ethiopia (G A Gedefaw MS); Advanced Diagnostic and Interventional Radiology Research Center (H Abbastabar PhD), Cancer Biology Research Center (R Shirkoohi PhD), Cancer Research Institute (R Shirkoohi PhD), Department of Economics and Management Sciences for Health (M Moradi-Joo MS), Department of Environmental Health Engineering (M Fazlzadeh PhD), Department of Epidemiology and Biostatistics (M Hosseini PhD, M Mansournia PhD, M Yaseri PhD), Department of Health Management and Economics (S Mousavi PhD), Department of Microbiology (A Hasanazadeh PhD), Department of Pharmacology (A Haj-Mirzaian MD, A Haj-Mirzaian MD), Digestive Diseases Research Institute (Prof A Pourshams MD, H Poustchi PhD, H Salimzadeh PhD), Endocrinology and Metabolism Research Center (M Afarideh MD, Prof A Esteghamati MD, B Heidari MD), Hematology-Oncology and Stem Cell Transplantation Research Center (A Kasaeian PhD), Iran National Institute of Health Research (F Mohebi MD), Metabolomics and Genomics Research Center (F Rahim PhD), Multiple Sclerosis Research Center (S Eskandarieh PhD, Prof M Sahraian MD), Non-communicable Diseases Research Center (F Mohebi MD), Ophthalmology Department (F Ghassemi MD), School of Medicine (N Hafezi-Nejad MD), Sina Trauma and Surgery Research Center (Prof V Rahimi-Movaghar MD, M Safdarian MD), Tehran University of Medical Sciences, Tehran, Iran (A Etemadi PhD); Department of Medical Parasitology (M M Khater MD), Department of Neurology (Prof F Abd-Allah MD, Prof A Abdelalim MD, S I El-Jaafary MD), Endemic Medicine and Hepatogastroenterology Department (A Elsharkawy MD), Medical Parasitology Department, Faculty of Medicine (H S A Yousof MD), Public Health and Community Medicine Department (M R R Salem MD), Urology Department (Prof H Salem MD), Cairo University, Cairo, Egypt; Cardiovascular Research Institute (N Mohammadifard PhD), Neuroscience Research Center (I Abdollahpour PhD), Isfahan University of Medical Sciences, Isfahan, Iran; Department of Public Health (R S Abdulkader MD), Research Department Prince Mohammed Bin Abdulaziz Hospital (Prof Z A Memish MD), Ministry of Health, Riyadh, Saudi Arabia; Department of Epidemiology and Biostatistics (K A Bogale MPH, K M Mihretie MPH, T A

morbidity and mortality in low-income and middle-income

Zewale MS), Department of Medical Laboratory Sciences (G A Abebe MSc, C G Akal MS, F M Demekie MS, A Melese MSc), Department of Public Health Nutrition (N Fentahun PhD), Department of Reproductive Health and Population Studies (Y A Bekele MPH, D Nigatu MPH), School of Public Health (M A Yenesew PhD), Bahir Dar University, Bahir Dar, Ethiopia (A T Amare PhD, G A Gedefaw MS); Biostatistics and Health Informatics (K H Abegaz MPH), Public Health Department (D Handiso MPH), School of Health Sciences (G M Alamene BS), Madda Walabu University, Bale Robe, Ethiopia; Department of Microbial Cellular and Molecular Biology (F W Wada MS), Department of Microbiology, Immunology and Parasitology (B T Alemnew MS), Department of Nursing and Midwifery (K B Gebremedhin MSc), Department of Pharmacology (D Z Wondafrash MS), Department of Public Health (E M Roro MPH), Radiotherapy Center (K H Abegaz MPH), School of Allied Health Sciences (E Yisma MPH), School of Public Health (K Deribe PhD), Addis Ababa University, Addis Ababa, Ethiopia (B T Alemnew MS, G T Demoz MPharm); Department of Maternal and Child Nursing and Public Health (Prof D C Malta PhD), Department of Pediatric Dentistry (Prof L G Abreu PhD), Nutrition Department (Prof R M Claro PhD), Federal University of Minas Gerais, Belo Horizonte, Brazil; Research Department (M R M Abrigo PhD), Philippine Institute for Development Studies, Quezon City, Philippines; Bénin Clinical Research Institute (IRCB), Cotonou, Benin (M M K Accrombessi PhD); Department of Preventive Medicine (D Acharya MPH), Dongguk University, Gyeongju, South Korea; Department of Community Medicine (D Acharya MPH), Kathmandu University, Devdaha, Nepal; Autism Spectrum Disorders Research Center (E Jenabi PhD), Chronic Diseases (Home Care) Research Center (M Shamsizadeh MSc), Department of Biostatistics (N Mohammad Gholi Mezerji MSc), Department of Environmental Health Engineering (M Khazaei PhD, M Leili PhD), Department of Epidemiology (S Khazaei PhD), Social Determinants of Health Research Center (A Fazaeli PhD), Hamadan University of Medical Sciences, Hamadan, Iran (M Adabi PhD); Department of Medicine (O M Adebayo MD), University College Hospital, Ibadan, Nigeria; Department of Medical Rehabilitation (Prof R A Adedoyin PhD), Obafemi Awolowo University, Ile-Ife, Nigeria; School of Medicine (V Adekanmbi PhD), Cardiff University, Cardiff, UK; Centre for Evidence Based Health Care (A Jaca PhD), Department of Global Health (O O Adetokunboh MD, O Okpala PhD), Health Systems and Public Health (C J Iwu MS), Stellenbosch University, South Africa; Cochrane South Africa (C J Iwu MS, A Jaca PhD, P W Mahasha PhD, C A Nnaji MPH, D E Ndwandwe PhD, E Z Sambala PhD, Prof C S Wiysonge MD), South African Medical Research Council, Cape Town, South Africa; Department of Community Medicine (H Zandian PhD), Department of Environmental Health Engineering (M Fazlzadeh PhD), School of Health (D Adham PhD), Social Determinants of Health Research Center (H Zandian PhD), Ardabil University of Medical Science, Ardabil, Iran; Biomedical Sciences Division (G B Hailu MSc), Department of Biostatistics (K Gezae MSc), Department of Microbiology and Immunology (S Muthupandian PhD), Department of Nursing (G Gebremeskel MSc), Department of Nutrition and Dietetics (A Kahsay MPH), Department of Pharmacology and Toxicology (D Z Wondafrash MS), Department of Public Health (G G Meles), School of Medicine (D T Mengistu MSc), School of Pharmacy (E M Yimer MSc), School of Public Health (B M Adhena MPH, K T Gebremariam MS, N B Zepro MS), Mekelle University, Mekelle, Ethiopia (F H Tesfay MPH); Environmental Technologies Research Center (M Ahmadi PhD), Medical Physics Department (A Yadollahpour PhD), Social Determinants of Health Research Center (M A Khafaie PhD), Thalassemia and Hemoglobinopathy Research Center (F Rahim PhD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Lincoln Medical School (K Ahmadi PhD), Universities of Nottingham & Lincoln, Lincoln, UK; Faculty of Economics and Rural Development (A E Ahmed PhD), University of Gezira, Wad Madani, Sudan; Department of Epidemiology (M B Ahmed MPH), School of Nursing (A B Demis MS), Jimma University, Jimma, Ethiopia; James P Grant School of Public Health (R Ahmed MPH, R Das Gupta MPH), BRAC University, Dhaka, Bangladesh; Health Systems and Population Studies Division (R Ahmed MPH), International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; School of Community Health Sciences (O Ajumobi MPH), University of Nevada Reno, Reno, NV, USA; National Malaria Elimination Program (O Ajumobi MPH), Federal Ministry of Health, Abuja, Nigeria; Department of Clinical Chemistry (A F Ashagre MS), Department of Epidemiology and Biostatistics (T Y Akalu MPH, A G Muluneh MPH, M M Sisay MPH, K S Tamirat MPH, Z T Tessema MS, H F Wolde MPH), Department of Medical Parasitology (A J Zeleke MS), Institute of Public Health (A A Tassew MPH), University of Gondar, Gondar, Ethiopia (A A Ayele MSc, A Endalamaw MSc); Department of Civil and Environmental Engineering (A S Akanda PhD), University of Rhode Island, Kingston, RI, USA; Department of Health Information Management and Technology (T M Alanzi PhD), Forensic Medicine Division (Prof R G Menezes MD), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; Center for Health Systems Research (L Avila-Burgos PhD, D D V Ortega-Altamirano DrPH, M Rios-Blancas MPH), Center for Nutrition and Health Research (E Denova-Gutiérrez DSc), Centre of Health System (J E Alcalde Rabanal PhD), National Institute of Public Health, Cuernavaca, Mexico (I R Campos-Nonato PhD, J Campuzano Rincon PhD); College of Health Sciences (B T Alemnew MS), Department of Medical Laboratory Science (M A Reta MS), Department of Nursing (A B Demis MS, K G Tlaye MS), Woldia University, Woldia, Ethiopia; Department of Nursing (G A Dessie MSc), Department of Public Health (D B Ketema MPH, T E Wonde MPH), Department of Statistics (D A Elemineh MS), Debre Markos University, Debre Markos, Ethiopia (Z A Alemu MPH); Medical Technical Institute (B A Ali PhD), Erbil Polytechnic University, Erbil, Iraq; Faculty of Pharmacy (B A Ali PhD), Ishik University, Erbil, Iraq; Department of Biotechnology (M Ali PhD), Qaid-i-Azam University Islamabad, Islamabad, Pakistan; Social Determinants of Health Research Center (M Alijanzadeh PhD), Qazvin University of Medical Sciences, Qazvin, Iran; Department of Community and Family Medicine (Prof M Nojomi MD, A Tehrani-Banihashemi PhD), Department of Epidemiology (M Asadi-Lari PhD), Department of Health Policy (H Shabaninejad PhD), Department of Health Services Management (A Ghashghaee BSc), Department of Neuroscience (M Safdarian MD), Department of Neurosurgery (M Khosravi MD), Health Economics Department (V Alipour PhD), Health Management and Economics Research Center (V Alipour PhD, J Arabloo PhD, S Azari PhD), Minimally Invasive Surgery Research Center (A Kabir MD), Ophthalmology Department (N Manafi MD), Pars Advanced and Minimally Invasive Medical Manners Research Center (A Kasaeian PhD), Preventive Medicine and Public Health Research Center (E Babae PhD, M Moradi-Lakeh MD, Prof M Nojomi MD, A Tehrani-Banihashemi PhD), Iran University of Medical Sciences, Tehran, Iran (T Beyranvand PhD); Department of Health Policy and Management (Prof S M Aljunid PhD), Kuwait University, Safat, Kuwait; International Centre for Casemix and Clinical Coding (Prof S M Aljunid PhD), National University of Malaysia, Bandar Tun Razak, Malaysia; Clinical Research Development Center (A Khatony PhD, M Naderi MS), Department of Anatomical Sciences (M R Salahshoor PhD), Department of Environmental Health Engineering (Prof A Almasi PhD), Department of Epidemiology & Biostatistics (Prof F Najafi PhD, Y Salimi PhD), Department of Health Education & Promotion (S Siabani PhD, A Ziapour PhD), Department of Psychiatry (A Jalali PhD), Department of Public Health (A Kazemi Karyani PhD), Department of Radiology and Nuclear Medicine (M Hoseini-Ghahfarokhi PhD, E Khodamoradi PhD, S Salehi Zahabi PhD), Department of Sports Medicine & Rehabilitation (M Shamsi PhD), Department of Vascular & Endovascular Surgery (M Sobhyeh MD), Medical Biology Research

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Center (F Heydari PhD), Research Center for Environmental Determinants of Health (Prof B Karami Matin PhD, A Kazemi Karyani PhD, M Moradi PhD, F Rajati PhD, S Rezaei PhD, Prof E Sadeghi PhD), Social Development and Health Promotion Research Center (A Khatony PhD, Y Salimi PhD, M Soofi PhD), Taleghani Hospital (F Salehi MA), Kermanshah University of Medical Sciences, Kermanshah, Iran (H Farzam MD, M Moradi PhD, M Sobhiyeh MD); Department of Epidemiology (A Almasi-Hashiani PhD), Department of Pediatrics (J Nazari PhD), Health Services Management Department (S Amini PhD), Arak University of Medical Sciences, Arak, Iran; Medical Research Center (H M Al-Mekhlafi PhD), Jazan University, Jazan, Saudi Arabia (Prof N Bedi MD); Department of Medical Parasitology (H M Al-Mekhlafi PhD), Sana'a University, Sana'a, Yemen; Department of Pediatrics (M Tamsah MD), Internal Medicine Department (Y Mohammad MD), King Saud University, Riyadh, Saudi Arabia (K Altirkawi MD); Research Group in Health Economics (Prof N Alvis-Guzman PhD), University of Cartagena, Cartagena, Colombia; Research Group in Hospital Management and Health Policies (Prof N Alvis-Guzman PhD), University of the Coast, Barranquilla, Colombia; Departamento de Ciencias Económicas (N J Alvis-Zakzuk MS), Universidad de la Costa, Barranquilla, Colombia; Observatorio Nacional de Salud (N J Alvis-Zakzuk MS), National Institute of Health, Bogotá, D.C., Colombia; Sansom Institute (A T Amare PhD), South Australian Health and Medical Research Institute, Adelaide, SA, Australia; Department of Epidemiology and Biostatistics (A L Amit BS), Department of Health Policy and Administration (C A T Antonio MD, E A Faraon MD), Medical Informatics Unit (E A Faraon MD), University of the Philippines Manila, Manila, Philippines; Center for Clinical Global Health Education (S R Atre PhD), Department of International Health (M N Kosek MD), Department of Radiology and Radiological Sciences (N Hafezi-Nejad MD, A Haj-Mirzaian MD), Online Programs for Applied Learning (A L Amit BS), Johns Hopkins University, Baltimore, MD, USA; Department of Infectious Diseases (L Preotescu PhD), Department of General Surgery (D V Davitoiu PhD, I Negoii PhD), Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (C Andrei PhD); Division of Human Nutrition and Health (M T Anegago PharmD), Wageningen University & Research, Wageningen, Netherlands; Nutrition & Food Science Research Directorate (M T Anegago PharmD), Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Social Determinants of Health Research Center (M Anjomshoa PhD), Rafsanjan University of Medical Sciences, Rafsanjan, Iran; Department of Pharmacology and Toxicology (A Eftekhari PhD), Research Center for Evidence Based Medicine-Health Management and Safety Promotion Research Institute (F Ansari PhD), School of Nursing and Midwifery (H Hassankhani PhD), Tabriz University of Medical Sciences, Tabriz, Iran (H Haririan PhD); Ravi Vaccine and Serum Research Institute (F Ansari PhD), Agricultural Research, Education and Extension Organization (AREEO), Tehran, Iran; Department of Applied Social Sciences (C A T Antonio MD), School of Nursing (P H Lee PhD), Hong Kong Polytechnic University, Hong Kong, China; Agribusiness Study Program (E Antriyandarti PhD), Universitas Sebelas Maret, Surakarta, Indonesia; Department of Sociology and Social Work (S Appiah Mphil), Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; Center for International Health (S Appiah Mphil), Ludwig Maximilians University, Munich, Germany; School of Health Sciences (O Aremu PhD), Birmingham City University, Birmingham, UK; School of Nursing and Midwifery (B Armoon PhD), Social Determinants of Health Research Center (B Armoon PhD), Saveh University of Medical Sciences, Saveh, Iran; Monitoring Evaluation and Operational Research Project (K K Aryal PhD), Abt Associates Nepal, Lalitpur, Nepal; Department of Clinical Biochemistry (S Mir MSc, A Mospour PhD), Fatemeh Zahra Infertility and Reproductive Health Center (P Mirabi PhD), Infectious Diseases and Tropical Medicine Research Center (A Rostami PhD), Nursing and Midwifery School (A Arzani DrPH), Social Determinants of Health Research Center (A Bijani PhD), Student Research Committee (M Zamani MD), Babol University of Medical Sciences, Babol, Iran (A Arzani DrPH, S Mouodi MD); Development of Research and Technology Center (S Djalalinia PhD), International Relations Department (M Asadi-Lari PhD), Ministry of Health and Medical Education, Tehran, Iran; Department of Nursing (H T Atalay MS, G Gebremeskel MSc, G T Weldesamuel MS), School of Pharmacy (G T Demoz MPharm, G G Kasahun MS), Aksum University, Aksum, Ethiopia; Department of Family and Community Medicine (Prof I A Ginawi MD), Department of Health Informatics (S Atique PhD), University of Ha'il, Ha'il, Saudi Arabia; Dr D Y Patil Medical College (S R Atre PhD), Dr D Y Patil University, Pune, India; School of Business (Prof M Ausloos PhD), University of Leicester, Leicester, UK; Department of Statistics and Econometrics (Prof M Ausloos PhD, Prof C Herteliu PhD, A Pana MD), Bucharest University of Economic Studies, Bucharest, Romania; Indian Institute of Public Health (A Awasthi PhD, Prof S Zodey PhD), Indian Institute of Public Health, Gurugram, India (D K Lal MD, M R Mathur PhD); Department of Medicine (F W Wada MS), Department of Midwifery (K Paulos MS), Department of Nursing (N Awoke MS), School of Public Health (T L Lenjebo MPH), Wolaita Sodo University, Wolaita Sodo, Ethiopia; The Judith Lumley Centre (B Ayala Quintanilla PhD), La Trobe University, Melbourne, VIC, Australia; General Office for Research and Technological Transfer (B Ayala Quintanilla PhD), Peruvian National Institute of Health, Lima, Peru; School of Public Health (G Ayano MS), Curtin University, Perth, WA, Australia (B Duko Adema MPH); Department of Family and Community Health (N Kugbey PhD), Department of Health Policy Planning and Management (M A Ayanore PhD), University of Health and Allied Sciences, Ho, Ghana; School of Health (A A Ayele MSc), University of New England, Armidale, NSW, Australia; Department of Nursing (Y A Aynalem MSc, W S Shiferaw MS), Debre Berhan University, Debre Berhan, Ethiopia; Public Health Risk Sciences Division (A Badawi PhD), Public Health Agency of Canada, Toronto, ON, Canada; Department of Medicine (V Chattu MD), Department of Nutritional Sciences (A Badawi PhD), Joint Centre for Bioethics (F Manafi MD), University of Toronto, Toronto, ON, Canada; Department of Forensic Medicine (S M Bakkannavar MD, J Padubidri MD), Transdisciplinary Centre for Qualitative Methods (P Hoogar PhD), Manipal Academy of Higher Education, Manipal, India; Department of Hypertension (Prof M Banach PhD), Medical University of Lodz, Lodz, Poland; Polish Mothers' Memorial Hospital Research Institute, Lodz, Poland (Prof M Banach PhD); Clinic for Infectious and Tropical Diseases (A Barac PhD), Clinical Center of Serbia, Belgrade, Serbia; Faculty of Medicine (A Barac PhD, E Dubljanin PhD), University of Belgrade, Belgrade, Serbia; Department of Ophthalmology (Prof J B Jonas MD), Heidelberg Institute of Global Health (HIGH) (Prof T W Bärnighausen MD, C Chansa MPH, Prof J De Neve MD, S Mohammed PhD), Medical Clinic V (Nephrology, Hypertensiology, Endocrinology, Diabetology, Rheumatology) (Prof W März MD), Heidelberg University, Heidelberg, Germany; Department of Genetics (A Pereira PhD), Department of Global Health and Population (Prof S Vollmer PhD), Department of Nutrition (E L Ding DSc), Medical School (M U G Kraemer PhD), T.H. Chan School of Public Health (Prof T W Bärnighausen MD), Harvard University, Boston, MA, USA; University of Aden, Aden, Yemen (H Basaleem PhD); Barcelona Institute for Global Health (Prof Q Bassat MD), University of Barcelona, Barcelona, Spain; Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain (Prof Q Bassat MD, A Koyanagi MD); Health Human Resources Research Center (M Bayati PhD), Shiraz University of Medical Sciences, Shiraz, Iran; Department of Community Medicine (Prof N Bedi MD), Gandhi Medical College Bhopal, Bhopal, India; Department of Epidemiology and Biostatistics (M Behzadifar MSc), Social Determinants of Health Research Center (M Behzadifar PhD), Lorestan University of Medical Sciences, Khorramabad, Iran; School of Forestry and

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Environmental Studies (Prof M L Bell PhD), Yale University, New Haven, CT, USA; Centre for Tropical Medicine and Global Health (C Dolecek MD, S J Dunachie PhD, S Lewycka PhD), Department of Zoology (M U G Kraemer PhD), Nuffield Department of Population Health (D A Bennett PhD, B Lacey DPhil), University of Oxford, Oxford, UK (Prof V Jha MD); Department of Public Health (D A Berhada MPH, Y C D Geramo MS, D H Hayelom MPH, M B Sorrie MPH), Arba Minch University, Arba Minch, Ethiopia; Internal Medicine (A G Bhat MD), University of Massachusetts Medical School, Springfield, MA, USA; Department of Statistical and Computational Genomics (K Bhattacharyya MSc), National Institute of Biomedical Genomics, Kalyani, India; Department of Statistics (K Bhattacharyya MSc), University of Calcutta, Kolkata, India; Department of Global Health (S Bhattacharai MD), Global Institute for Interdisciplinary Studies, Nepal; Research Department (P K Maulik PhD), The George Institute for Global Health, New Delhi, India (S Bhaumik MBBS, Prof V Jha MD); Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Ranica, Italy (B Bikbov MD, N Perico MD, Prof G Remuzzi MD); School of Medicine (P K Maulik PhD), School of Optometry and Vision Science (Prof K Pesudovs PhD), School of Public Health and Community Medicine (S Karki PhD), Transport and Road Safety (TARS) Research Center (R Biswas MS), University of New South Wales, Sydney, NSW, Australia; School of Health Sciences (R Biswas MS), Swinburne University of Technology, Melbourne, VIC, Australia; Department of Basic Sciences (Prof M Sharif PhD), Department of Computer Engineering (M Hosseinzadeh PhD), Department of Laboratory Sciences (Prof M Sharif PhD), Department of Microbiology (S Valadan Tahbaz PhD), Department of Veterinary Medicine (S Bohlouli PhD), Islamic Azad University, Kermanshah, Iran; Department of Infectious Disease Epidemiology (O J Brady PhD), Faculty of Infectious and Tropical Diseases (Prof B Sartorius PhD), London School of Hygiene & Tropical Medicine, London, UK; University of Genoa, Genoa, Italy (N L Bragazzi PhD); Department of Biomedical Technologies (A N Briko MSc), Bauman Moscow State Technical University, Moscow, Russia; Department of Epidemiology and Evidence Based Medicine (Prof N I Briko DSc, P D Lopukhov Cand Of Sci [Med]), I M Sechenov First Moscow State Medical University, Moscow, Russia; Department of Community Medicine (S Burugina Nagaraja MD), Employees' State Insurance Model Hospital, Bangalore, India; School of Public Health and Health Systems (Z A Butt PhD), University of Waterloo, Waterloo, ON, Canada; Al Shifa School of Public Health (Z A Butt PhD), Al Shifa Trust Eye Hospital, Rawalpindi, Pakistan; School of Medicine (J Campuzano Rincon PhD), University of the Valley of Cuernavaca, Cuernavaca, Mexico; Department of Population and Health (Prof R Cárdenas DSc), Metropolitan Autonomous University, Mexico City, Mexico; Department of Chemistry (N G M Gomes PhD), EPIUnit - Public Health Institute University Porto (ISPUP) (A Ribeiro PhD), REQUIMTE/LAQV (Prof E Fernandes PhD), Research Unit on Applied Molecular Biosciences (UCIBIO) (Prof F Carvalho PhD, Prof V M Costa PharmD), University of Porto, Porto, Portugal; Gorgas Memorial Institute for Health Studies, Panama City, Panama (F Castro MD, H Quintana PhD); Health, Nutrition and Population Global Practice (C Chansa MPH), World Bank, Lusaka, Zambia; Division of Epidemiology (P Chatterjee MD), National Institute of Cholera and Enteric Diseases, Kolkata, India; Population Research Centre (B Chauhan MPhil), Gokhale Institute of Politics and Economics, Pune, India; Department of Mathematical Demography & Statistics (P Dhillion PhD), Department of Population Studies (A Patle MPH, J Khan MPhil), International Institute for Population Sciences, Mumbai, India (B Chauhan MPhil, S Goli PhD, P Kumar PhD); Department of Epidemiology and Preventive Medicine (K L Chin PhD), School of Public Health and Preventive Medicine (Prof Y Guo PhD, S Li PhD, S Si PhD), Monash University, Melbourne, VIC, Australia; Department of Endocrinology (N Thomas), Department of Pulmonary Medicine (Prof D J Christopher MD), Christian Medical College and Hospital (CMC), Vellore, India (Prof S Varughese MD); Faculty of Biology (D Chu PhD), Hanoi National University of Education, Hanoi, Vietnam; Department of Dermatology (G Damiani MD), Department of Nutrition and Preventive Medicine (Prof J Sanabria MD), Case Western Reserve University, Cleveland, OH, USA; Clinical Medicine and Community Health (Prof C La Vecchia MD), Department of Dermatology (G Damiani MD), University of Milan, Milan, Italy; Public Health Foundation of India, Gurugram, India (Prof L Dandona, Prof R Dandona, G A Kumar PhD); Indian Council of Medical Research, New Delhi, India (Prof L Dandona); Department of Pediatrics (A H Darwish MD), Tanta University, Tanta, Egypt; Department of Immunology (Prof A Rafiei PhD), Department of Medicinal Parasitology (Prof R Faridnia PhD); Molecular and Cell Biology Research Center (Prof A Rafiei PhD), Toxoplasmosis Research Center (Prof A Daryani PhD), Mazandaran University of Medical Sciences, Sari, Iran; Division of Women and Child Health (J K Das MD), Aga Khan University, Karachi, Pakistan; Department of Epidemiology and Biostatistics, Arnold School of Public Health (R Das Gupta MPH), University of South Carolina, Columbia, SC, USA; Population and Development (C A Davila PhD), Facultad Latinoamericana de Ciencias Sociales Mexico, Mexico City, Mexico; Department of Surgery (D V Davitov PhD), Clinical Emergency Hospital Sf. Pantelimon, Bucharest, Romania; Department of Global Health and Infection (K Deribe PhD), Brighton and Sussex Medical School, Brighton, UK; Department of Community Medicine (S D Dharmaratne MD), University of Peradeniya, Peradeniya, Sri Lanka; Health Research Section (M Dhimal PhD), Nepal Health Research Council, Kathmandu, Nepal; Department of Microbiology (G P Dhungana MSc), Far Western University, Mahendranagar, Nepal; Center of Complexity Sciences (Prof D Diaz PhD), National Autonomous University of Mexico, Mexico City, Mexico; Facultad de Medicina Veterinaria y Zootecnia (Prof D Diaz PhD), Autonomous University of Sinaloa, Culiacan Rosales, Mexico; Center of Excellence in Behavioral Medicine (H P Do PhD, C L Hoang BMedSc, T H Nguyen BMedSc), Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam; Department of Population Health (D T Doku PhD), University of Cape Coast, Cape Coast, Ghana; Faculty of Social Sciences, Health Sciences (D T Doku PhD), University of Tampere, Tampere, Finland; Mahidol-Oxford Tropical Medicine Research Unit (C Dolecek MD, S J Dunachie PhD), Mahidol University, Bangkok, Thailand; World Food Programme, New Delhi, India (M Dubey PhD); Public Health (B Duko Adema MPH), Hawassa University, Hawassa, Ethiopia; Institute of Public Health (Prof D Rasella PhD), School of Medicine (Prof A R Durães PhD), Federal University of Bahia, Salvador, Brazil; Medicina Interna (Prof A R Durães PhD), Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil; Department of Marine Biotechnology (S Duraisamy PhD), Bharathidasan University, Tiruchirappalli, India; Clinical Epidemiology and Biostatistics (A Effiong MB), Department of Public Health (M N Khan MSc), University of Newcastle, Newcastle, NSW, Australia; Department of Microbiology (A Hasanzadeh PhD), Department of Nutrition and Food Sciences (H Poujafar PhD), Department of Pharmacology and Toxicology (A Eftekhari PhD), Department of Public Health (H Pourjafar PhD), Maragheh University of Medical Sciences, Maragheh, Iran; Biomedical Informatics and Medical Statistics (I El Sayed PhD), Pediatric Dentistry and Dental Public Health Department (Prof M El Tantawi PhD), Alexandria University, Alexandria, Egypt; Department of Clinical Pathology (Prof M El Sayed Zaki PhD), Mansoura University, Mansoura, Egypt; Department of Community Medicine (H Elkout PhD), Tripoli University, Tripoli, Libya; World Health Organization (WHO), Tripoli, Libya (H Elkout PhD); Department of Microbiology and Immunology (S Enany PhD), Department of Physiology (Prof S Magdeldin PhD), Suez Canal University, Ismailia, Egypt; Department of Midwifery (D A Endalew MS), Wolkite University, Wolkite, Ethiopia (A Yeshaneh BHLthSci); Division of Cancer Epidemiology and Genetics (A Etemadi PhD),

Local Burden of Disease Diarrhoea Collaborators*

National Cancer Institute, Bethesda, MD, USA; College of Medicine (M Fareed PhD), Department of Pathology (N Salam PhD), Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia; Department of Medical and Surgical Sciences (A Farioli PhD, Prof F S Violante MD), University of Bologna, Bologna, Italy; Department of Psychology (Prof A Faro PhD), Federal University of Sergipe, São Cristóvão, Brazil; Department of Medicine (D K Mohammad PhD), Department of Neurobiology (S Fereshtehnejad PhD), Karolinska Institutet, Stockholm, Sweden; Division of Neurology (S Fereshtehnejad PhD), University of Ottawa, Ottawa, ON, Canada; Psychiatry Department (I Filip MD), Kaiser Permanente, Fontana, CA, USA; College of Graduate Health Sciences (A Radfar MD), School of Health Sciences (I Filip MD), AT Still University, Mesa, AZ, USA; Department of Population Medicine and Health Services Research (F Fischer PhD), Bielefeld University, Bielefeld, Germany; Abadan Faculty of Medical Sciences (M Foroutan PhD), Abadan School of Medical Sciences, Abadan, Iran; Department of Family Medicine and Primary Care (J M Francis PhD), University of the Witwatersrand, Johannesburg, South Africa; College of Public Health, Medical and Veterinary Science (R C Franklin PhD), James Cook University, Douglas, QLD, Australia; Department of Dermatology (T Fukumoto PhD), Kobe University, Kobe, Japan; Gene Expression & Regulation Program (T Fukumoto PhD), The Wistar Institute, Philadelphia, PA, USA; Department of Public Health (M T Yilma MPH), Nursing Department (R T Gayesa MS), Public Health Department (E M Roro MPH), Wollega University, Nekemte, Ethiopia; Department of Pharmacy (B Geta MS, G Mengistu MS), Wollo University, Dessie, Ethiopia; Unit of Academic Primary Care (Prof P S Gill DM), University of Warwick, Coventry, UK; Center for the Study of Regional Development (S Goli PhD), Jawahar Lal Nehru University, New Delhi, India; Department of Biostatistics and Epidemiology (S V Gopalani MPH), University of Oklahoma, Oklahoma City, OK, USA; Department of Health and Social Affairs (S V Gopalani MPH), Government of the Federated States of Micronesia, Palikir, Federated States of Micronesia; Postgraduate Program in Epidemiology (Prof B N G Goulart DSc), Federal University of Rio Grande do Sul, Porto Alegre, Brazil; Department of Dermatology (A Grada MD), Boston University, Boston, MA, USA; Department of Epidemiology (Prof H C Gugnani PhD), Department of Microbiology (Prof H C Gugnani PhD), Saint James School of Medicine, The Valley, Anguilla; Epidemiology Unit (D Guido PhD), Agency for Health Protection, Milano, Italy; Instituto de Patologia Tropical e Saúde Pública (R A Guimarães MS), Federal University of Goiás, Goiânia, Brazil; Department of Epidemiology and Biostatistics (Prof Y Guo PhD), Zhengzhou University, Zhengzhou, China; March of Dimes, Arlington, VA, USA (Prof R Gupta MD); School of Public Health (Prof R Gupta MD), West Virginia University, Morgantown, WV, USA; Academics and Research Department (Prof R Gupta MD), Rajasthan University of Health Sciences, Jaipur, India; Department of Medicine (Prof R Gupta MD), Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, India; Department of Nursing (M T Haile MS), St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia; Cancer Research Center (M Khayamzadeh MD), Department of Epidemiology (S Sabour PhD), Department of Pharmacology (K Ramezanzadeh PharmD), Emergency Department (S Safari MD), Obesity Research Center (A Haj-Mirzaian MD), Ophthalmic Research Center (M Yaseri PhD), Research Institute for Endocrine Sciences (S N Irvani MD), Safety Promotion and Injury Prevention Research Center (N Jahanmehr PhD), School of Management and Medical Education (N Jahanmehr PhD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; Global and Community Mental Health Research Group (B J Hall PhD), University of Macau, Macao, China; Department of Dental Public Health (N Hariyani PhD), Universitas Airlangga Indonesia, Surabaya, Indonesia; Australian Research Centre for Population Oral Health (N Hariyani PhD), University of Adelaide, Adelaide, SA, Australia; Department of Zoology (A I Hasaballah PhD), Al-Azhar University, Cairo, Egypt; Institute for Social Science Research (M Hasan MPH, A A Mamun PhD), The University of Queensland, Indooroopilly, QLD, Australia; Independent Consultant, Tabriz, Iran (H Hassankhani PhD); Department of Public Health (H Y Hassen MPH), Mizan-Tepi University, Teppi, Ethiopia; Unit of Epidemiology and Social Medicine (H Y Hassen MPH), University Hospital Antwerp, Wilrijk, Belgium; Department of Biostatistics and Epidemiology (H D de Hídra MPH), Department of Public Health (B E Tesfay MPH), Adigrat University, Adigrat, Ethiopia; Department of Pharmacology and Therapeutics (N Hossain MPH), Dhaka Medical College, Dhaka, Bangladesh; Department of Pharmacology (N Hossain MPH), Bangladesh Industrial Gases Limited, Tangail, Bangladesh; Computer Science Department (M Hosseinzadeh PhD), Department of Information Technology (A Mohammad Darwesh PhD), Diplomacy and Public Relations Department (A Omar Bali PhD), University of Human Development, Sulaymaniyah, Iraq; Division of Information and Computing Technology, College of Science and Engineering (Prof M Househ PhD), Hamad Bin Khalifa University, Doha, Qatar; Qatar Foundation for Education, Science, and Community Development, Doha, Qatar (Prof M Househ PhD); Department of Epidemiology and Health Statistics (Prof G Hu PhD), Central South University, Changsha, China; Department of Public Health and Community Medicine (Prof A Humayun PhD), Shaikh Khalifa Bin Zayed Al-Nahyan Medical and Dental College, Lahore, Pakistan; Dow Medical College (S A Hussain MD), Dow University of Health Sciences, Karachi, Pakistan; Department of Community Medicine (O S Ilesanmi PhD), Department of Health Promotion and Education (S E Ibitoye MPH), Institute for Advanced Medical Research and Training (Prof M O Owolabi DrM), University of Ibadan, Ibadan, Nigeria; Department of Epidemiology (Prof M D Ilic PhD), University of Kragujevac, Kragujevac, Serbia; Department of Family Medicine (L R Inbaraj MD), Bangalore Baptist Hospital, Bangalore, India; Institute for Physical Activity and Nutrition (S Islam PhD), National Centre for Farmer Health (M Rahman PhD), Deakin University, Burwood, VIC, Australia; Sydney Medical School (S Islam PhD), University of Sydney, Sydney, NSW, Australia; Department of Psychosis (N Jafari Balalami PhD), Babol Noshirvani University of Technology, Babol, Iran; Department for Health Care and Public Health (Prof M Jakovljevic PhD), Sechenov First Moscow State Medical University, Moscow, Russia; Faculty of Graduate Studies (A U Jayatilleke PhD), Institute of Medicine (A U Jayatilleke PhD), University of Colombo, Colombo, Sri Lanka; Department of Community Medicine (R P Jha MSc), Banaras Hindu University, Varanasi, India; Environmental Research Center (J S Ji DSc), Duke Kunshan University, Kunshan, China; Nicholas School of the Environment (J S Ji DSc), Duke University, Durham; Department of Earth Observation Science (P Jia PhD), Faculty of Geoinformation Science and Earth Observation (F B Osei PhD), University of Twente, Enschede, Netherlands; Beijing Ophthalmology & Visual Science Key (Prof J B Jonas MD), Beijing Tongren Hospital, Beijing, China; Department of Family Medicine and Public Health (J J Jó viak PhD), University of Opole, Opole, Poland; School of Public Health (Z Kabir PhD), University College Cork, Cork, UK; Infectious Diseases Research Center (H Kalani PhD), Golestan University of Medical Sciences, Gorgan, Iran (S Mir MSc); Department of Forensic Medicine and Toxicology (T Kanchan MD), Department of Paediatrics (Prof R Lodha MD), Department of Psychiatry (Prof R Sagar MD), All India Institute of Medical Sciences, Jodhpur, India; Institute for Epidemiology and Social Medicine (A Karch MD), University of Münster, Münster, Germany; Research and Development Team (S Karki PhD), Australian Red Cross Blood Service, Sydney, NSW, Australia; International Research Center of Excellence (G A Kayode PhD), Institute of Human Virology Nigeria, Abuja, Nigeria; Julius Centre for Health Sciences and Primary Care (G A Kayode PhD), Utrecht University, Utrecht, Netherlands; Department of Psychiatry (M Kumar PhD), Open, Distance and eLearning Campus (Prof P

Summary

N Keiyoro PhD), School of Economics (M K Muriithi PhD), University of Nairobi, Nairobi, Kenya; Department of Public Health (Prof Y S Khader PhD), Jordan University of Science and Technology, Irbid, Jordan; School of Food and Agricultural Sciences (N Khalid PhD), University of Management and Technology, Lahore, Pakistan; Department of Biotechnology (A Khalil PhD), Qarshi University, Lahore, Pakistan; Department of Physiology (R Khalilov PhD), Baku State University, Baku, Azerbaijan; Epidemiology and Biostatistics Department (E A Khan MPH), Health Services Academy, Islamabad, Pakistan; Department of Medical Microbiology & Immunology (Prof G Khan PhD), United Arab Emirates University, Al Ain, United Arab Emirates; Department of Population Sciences (M N Khan MSc), Jatiya Kabi Kazi Nazrul Islam University, Mymensingh, Bangladesh; Faculty of Health and Wellbeing (K Khatab PhD), Sheffield Hallam University, Sheffield, UK, Sheffield, UK; College of Arts and Sciences (K Khatab PhD), Ohio University, Zanesville, OH, USA; Internal Medicine and Gastroenterology Department (A Khater MD), National Hepatology and Tropical Research Institute, Cairo, Egypt; Academy of Medical Science, Tehran, Iran (M Khayamzadeh MD); Department of Nutrition and Health Science (Prof J Khubchandani PhD), Ball State University, Muncie, IN, USA; Clinical Epidemiology Unit (A A Kiadaliri PhD), Lund University, Lund, Sweden; School of Medicine (Y Kim PhD), Xiamen University Malaysia, Sepang, Malaysia; Department of Nutrition (R W Kimokoti MD), Simmons University, Boston, MA, USA; School of Health Sciences (Prof A Kisa PhD), Kristiania University College, Oslo, Norway; Department of Nursing and Health Promotion (S Kisa PhD), Oslo Metropolitan University, Oslo, Norway; Department of Pediatrics (Prof N Kisson MD), School of Population and Public Health (F Pourmalek PhD), University of British Columbia, Vancouver, BC, Canada; Public Health Dentistry, School of Dental Sciences (Prof S K M Kondlahalli MDS), Deemed University, Karad, India; Investigaciones Biomedicas (M N Kosek MD), Asociación Benéfica PRISMA, Iquitos, Peru; CIBERSAM (A Koyanagi MD), San Juan de Dios Sanitary Park, Sant Boi de Llobregat, Spain; Department of Anthropology (K Krishan PhD), Panjab University, Chandigarh, India; Department of Psychology and Health Promotion (N Kugbey PhD), Department of Public Health Medicine (Y Moodley PhD), Discipline of Public Health Medicine (B Tlou DrPH), University of KwaZulu-Natal, Durban, South Africa; Department of Epidemiology and Public Health (M R Mathur PhD), Division of Psychology and Language Sciences (M Kumar PhD), University College London, London, UK; Department of Primary Care and Public Health (Prof S Rawaf MD), Imperial College Business School (D Kusuma DSc), WHO Collaborating Centre for Public Health Education and Training (D L Rawaf MD), Imperial College London, London, UK; Faculty of Public Health (D Kusuma DSc, Prof I Trihandani PhD), University of Indonesia, Depok, Indonesia; National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford, UK (B Lacey DPhil); National Centre for Epidemiology and Population Health (A Lal PhD), Australian National University, Canberra, ACT, Australia; Department of Community and Family Medicine (F H Lami PhD), University of Baghdad, Baghdad, Iraq; HelpMeSee, New York, NY, USA (Prof V C Lansingh PhD); International Relations (Prof V C Lansingh PhD), Mexican Institute of Ophthalmology, Queretaro, Mexico; Department of Otorhinolaryngology (ENT) (S Lasrado MS), Father Muller Medical College, Mangalore, India; Oxford University Clinical Research Unit (S Lewycka PhD), Wellcome Trust Asia Programme, Hanoi, Vietnam; School of Public Health (Prof S Linn DrPH), University of Haifa, Haifa, Israel; Department of Vector Biology (J Longbottom MS), Liverpool School of Tropical Medicine, Liverpool, UK; Proteomics and Metabolomics Unit (Prof S Magdeldin PhD), Children's Cancer Hospital Egypt, Cairo, Egypt; Institute of Medicine (N B Mahotra MD), Tribhuvan University, Kathmandu, Nepal; Ophthalmology Department (N Manafi MD), University of Manitoba, Winnipeg, MB, Canada; Surgery Department (A Manda MD), Emergency University Hospital Bucharest, Bucharest, Romania; Department of Population Studies (C Mapoma PhD), University of Zambia, Lusaka, Zambia; Campus Caucaia (F R Martins-Melo PhD), Federal Institute of Education, Science and Technology of Ceará, Caucaia, Brazil; Clinical Institute of Medical and Chemical Laboratory Diagnostics (Prof W März MD), Medical University of Graz, Graz, Austria; Public Health Department (A Masaka MPH), Botho University-Botswana, Gaborone, Botswana; ICF International (B K Mayala PhD), ICF International, Rockville, MD, USA; Department of Ophthalmology (C McAlinden PhD, E Skiadaresi MD), Hywel Dda University Health Board, Carmarthen, UK; Neurology Department (Prof M Mehndiratta MD), Janakpuri Super Specialty Hospital Society, New Delhi, India; Department of Neurology (Prof M Mehndiratta MD), Govind Ballabh Institute of Medical Education and Research, New Delhi, India; Division of Preventive Oncology (Prof R Mehrotra PhD), National Institute of Cancer Prevention and Research, Noida, India; Department of Epidemiology and Biostatistics (K M Mehta DSc), University of California San Francisco, San Francisco, CA, USA; College of Medicine (Prof Z A Memish MD, M Tamsah MD), Alfaisal University, Riyadh, Saudi Arabia; Department of Pharmacology (A T Mena PhD), ACS Medical College and Hospital, Hawassa, Ethiopia; Breast Surgery Unit (T J Meretoja MD), Helsinki University Hospital, Helsinki, Finland; University of Helsinki, Helsinki, Finland (T J Meretoja MD); Center for Innovation in Medical Education (B Miazgowski MD), Pomeranian Medical University, Szczecin, Poland (B Miazgowski MD); Department of Health Research Methods, Evidence and Impact (E J Mills PhD), Department of Psychiatry and Behavioural Neurosciences (A T Olagunju MD), McMaster University, Hamilton, ON, Canada; Faculty of Internal Medicine (Prof E M Mirrakhimov MD), Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan; Department of Atherosclerosis and Coronary Heart Disease (Prof E M Mirrakhimov MD), National Center of Cardiology and Internal Disease, Bishkek, Kyrgyzstan; Department of Epidemiology and Biostatistics (G Moradi PhD), Environmental Health Research Center, Research Institute for Health Development (T Pashaei PhD), Social Determinants of Health Research Center (A Mohamadi-Bolbanabad PhD, G Moradi PhD, B Pirooz PhD), Kurdistan University of Medical Sciences, Sanandaj, Iran; Department of Food Technology (D K Mohammad PhD), Research Center (K A Mohammad PhD), Salahaddin University, Erbil, Iraq; Ishik University, Erbil, Iraq (K A Mohammad PhD); Department of Public Health (J A Mohammed MPH, N B Zepro MS), Samara University, Samara, Ethiopia; Department of Community Medicine (M B Sufiyan MD), Health Systems and Policy Research Unit (S Mohammed PhD), Ahmadu Bello University, Zaria, Nigeria; Department of Mathematical Sciences (P Moraga PhD), University of Bath, Bath, UK; Department of Clinical Biochemistry (A Mospap PhD), Tarbiat Modares University, Tehran, Iran; Department of Biochemistry (M Mozaffor MD), Medical College for Women & Hospital, Dhaka, Bangladesh; Research Team (M Mozaffor MD), Biomedical Research Foundation, Dhaka, Bangladesh; School of Medical Sciences (K Musa PhD), Science University of Malaysia, Kubang Kerian, Malaysia; Indian Institute of Public Health (Prof G Murthy MD), Public Health Foundation of India, Hyderabad, India; Department of Pediatric Medicine (Prof G Mustafa MD), Nishtar Medical University, Multan, Pakistan; Department of Pediatrics & Pediatric Pulmonology (Prof G Mustafa MD), Institute of Mother & Child Care, Multan, Pakistan; Research and Analytics (A J Nagarajan MTech), Initiative for Financing Health and Human Development, Chennai, India; Research and Analytics (A J Nagarajan MTech), Bioinsilico Technologies, Chennai, India; Suraj Eye Institute, Nagpur, India (V Nangia MD); Iranian Ministry of Health and Medical Education, Tehran, Iran (J Nazari PhD); Emergency Hospital of Bucharest, Bucharest, Romania (I Negoii PhD); Department of Biological Sciences (J W Ngunjiri DrPH), University of Embu, Embu, Kenya; Institute for Global Health Innovations (C T Nguyen MPH), Duy Tan University, Hanoi, Vietnam; Public Health

Background—Across low-income and middle-income countries (LMICs), one in ten deaths in

Department (D N A Ningrum MPH), Universitas Negeri Semarang, Kota Semarang, Indonesia; Graduate Institute of Biomedical Informatics (D N A Ningrum MPH), Taipei Medical University, Taipei City, Taiwan; Department of Medicine (J Noubiap MD, M S Shey PhD), Institute of Infectious Disease and Molecular Medicine (M S Shey PhD), School of Public Health and Family Medicine (C A Nnaji MPH, Prof C S Wiysonge MD), University of Cape Town, Cape Town, South Africa; Department of Preventive Medicine (I Oh PhD), Kyung Hee University, Dongdaemun-gu, South Korea; International Institute for Tropical Agriculture, Ibadan, Nigeria (O Okpala PhD); Department of Psychiatry (A T Olagunju MD), University of Lagos, Lagos, Nigeria; Department of Pharmacology and Therapeutics (Prof O E Onwujekwe PhD), University of Nigeria Nsukka, Enugu, Nigeria; Department of Environmental Management and Toxicology (O Osarenotor MS), University of Benin, Benin City, Nigeria; Department of Mathematics and Statistics (F B Osei PhD), University of Energy and Natural Resources, Sunyani, Ghana; Department of Respiratory Medicine (Prof M P A DNB), Jagadguru Sri Shivarathreeswara Academy of Health Education and Research, Mysore, India; Center for Health Outcomes & Evaluation, Bucharest, Romania (A Pana MD); Regional Medical Research Centre (S Pati MD), Indian Council of Medical Research, Bhubaneswar, India; International Institute of Health Management Research, New Delhi, India (A Patle MPH); Department of Agriculture and Food Systems (H Suleria PhD), Department of Medicine (Prof T Wijeratne MD), Department of Paediatrics (Prof G C Patton MD), Department of Psychology and Counselling (Prof T Wijeratne MD), University of Melbourne, Melbourne, VIC, Australia; Population Health Theme (Prof G C Patton MD), Murdoch Childrens Research Institute, Melbourne, VIC, Australia; Center for Research and Innovation (V F Pepito BS), Ateneo De Manila University, Pasig City, Philippines; Department of Internal Medicine (Prof I S Santos PhD), Department of Pathology and Legal Medicine (M R Tovani-Palone MSc), Department of Psychiatry (Y Wang PhD), Laboratory of Genetics and Molecular Cardiology (A Pereira PhD), University of São Paulo, Sao Paulo, Brazil; Division of Infectious Diseases and International Health (J A Platts-Mills MD), University of Virginia, Charlottesville, VA, USA; Institute of Microbiology and Immunology (Prof M Poljak PhD), University of Ljubljana, Ljubljana, Slovenia; Faculty of Economics and Business (Prof M J Postma PhD), University Medical Center Groningen (Prof M J Postma PhD), University of Groningen, Groningen, Netherlands; Fundación Valle del Lili, Cali, Colombia (S I Prada PhD); Infectious Diseases (L Preotescu PhD), National Institute of Infectious Diseases, Bucharest, Romania; Biomedical Engineering Department (Prof M Rabiee PhD), Amirkabir University of Technology, Tehran, Iran; Department of Chemistry (N Rabiee PhD), Sharif University of Technology, Tehran, Iran; College of Medicine (A Radfar MD), University of Central Florida, Orlando, FL, USA; School of Nursing and Healthcare Professions (M Rahman PhD), Federation University, Heidelberg, VIC, Australia; University Institute of Public Health (Prof S M Rana PhD), University of Lahore, Lahore, Pakistan; Public Health Department (Prof S M Rana PhD), University of Health Sciences, Lahore, Pakistan; Policy Research Institute, Kathmandu, Nepal (C L Ranabhat PhD); College of Medicine (Prof J Shin MD), Institute for Poverty Alleviation and International Development (C L Ranabhat PhD), Yonsei University, Wonju, South Korea; Gonçalo Moniz Institute (Prof D Rasella PhD), Oswaldo Cruz Foundation, Salvador, Brazil; University College London Hospitals, London, UK (D L Rawaf MD); Academic Public Health Department (Prof S Rawaf MD), Public Health England, London, UK; School of Health, Medical and Applied Sciences (L Rawal PhD), CQ University, Sydney, NSW, Australia; Neurology Department (V Renjith PhD), Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India; School of Social Sciences and Psychology (Prof A M N Renzaho PhD), Translational Health Research Institute (Prof A M N Renzaho PhD), Western Sydney University, Penrith, NSW, Australia; Medical Microbiology (M A Reta MS), University of Pretoria, Pretoria, South Africa; Surgery Department (J Rickard MD), University of Minnesota, Minneapolis, MN, USA; Surgery Department (J Rickard MD), University Teaching Hospital of Kigali, Kigali, Rwanda; Research Directorate (C M Rios González MED), Nihon Gakko University, Fernando de la Mora, Paraguay; Research Direction (C M Rios González Med), Universidad Nacional de Caaguazú, Coronel Oviedo, Paraguay; Department of Clinical Research (L Roever PhD), Federal University of Uberlândia, Uberlândia, Brazil; Clinical Epidemiology and Public Health Research Unit (L Ronfani PhD, E Traini MSc), Burlo Garofolo Institute for Maternal and Child Health, Trieste, Italy; Institute of Epidemiology and Medical Biometry (Prof D Rothenbacher MD), Ulm University, Ulm, Germany; Centro de Investigación Palmira (E Rubagotti PhD), Agrosavia, Palmira, Colombia; Department of Ocean Science and Engineering (E Rubagotti PhD), Southern University of Science and Technology, Shenzhen, China; Department of Biomedical Sciences (Prof S Rubino PhD), University of Sassari, Sassari, Italy; Department of Entomology (A M Samy PhD), Department of Neurology (Prof A S Shalash MD), Faculty of Medicine (A M Saad MBCh), Ain Shams University, Cairo, Egypt; Nanobiotechnology Center (Prof S Sajadi PhD), Soran University, Soran, Iraq; Research Deputy (S Salehi Zahabi PhD), Taleghani Hospital, Kermanshah, Iran; Department of Surgery (Prof J Sanabria MD), Marshall University, Huntington, WV, USA; Department of Community Medicine (S Y Saraswathy PhD), PSG Institute of Medical Sciences and Research, Coimbatore, India; PSG-FAIMER South Asia Regional Institute, Coimbatore, India (S Y Saraswathy PhD); Health Economics (A R Sarker PhD), Bangladesh Institute of Development Studies (BIDS), Dhaka, Bangladesh; Surgery Department (B Sathian PhD), Hamad Medical Corporation, Doha, Qatar; Faculty of Health & Social Sciences (B Sathian PhD), Bournemouth University, Bournemouth, UK; UGC Centre of Advanced Study in Psychology (M Satpathy PhD), Utkal University, Bhubaneswar, India; Udyam-Global Association for Sustainable Development, Bhubaneswar, India (M Satpathy PhD); Department of Medicine (Prof J A Singh MD), Department of Psychology (D C Schwebel PhD), University of Alabama at Birmingham, Birmingham, AL, USA; Department of Food Science and Nutrition (A M Senbeta MS), Jigjiga University, Jigjiga, Ethiopia (A A Tassew MPH); Emergency Department (S Senthilkumaran MD), Manian Medical Centre, Erode, India; Public Health Division (A A Shaheen PhD), An-Najah National University, Nablus, Palestine; Independent Consultant, Karachi, Pakistan (M A Shaikh MD); Public Health Department (S A Shallo MPH), Ambo University, Ambo, Ethiopia; School of Medicine (M Shams-Beyranvand MSc), Dezfoul University of Medical Sciences, Dezfoul, Iran; School of Medicine (M Shams-Beyranvand MSc), Alborz University of Medical Sciences, Karaj, Iran; Institute for Population Health (Prof K Shibuya MD), King's College London, London, UK; National Institute of Infectious Diseases, Tokyo, Japan (M Shigematsu PhD); Department of Public Health (A Shil MPhil), Ben Gurion University of the Negev, Beersheva, Israel; Division of Cardiology (Prof J Shin MD), Emory University, Atlanta, GA, USA; Finnish Institute of Occupational Health, Helsinki, Finland (R Shiri PhD); School of Health (S Siabani PhD), University of Technology Sydney, Sydney, NSW, Australia; Medicine Service (Prof J A Singh MD), US Department of Veterans Affairs (VA), Birmingham, AL, USA; Max Hospital, Ghaziabad, India (Prof N P Singh MD); Department of Epidemiology (D N Sinha PhD), School of Preventive Oncology, Patna, India; Department of Epidemiology (D N Sinha PhD), Healis Sekhsaria Institute for Public Health, Mumbai, India; Department of Physiotherapy and Occupational Therapy (M M Sisay MPH), Næstved-Slagelse-Ringsted Hospitals, Slagelse, Denmark; Department of Infectious Diseases (A Sokhan PhD), Kharkiv National Medical University, Kharkiv, Ukraine; Hospital Universitario de la Princesa (Prof J B Soriano MD), Autonomous University of Madrid, Madrid, Spain; Centro de Investigación Biomédica en Red

children younger than 5 years is attributable to diarrhoea. The substantial between-country

Enfermedades Respiratorias (CIBERES), Madrid, Spain (Prof J B Soriano MD); Hull York Medical School (I N Soyiri PhD), University of Hull, Hull City, UK; Usher Institute of Population Health Sciences and Informatics (I N Soyiri PhD), University of Edinburgh, Edinburgh, UK; Division of Community Medicine (C T Sreeramareddy MD), International Medical University, Kuala Lumpur, Malaysia; Department of Nursing (A Sudaryanto MPH), Muhammadiyah University of Surakarta, Surakarta, Indonesia; Department of Public Health (A Sudaryanto MPH), China Medical University, Taiwan; Department of Criminology, Law and Society (Prof B L Sykes PhD), University of California Irvine, Irvine, CA, USA; University Institute "Egas Moniz", Monte da Caparica, Portugal (Prof N Taveira PhD); Research Institute for Medicines, Faculty of Pharmacy of Lisbon (Prof N Taveira PhD), University of Lisbon, Lisbon, Portugal; Colgate University, Hamilton, NY, USA (B Taye PhD); South Gate Institute for Health Society and Equity (F H Tesfay MPH), Flinders University, Adelaide, SA, Australia; Department of Public Health and Community Medicine (Prof K R Thankappan MD), Central University of Kerala, Kasaragod, India; Nanyang Technological University, Singapore, Singapore (S Thirunavukkarasu PhD); Department of Molecular Medicine and Pathology (K B Tran MD), University of Auckland, Auckland, New Zealand; Clinical Hematology and Toxicology (K B Tran MD), Military Medical University, Hanoi, Vietnam; Gomal Center of Biochemistry and Biotechnology (I Ullah PhD), Gomal University, Dera Ismail Khan, Pakistan; TB Culture Laboratory (I Ullah PhD), Mufti Mehmood Teaching Hospital, Dera Ismail Khan, Pakistan; Department of Community Medicine (Prof B Unnikrishnan MD), Manipal Academy of Higher Education, Mangalore, India; Clinical Cancer Research Center (S Valadan Tahbaz PhD, S Yahyazadeh Jabbari MD), Milad General Hospital, Tehran, Iran; Argentine Society of Medicine, Buenos Aires, Argentina (Prof P R Valdez MEd); Velez Sarsfield Hospital, Buenos Aires, Argentina (Prof P R Valdez MEd); Psychosocial Injuries Research Center (Y Veisani PhD), Ilam University of Medical Sciences, Ilam, Iran; Occupational Health Unit (Prof F S Violante MD), Sant'Orsola Malpighi Hospital, Bologna, Italy; Department of Economics (Prof S Vollmer PhD), University of Göttingen, Göttingen, Germany; Foundation University Medical College (Y Waheed PhD), Foundation University, Islamabad, Pakistan; Department of Epidemiology and Biostatistics (Y Wang BSA, Prof C Yu PhD), Global Health Institute (Prof C Yu PhD), Wuhan University, Wuhan, China; Competence Center of Mortality-Follow-Up of the German National Cohort (R Westerman DSc), Federal Institute for Population Research, Wiesbaden, Germany; Department of Physical Therapy (T Wiangkham PhD), Naresuan University, Meung District, Thailand; Department of Orthopaedics, The Second Affiliated Hospital and Yuying Children's Hospital (Prof A Wu PhD), Wenzhou Medical University, Wenzhou, China; School of Medicine (Prof G Xu MD), Nanjing University, Nanjing, China; Department of Diabetes and Metabolic Diseases (T Yamada MD), University of Tokyo, Tokyo, Japan; Centre for Suicide Research and Prevention (Prof P Yip PhD), Department of Social Work and Social Administration (Prof P Yip PhD), University of Hong Kong, Hong Kong, China; University of South Australia, Adelaide, NSW, Australia (B D Yirsaw PhD); Department of Psychopharmacology (N Yonemoto MPH), National Center of Neurology and Psychiatry, Tokyo, Japan; Department of Health Policy & Management (Prof M Z Younis PhD), Jackson State University, Jackson, MS, USA; School of Medicine (Prof M Z Younis PhD), Tsinghua University, Beijing, China; Department of Health Economics and Management (H Yusefzadeh PhD), Urmia University of Medical Science, Urmia, Iran; EcoHealth Alliance, New York, NY, USA (C Zambrana-Torrel PhD); Department of Oncology (D Zhang PhD), Georgetown University, Washington, DC, USA; Hubei Province Key Laboratory of Occupational Hazard Identification and Control (Y Zhang PhD), School of Public Health (Y Zhang PhD), Wuhan University of Science and Technology, Wuhan, China; Wuhan Polytechnic University, Wuhan, China (X Zhao PhD).

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Contributors

SIH had the idea for the study. RCR designed and implemented the study and wrote the first draft of the report. PAL, MB, and GMG obtained, extracted, processed, and geopositioned data. KEW and PAL vetted data. KEW wrote the computer code, produced the estimates, and vetted models and results, with input from RCR, AD, and SIH. LE, MB, CAW, and PAL prepared tables and figures. SBM, PAL, BFB, and RCR finalised the report based on comments from other authors and reviewers' feedback. BFB, PAL, and SBM managed the appendix. BFB managed the project. All authors provided intellectual inputs into aspects of this study. All other authors provided data or developed models for indicators, reviewed results, initiated modelling infrastructure, or reviewed and contributed to the report.

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variation in both diarrhoea incidence and mortality is attributable to interventions that protect children, prevent infection, and treat disease. Identifying subnational regions with the highest burden and mapping associated risk factors can aid in reducing preventable childhood diarrhoea.

Methods—We used Bayesian model-based geostatistics and a geolocated dataset comprising 15 072 746 children younger than 5 years from 466 surveys in 94 LMICs, in combination with findings of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, to estimate posterior distributions of diarrhoea prevalence, incidence, and mortality from 2000 to 2017. From these data, we estimated the burden of diarrhoea at varying subnational levels (termed units) by spatially aggregating draws, and we investigated the drivers of subnational patterns by creating aggregated risk factor estimates.

Findings—The greatest declines in diarrhoeal mortality were seen in south and southeast Asia and South America, where 54.0% (95% uncertainty interval [UI] 38.1–65.8), 17.4% (7.7–28.4), and 59.5% (34.2–86.9) of units, respectively, recorded decreases in deaths from diarrhoea greater than 10%. Although children in much of Africa remain at high risk of death due to diarrhoea, regions with the most deaths were outside Africa, with the highest mortality units located in Pakistan. Indonesia showed the greatest within-country geographical inequality; some regions had mortality rates nearly four times the average country rate. Reductions in mortality were correlated to improvements in water, sanitation, and hygiene (WASH) or reductions in child growth failure (CGF). Similarly, most high-risk areas had poor WASH, high CGF, or low oral rehydration therapy coverage.

Interpretation—By co-analysing geospatial trends in diarrhoeal burden and its key risk factors, we could assess candidate drivers of subnational death reduction. Further, by doing a counterfactual analysis of the remaining disease burden using key risk factors, we identified potential intervention strategies for vulnerable populations. In view of the demands for limited resources in LMICs, accurately quantifying the burden of diarrhoea and its drivers is important for precision public health.

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Introduction

Across low-income and middle-income countries (LMICs), diarrhoea causes more than half a million childhood deaths annually.¹ In addition to this staggering loss of life, more than 910 million childhood cases of diarrhoea per year² are distributed unequally across the population, causing not only acute morbidity but also long-term disability in children who suffer repeatedly with enteric infections.³ National-level analyses of the burden of childhood diarrhoea, measured by both death rates and incidence, have exposed substantial variation. In LMICs in 2017, the incidence of diarrhoea ranged from less than one episode per child per year to more than four episodes per child per year.² In the same population, the case-

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Data sharing

The [source code and data](#) used to generate estimates are available online. The [full sets of estimates](#) at all geographical levels produced can be found online.

fatality rate of diarrhoea can vary from one per 10 000 infections to more than 20 per 10 000 infections.⁴

WHO's integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) identified three approaches to reduce the burden of diarrhoea: protect, prevent, and treat.⁵ Healthy children are less likely to have severe diarrhoea episodes,⁶ so diarrhoeal burden can be reduced by prioritising good health practices from birth. As such, reducing general health risk factors, such as child growth failure (CGF) indicators of stunting, wasting, and underweight,^{4,7} can protect a child from diarrhoea. Preventing illness by promoting vaccination and improved water, sanitation, and hygiene (WASH) can similarly reduce diarrhoeal burden.^{8,9} Finally, appropriate treatment, such as oral rehydration solution (ORS), the efficacy of which exceeds 90%,¹⁰ can substantially reduce death resulting from disease-associated dehydration.^{11,12}

Distal determinants of diarrhoeal mortality, such as measurable indicators of child welfare,¹³ have been geospatially mapped at the local level in Africa, including under-5 mortality,¹⁴ CGF,¹⁵ and education levels of the broader population.¹⁶ Country-level assessment of these determinants can mask subnational variation and provide limited information with which to formulate policy.¹⁷ Furthermore, mapping interventions such as malaria nets¹⁸ and vaccines¹⁹ has shown the positive effects of these strategies on reducing diseases. Subsequently, precise mapping of diarrhoea-related interventions, including ORS coverage²⁰ and access to safe water and sanitation (Deshpande A, unpublished data), in addition to diarrhoea incidence and death, provides in-depth analysis to aid in the prevention of deaths associated with diarrhoea.

National trends in diarrhoeal burden are associated with (and in many cases driven by) national trends in risk factors associated with the protect, prevent, and treat strategy. Childhood stunting, poor sanitation access, and low ORS coverage are risk factors most strongly associated with changes in diarrhoeal burden.⁴ To date, no comprehensive attempt has been made to quantify either the subnational variation in diarrhoea or these key risk factors across LMICs. Several isolated studies of subnational variation in diarrhoea,²¹ childhood stunting,¹⁵ WASH,²² and ORS coverage²³ have shown striking variation at the spatial scale investigated. However, without estimates designed to be comparable across space and time, it is difficult to analyse such scattered information as a cohesive body of knowledge.

Reducing morbidity and mortality could be accomplished by targeting regions with the highest mortality rate, or those with the greatest total number of deaths. At the national scale, for example, Central African Republic was estimated to have the highest childhood mortality rate attributable to diarrhoea globally, at 6.9 deaths per 1000 children. Because of this country's relatively small population, however, this rate translates to approximately 4156 children dying per year.²¹ By contrast, in Nigeria, which has a much larger population than Central African Republic, an estimated 104 000 children a year die from diarrhoea, but the mortality rate is less than half that of Central African Republic (3.0 deaths per 1000 children).²⁴ A location within a country could have a relatively low risk of mortality but a sufficiently large population so it is a greater contributor to overall burden than other areas in

that country. Thus, decisions aimed at optimum burden reduction might overlook those at highest risk. Mapping both rates and counts can aid in the design of intervention strategies that efficiently save lives while also highlighting entrenched geographical disparities in diarrhoeal burden.

Here, we present an analysis of local variation in diarrhoeal morbidity and mortality in children younger than 5 years across 94 LMICs between 2000 and 2017. We used Bayesian model-based geostatistics and an extensive geolocated dataset (describing 3 738 327 diarrhoea episodes across 15 072 746 children) in combination with methods from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 to estimate posterior distributions of continuous continent-wide surfaces of diarrhoea prevalence, incidence, and mortality.^{1,2} We then aggregated our estimates at second administrative-level units (eg, districts in Uganda or divisions in Kenya; henceforth referred to as units), to identify regions with the most pronounced rate of burden reduction versus those that continue to have higher-than-average burden. We combined this analysis with published estimates of subnational CGF variation¹⁵ and new estimates of subnational variation in WASH (Deshpande A, unpublished data) and ORS²⁰ to break down diarrhoeal burden. Finally, through these linked analyses, we identified regions most in need of tailored interventions to reduce the burden of this largely preventable disease.

Methods

Definitions

Diarrhoea episodes were defined as three or more loose stools over a 24-h period.⁴ Diarrhoea prevalence was defined as the point prevalence of children younger than 5 years with diarrhoea. Incidence was defined as the number of cases of diarrhoea in children younger than 5 years per child per year. Mortality was defined as the number of deaths among children younger than 5 years due to diarrhoea per child per year. Rates per 1000 are presented in the figures and represent prevalence, incidence, or mortality rates per child multiplied by 1000). Diarrhoea burden is used throughout this Article to refer to the combined burden of prevalence, incidence, and mortality.

Data

We included 94 LMICs in our analysis; these countries were defined according to the Socio-demographic Index (SDI), which assesses development based on education, fertility, and income.²⁴ Where appropriate, we use designated ISO 3166-1 alpha-3 codes for countries. Our study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix 1 pp 84–85).²⁵

Surveys—We compiled 466 household surveys (including the Demographic and Health Survey [DHS], Multiple Indicator Cluster Survey [MICS], and other country-specific surveys) from 2000 to 2017 with geocoded information from 207 021 coordinates corresponding to survey clusters and 17 954 subnational polygon boundaries. We included surveys that asked if children younger than 5 years had diarrhoea, typically within the preceding 2 weeks. Potential bias attributable to seasonal variation in diarrhoea was

addressed, as described in appendix 1 (p 5). Data were vetted for representativeness at the national level and subnational level, as appropriate. Data inclusion, coverage, and validation are further described in appendix 1 (pp 3, 9).

Spatial covariates—We compiled 15 covariates that were indexed at the subnational level and could possibly be related to diarrhoea prevalence, including access to roads, ratio of child dependents (aged 0–14 years) to working-age adults (aged 15–64 years), distance from rivers or lakes, night-time lights (time-varying covariate), elevation, population ratio of women of maternal age to children, population (time-varying covariate), aridity (time-varying covariate), urban or rural (time-varying covariate), urban proportion of the location (time-varying covariate), irrigation, number of people whose daily vitamin A needs could be met, prevalence of under-5 stunting (time-varying covariate), prevalence of under-5 wasting (time-varying covariate), and diphtheria-tetanus-pertussis immunisation coverage (time-varying covariate). We also included the Healthcare Access and Quality Index,²⁶ percentage of the population with access to improved toilet types, and percentage of the population with access to improved water sources (as defined by WHO and UNICEF's [Joint Monitoring Programme](#)) as national-level time-varying covariates. We filtered these covariates for multicollinearity in each modelling region (appendix 1 pp 5–6) using variance inflation factor (VIF) analysis with a VIF threshold of 3.²⁷ Covariate information, including plots of all covariates, is detailed in the appendix 1 (pp 25–26, 90–96).

Statistical analysis

Geostatistical model—Prevalence data were used as inputs to a Bayesian model-based geostatistical framework. Briefly, this framework uses a spatially and temporally explicit hierarchical logistic regression model to predict prevalence. Potential interactions and non-linear relations between covariates and diarrhoea prevalence were incorporated using a stacked generalisation technique.²⁸ Posterior distributions of all parameters and hyperparameters were estimated using R-INLA version 19.05.30.9000.^{29,30} Uncertainty was calculated by taking 250 draws from the estimated posterior joint distribution of the model, and each uncertainty interval (UI) reported represents the 2.5th and 97.5th percentiles of those draws. Models were run independently in 14 geographically distinct modelling regions based on the GBD 2010 study,³¹ and one country-specific model in India. Analyses were done using R version 3.5.0. Maps were produced using ArcGIS Desktop 10.6. Additional details are provided in appendix 1 (pp 6–8).

Post estimation—Estimated prevalence was converted into incidence using an average duration of a diarrhoea episode of 4.2 days⁴ (appendix 1 p 9). We converted incidence surfaces to mortality surfaces by multiplying the incidence values by country-specific and year-specific case-fatality rates (which did not vary subnationally). We calibrated our continuous prevalence estimates to those of prevalence, mortality, and incidence from GBD 2017. However, we did not calibrate prevalence or incidence in South Africa because of unreasonably low estimates in this location in the GBD 2017 study. We then calculated population-weighted aggregations of the 250 draws of diarrhoea prevalence, mortality, and incidence estimates at the country level, first administrative-level unit, and second administrative-level unit (hereafter referred to as unit). This calculation resulted in estimates

for 24 143 units within 94 countries. Geographical inequalities were quantified as the relative difference between each unit and the respective country average. We also estimated inequality using the Gini coefficient,³² which summarises the distribution of each indicator across the population, with a value of 0 representing perfect equality and 1 representing maximum inequality (appendix 1 p 12).

Counterfactual analyses using diarrhoea risk factors—Following the GAPPD framework, we did a post-hoc counterfactual analysis using subnational estimates of risk factors according to GBD 2017, including reducing prevalence of childhood stunting and childhood wasting (protect), access to improved sanitation and improved water (prevent), and increasing ORS coverage (treat). Some known diarrhoea risk factors (eg, low coverage of rotavirus vaccine, or no or partial breastfeeding) were not included because subnational estimates are currently not available for all 94 LMICs included in this study. We used the counterfactual analysis to estimate the number of deaths averted because of changes in CGF and WASH risk factors (appendix 1 pp 61–62).

Model validation—Models were validated using source-stratified five-fold cross validation. Holdout sets were created by combining randomised sets of second administrative unit cluster-level datapoints. Model performance was summarised by the bias (mean error), total variance (root-mean-square error), 95% data coverage within prediction intervals, and correlation between observed data and predictions. When possible, estimates were compared against existing estimates. All validation procedures and corresponding results are provided in appendix 1 (p 9).

Role of the funding source

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

Results

Our model produced estimates of local diarrhoea prevalence, incidence, and mortality for 94 LMICs yearly from 2000 to 2017, showing subnational spatial and temporal variation. A large variation in diarrhoeal burden was seen, both between and within countries, and striking differences in trends were noted over time by location. Although, in many countries, rates of diarrhoeal morbidity and mortality were disproportionately high in less-populated rural areas, the absolute burden of diarrhoeal mortality was typically concentrated in highly populated urban centres. By integrating these subnational estimates of mortality with similar estimates of leading risk factors, improvements in WASH (Deshpande A, unpublished data) and prevention of CGF (relative to levels in 2000) were estimated to avert 46 000 (95% UI 32 000–170 000) and 245 000 (177 000–940 000) child deaths in 2017, respectively. The [full array of our model outputs](#) is provided in appendix 2 (pp 1–950), and online.

Incidence of diarrhoea

In 2017, Yemen had the most units exceeding five cases of diarrhoea per child per year (124 units), with Afghanistan (16 units) the only other country with such high incidence (figure 1A). It is unsurprising that Yemen had the most subnational units with high incidence, because the country had had the highest national incidence of diarrhoea globally, with 4.7 (95% UI [4.0–5.7]) cases per child per year. In 2017, the highest incidence of diarrhoea for sub-Saharan Africa was in Cameroon (4.8 [95% UI 2.9–7.4] cases per child per year in Mayo-Danay department, Extrême-Nord); for Latin America the highest incidence was in Guatemala (4.7 [3.7–5.8] cases per child per year in San Antonio Suchitepéquez department, Suchitepéquez; and 4.4 [3.5–5.5] cases per child per year in San Miguel Panán department, Suchitepéquez); and for southeast Asia the highest incidence of diarrhoea was in Papua New Guinea (3.5 [2.7–4.5] cases per child per year in Koroba-Kopiago district, Hela). Massive variation within regions is exemplified in central Asia and south Asia, where the highest incidence of diarrhoea by country spanned from 2506th to 24 391st across all LMICs (2.8 [95% UI 2.1–3.6] cases per child per year in Moskva district, Khatlon, Tajikistan; and 0.7 [0.4–1.3] cases per child per year in A gabat district, A gabat, Turkmenistan; figure 1A). Maps of upper and lower bounds for the uncertainty on incidence can be found in appendix 1 (p 47).

As with variation between countries, substantial variation was seen within most countries. 16 countries had at least one unit with an estimated incidence of diarrhoea more than 1.0 case per child per year higher than the national average (figure 1B). The district of Darqad, Takhar, Afghanistan, had an incidence of 6.3 (95% UI 4.2–9.5) cases per child per year, which was 2.3 cases per child per year higher than the national average (4.0 [2.8–5.3] cases per child per year). Conversely, only nine countries had units with incidence less than 1.0 case per child per year lower than their country average (appendix 2 pp 3–4, 478–950). Countries with large relative geographical inequality include Guyana, where the rate in the Marudi council, Upper Takutu-Upper Essequibo, was 2.4 (95% UI 2.0–3.1) cases per child per year, which is much higher than the country average of 1.2 (0.9–1.5) cases per child per year. It is important to note that the comparison in Afghanistan also illustrates a technical difficulty in summarising correlated uncertainty. In Afghanistan, the 95% UI for the estimated incidence of diarrhoea in Darqad overlaps that for average incidence across the country, but these UIs are based on summarising aggregations from draws of correlated incidence surfaces. In every draw from the posterior distribution of incidence, Darqad had an incidence at least 86.0% higher than that draw's estimated country incidence.

The substantial reduction in overall diarrhoeal burden since 2000 has not translated into a consistent reduction in incidence of diarrhoea. 5729 (24%) of 24 139 units had an increase in childhood diarrhoea incidence from 2000 to 2017 (figure 1C). Laos in particular contained 24 units with annual rates of change in diarrhoea incidence exceeding 5% per year. Conversely, among all units that had decreases in incidence, Nigeria saw the greatest number of units (n=40) with annual declines in diarrhoea incidence of 7% or more.

Incidence data provide information on the per person risk of disease. However, some units with the highest incidence of diarrhoea are sparsely populated. On the other hand, many units with the highest incidence of diarrhoea and moderate rates of diarrhoea have

considerable populations. For example, in 2017, five units in Punjab, Pakistan (Dera Ghazi Khan, Faisalabad, Gujranwala, Lahore, and Multan) were estimated to have more than 21 (95% UI 14.8–28.9) million cases of diarrhoea in children younger than 5 years (figure 1D). Each of these units had an incidence less than 1.9 (95% UI 1.3–3.0) cases per child per year. By contrast, Wadhrah district in Hajjah, Yemen, had a high incidence of diarrhoea (5.5 [95% UI 4.3–7.0] cases per child per year), but because of this district's relatively small child population, there were only 9890 (7766–12 723) cases of diarrhoea (figure 1D). These incidence data suggest that interventions focused on lowering the absolute burden of diarrhoea might best be focused on urban areas, although this focus risks exacerbating existing geographical disparities.

Mortality from diarrhoea

Similar to patterns noted previously on a subnational map of diarrhoeal mortality in Africa,²¹ substantial diarrhoeal burden was seen in several countries in the Sahel region of Africa, with Birao in Vakaga, Central African Republic, having the highest mortality rate globally of 8.2 (95% UI 6.8–9.7) deaths per 1000 children in 2017 (figure 2A). Seven countries had at least one unit exceeding five deaths per 1000 children, and all were located in Africa. For 46 countries, the GAPPD goal of decreasing childhood diarrhoeal mortality to less than one death per 1000 children was achieved in every second administrative-level unit by 2017 (appendix 2 pp 5–477). Global variation in diarrhoea mortality was so vast that rates for many countries remain several orders of magnitude lower than those in central sub-Saharan Africa (figure 2A).

Similar to incidence, substantial within-country variation was noted in diarrhoeal mortality. As previously highlighted in our Africa-focused analysis,²¹ some units in Nigeria in 2017 were far above the country average. Of the 100 largest deviations above the national mean mortality rate, 86 occurred in northern Nigeria (figure 2B). Only units in Chad, Kenya, and Nigeria had rates greater than one death per 1000 less than their country average mortality rate (figure 2B). When the analysis was done in terms of relative deviation from the mean, different patterns of subnational variation became apparent. Indonesia stood out as having many units within Papua that were more than three-fold the country average; in particular, the Boven Digoel Regency of Papua, Indonesia, was estimated to have a diarrhoeal mortality rate 3.4 times the national average (figures 3A, B). Similarly, 736 units of Mexico were estimated to have mortality rates more than double the national average (figure 2B). Although Nigeria had massive absolute deviations, units with the highest absolute deviations were 169.0% (95% UI 114.2–256.5) the national average (figure 2B). Maps of upper and lower bounds for uncertainty on incidence can be found in appendix 1 (p 48).

Unlike incidence of diarrhoea, diarrhoeal mortality declined in most units from 2000 to 2017. 8658 (36%) of 24 143 units showed reduced rates of childhood diarrhoeal mortality, by more than 10% per year (figure 2C). The greatest declines in diarrhoeal mortality were seen in south and southeast Asia and South America, where 54.0% (95% UI 38.1–65.8), 17.4% (7.7–28.4), and 59.5% (34.2–86.9) of units, respectively, recorded decreases in deaths from diarrhoea greater than 10%. Diarrhoeal mortality was estimated to have increased in only 112 (0.5%) units over this time, exclusively in Central African Republic, Indonesia,

Kenya, South Sudan, and Tunisia. Although massive imbalances in mortality rates within Africa persisted in 2017, most diarrhoeal deaths in LMICs occurred outside of Africa. Importantly, because of the juxtaposition of mortality rate to population size, the five units with the largest number of diarrhoeal deaths were all outside of Africa, specifically in Punjab, Pakistan (Dera Ghazi Khan, Faisalabad, Gujranwala, Lahore, and Multan; figure 2D). By comparison, the total number of deaths in these five units was more than double the total estimated diarrhoeal deaths in Liberia, Rwanda, and Togo.

Geographical inequality in diarrhoeal mortality

Within analyses of geographical inequality, focusing on maximum deviations from the country mean can mask subnational variation in space and time. Two exemplars of this masking are Indonesia (where units with the greatest deviation changed over time) and Peru (where the shape of the distribution of inequality changed even though the maximum deviation remained mostly stable; figure 3). In 2000, the units within Indonesia farthest from the mean were all within the first administrative-level units (provinces) of modern-day Gorontalo, Nusa Tenggara Barat, Sulawesi Barat, and Sulawesi Tengah, with the largest relative deviation in the East Lombok Regency in Nusa Tenggara Barat (101.4% the national mortality rate; figures 3A, 4). By 2017, units in Papua were almost four times the Indonesian national average (figures 3B, 4). Units in Papua went from not ranking in the 60 units with the highest deviation in Indonesia in 2000 to having the 29 units with the highest deviations from the country average in 2017.

In Peru, several units had substantial deviations from the national average in 2000. The maximum relative geographical inequality occurred in Requena province, Loreto, with 0.80 (95% UI 0.65–0.97) deaths per 1000, versus a country mortality rate of 0.4 (0.4–0.5) deaths per 1000 children, a relative deviation of 83.7%. Since 2000, Peru has seen substantial reductions in diarrhoeal mortality, and yet, in 2017, mortality in Requena province, Loreto, was 56.8% higher than the country average. Although the maximum relative deviation increased over this period, the distribution of inequality shows a different pattern. In 2000, 58 of 196 provinces in Peru had mortality rates at least 20% higher than the country average (figure 3C); however, in 2017, only 34 provinces had mortality rates at least 20% higher than the country average (figure 3D).

Drivers of geographical inequality in diarrhoeal mortality

A risk factor can drive the risk of diarrhoeal mortality by increasing the chance that either a child is infected, infection develops into a disease episode, or an episode results in death. Both CGF and WASH risk factors were used as covariates in the diarrhoea prevalence model because they are predictive of infections that lead to diarrhoea.^{7,22} Conversely, ORS coverage was not used because there is clinical evidence that ORS prevents mortality from diarrhoea,^{11,12} but there is no evidence that it affects diarrhoea prevalence or incidence. Because of the possibility for circularity, post-hoc correlative analyses between the subnational variation in diarrhoeal mortality and the subnational variation in CGF and WASH must be interpreted carefully. However, consistent with the logic of previous risk factor analysis,³ excluding these known drivers of diarrhoea incidence would diminish the fit and usefulness of the output more than the potential loss of interpretation due to circularity.

It is important to note that by using both stacked generalisation and the Gaussian process, which incorporates estimates of spatial and temporal autocorrelation, diarrhoeal mortality patterns are not a simple direct function of the risk factors used. Most importantly, the counterfactual analysis is based on externally derived risk ratios for each level of each risk factor.

To assess drivers of the temporal trends in diarrhoeal mortality, we did a counterfactual analysis by comparing the estimated number of diarrhoeal deaths in 2017 to the scenario in which these risk factors had been at their 2000 levels. For the primary counterfactual analysis, we did not include ORS because only a few studies have quantified ORS efficacy precisely and, thus, there is no universally accepted risk ratio for its efficacy. A counterfactual analysis that includes ORS is presented in appendix 1 (pp 61–62). Additional factors that affect death rates and counts, such as changes in population structure and size and sociodemographic factors, were kept at their 2017 levels. Reductions in CGF averted 245 000 deaths, and 46 000 deaths were averted by improvements in WASH (figure 5D). In units where one or both risk factor groups improved from 2000 to 2017, we estimated 297 000 deaths were averted because of combined changes in WASH and CGF risk factors (figure 5B). The largest attributable relative reductions in diarrhoeal mortality in units where at least one child was estimated to have died from diarrhoea in 2017 were seen in India, Myanmar, Rwanda, and Somalia, where gains were mainly attributable to concurrent reductions in CGF (figures 5A, C). Conversely, the largest absolute attributable reductions in diarrhoeal mortality were in Ethiopia, India, Niger, and Pakistan. In Lahore, within the Punjab province of Pakistan, these gains were almost entirely due to improvements in WASH, whereas in the units within Ethiopia, India, and Niger, the averted deaths were almost entirely due to reductions in CGF (figures 5B, D). Although many regions that saw deaths averted because of WASH also had improvements associated with CGF, there were regions in Angola and Pakistan where the reduction in diarrhoea-related mortality was mainly driven by WASH (figure 5C). In 2000, across all LMIC units, 68·0–99·2% of childhood diarrhoeal deaths were attributable to either CGF or WASH risk factors. In 2017, the range increased slightly to 60·1–99·0% (appendix 1 pp 61–62).

Compared with other modelled regions, much of sub-Saharan Africa had a disproportionately high burden of diarrhoeal disease. Inequality, as measured by the Gini coefficient across units within sub-Saharan Africa, remained mostly constant in sub-Saharan Africa from 2000 (0·30) to 2017 (0·33). We identified units with child populations at highest risk of death due to diarrhoea, defined as units with 20% of the population in Africa living in areas with the highest mortality rates (figure 6A). No combination of risk factors that drove high diarrhoeal mortality was discernible; however, units had at least one risk factor at a high level (figures 6B–D). Of 565 units accounting for 20% of children with the highest diarrhoeal mortality risk in 2017, 447 were also among those with the highest risk in 2000. The other 118 units that became relatively worse from 2000 to 2017 were predominantly in South Sudan (n=45), Central African Republic (n=39), and Madagascar (n=21). In units in South Sudan, although ORS decreased slightly on average (2·7%), there was a notable decline in average prevalence of childhood stunting across the 45 units (9·6%; figure 6D). As with high-burden areas in 2017, the risk factors that correlated with improvements from 2000 to 2017 were varied. For example, of the 295 units that transitioned out of the lower 20% from 2000 to 2017, 53 came

from Liberia. In these units, surprisingly, both ORS coverage and access to improved sanitation declined on average from 2000 to 2017 (average ORS coverage declined by 14.1% and average access to improved sanitation declined by 11.7%; figures 6B, C). Conversely, and more consistent with the improvements in these units of Liberia, childhood stunting consistently improved from 2000 to 2017 (childhood stunting decreases ranged from 14.4% to 25.4%; figure 6D).

Discussion

Over the past 18 years, substantial reductions have been noted in diarrhoeal mortality, but these improvements have not been recorded uniformly across LMICs. Although only 112 (0.5%) of 24 143 units had increases in mortality rates from 2000 to 2017, 5729 (24%) units saw an increase in incidence of childhood diarrhoea over this period. While some units with high diarrhoeal burden in 2000 have subsequently noted impressive reductions, other units with historically high diarrhoeal burden have seen some of the most meagre improvements. Globally, most of the diarrhoeal burden is in sub-Saharan Africa and south Asia, but we recorded substantial variation within countries in these subcontinents. Moreover, even in regions with relatively low diarrhoeal burden, we identified units that far exceeded their respective country's averages. Our estimates identified the units of each country where diarrhoeal burden was disproportionately high, pinpointing the locations most in need of targeted interventions.

Identifying a country's worst-performing units also leads to awareness of the extent of geographical inequality, measured by the range of relative deviation from the mean. It likewise pinpoints if these units are left behind consistently over time. In Peru, some metrics of geographical inequality seem to be mostly consistent from 2000 to 2017. However, deeper analysis into the distribution of burden across the country showed that more than half of its worst-performing units substantially improved relative to others in the country. Only a few Peruvian units east of the Andes seem to be left behind. Conversely, in Indonesia, the worst-performing units in 2000 actually improved more than average, whereas units in Papua became substantially worse relative to the rest of the country, leading to units exceeding the country average by almost 350%.

The different subnational patterns that emerge between relative and absolute deviations are echoed when comparing units with the highest mortality rates versus those units where most children die from diarrhoea. Across all LMICs, even though units with the highest mortality risk were all in sub-Saharan Africa, the five units where most children died were all in Pakistan. These same patterns hold within many countries. In the Democratic Republic of the Congo, most deaths from diarrhoea occurred in the capital city of Kinshasa, where the death rate was 1.5 (95% UI 1.3–1.9) deaths per 1000 children; however, the second administrative-level unit with the highest death rate (Kazumba, Kasai; 2.0 [1.6–2.4] deaths per 1000 children) had an estimated 307 (251–368) childhood deaths in 2017 because of its small population size (figure 2). When attempting to further reduce diarrhoeal burden in a country or region, interventionists, policy makers, and other stakeholders must consider and balance the needs of both locations with the highest risk and locations with the highest burden.

Changes in diarrhoeal burden are due to myriad related drivers, but findings of a study³ showed that CGF and poor access to improved WASH were most associated with global reductions in the burden of diarrhoea. Although there are other important risk factors for diarrhoea (eg, poor rotavirus vaccine coverage), we did a counter-factual CGF and WASH risk factor analysis. Using newly available subnational estimates, we have provided a deeper understanding of the drivers of past success and location-specific needs to prevent future deaths. Large portions of sub-Saharan Africa have seen improvements because of reductions in CGF. Likewise, reductions in diarrhoeal deaths in Ethiopia have coincided with improvements in access to better sanitation. We identified second administrative-level units of Ethiopia, India, Niger, and Pakistan where reductions in CGF and WASH risk factors since 2000 have averted more than 1000 childhood deaths due to diarrhoea. Some of the regions that have seen the slowest improvements can also be linked to risk factors. In much of Pakistan, for example, small improvements in WASH have been overwhelmed by increases in CGF (figure 5). Although it is unlikely that risk factors will be eliminated completely, and thus counting all deaths still attributable to a risk factor is slightly misleading, we did identify patterns relating disproportionately high values of risk factors with disproportionately high burden. In sub-Saharan Africa, no combination of risk factors was found that needed reduction across the region; rather, in different locations of high burden, a different suite of risk factors seemed to be associated with the high risk of death due to diarrhoea (figure 6).

In the future, our analysis could aid in targeting of site-specific interventions, for example, to units of India, Indonesia, and Nigeria that did worse than their respective country average and had higher than country-average levels of childhood stunting. Although nationwide campaigns to reduce childhood stunting have a role in averting further unnecessary deaths, focused interventions in the worst-performing units might reduce the recorded substantial geographical inequality in diarrhoeal burden. Our results did not always indicate that every unit needing improvements required reductions in all risk factors, even within one country. As an example, although most poorly performing units within Nigeria had lower than average access to improved sanitation and ORS coverage, almost 10% of children in poorly performing units lived in locations estimated to have better than average sanitation and ORS coverage. Careful consideration of location-specific risk factors is necessary to optimally design intervention programmes.

Limitations associated with our analysis include inherent biases in survey data, which are associated with data obtained with recall biases. There is also uneven data coverage in space and time, in particular from zones of conflict and political instability (eg, Afghanistan, Iraq, Pakistan, Syria, and Yemen). Regarding the geospatial modelling framework, our approach is designed to optimise out-of-sample predictive validity and, as such, it is difficult to do inferential analyses. Our spatial and temporal autocorrelation assumptions might smooth over focal epidemics. Additionally, our model does not distinguish differences in rates of disease or death by causes of diarrhoea because we are currently unable to fully model all causes of diarrhoea. For this study, we assume that the case-fatality rate is constant for any particular year within any particular country. This assumption is unlikely, but since it is more likely that the places with higher than average prevalence are likely to be the same places with a higher than average case-fatality rate, our observations about subnational inequality in

diarrhoea mortality probably underestimate these quantities. As previously mentioned, the risk factor analyses must be interpreted with care. CGF and WASH risk factors are used as covariates within the diarrhoea model, so it is unsurprising that the final diarrhoeal burden estimates correlate with those covariates. On the other hand, because of both the spatiotemporal smoothing that occurs through the Gaussian process and the stacked generalisation beforehand, it is not necessary for the final output to correspond with the covariates used in the regression. Although ORS was not used in the prevalence model, many of the base covariates used in diarrhoea (eg, elevation or population density) were used in the ORS model.

Our counterfactual analysis assumed that each risk factor affects diarrhoeal mortality and changes through time independently of all other risk factors. Accurately capturing and quantifying the covariation of these risk factors in space and time would further improve the use of that analysis. Our study also does not address the protective effect of breastfeeding with potential for the reduction of diarrhoeal burden.³⁹ Breastfeeding can account for some of the lower rates of reduction in diarrhoea incidence and would be useful to investigate in future studies. Diarrhoea is a common symptom triggered by different causes and, to further focus preventive health-care strategies, a more in-depth analysis of diarrhoea causes should be done in future studies. Finally, despite the availability of vaccines to rotavirus, which is the leading cause of diarrhoea, we did not include coverage of this vaccine in our risk factor analysis because subnational estimates of rotavirus vaccine coverage are not yet available for all LMICs.

Because geospatial information is available for some causes of diarrhoea, estimating the subnational variation in those pathogens would help the interpretations and recommendations resultant from this work. Our current modelling framework aggregates ages to all children younger than 5 years but, in view of the strong relation between the case-fatality ratio and age, an age-specific model would be more informative. Our current framework prioritises prediction over inference. There is an increased need in building inferential models that can be used to infer the effect of interventions. Finally, our model assumes that every child within a population is equally likely to become infected and, on infection, is equally likely to develop disease or die. It does not address the vicious cycle of repeated enteric infections in the same individual that causes more severe symptoms. Incorporating these dynamics into our modelling framework can improve accurate accounting of the long-term burden of diarrhoea and quantification of those who are most vulnerable.

Every year, more than half a million children in LMICs die from diarrhoea; however, with treatment, most of these deaths can be averted. Our results serve as a new tool to pinpoint where these deaths occur. By establishment of good health practices from birth, children can be protected from enteric infections resulting in serious diarrhoeal episodes. Finally, by ensuring access to healthy environments, exposure to enteric pathogens can be prevented. Optimising reduction of diarrhoeal burden can be achieved by focusing on locations with the highest risk or those with the highest burden; either way, a detailed understanding of diarrhoeal morbidity and mortality, in addition to risk factors that drive diarrhoea, is necessary at the spatial scale at which policy is implemented. This work provides the data

necessary to formulate effective policies and precision public health programmes to ultimately stop the preventable loss of so many young lives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

In the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, diarrhoea was the third leading cause of death among children younger than 5 years and was reported to have caused an estimated 534 000 deaths. WHO's integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea calls for protection of children from disease by establishing good health practices, preventing infection from occurring, and treating infections when they occur. Over the past decade, large reductions in childhood mortality due to diarrhoea have been recorded across low-income and middle-income countries (LMICs), in part attributable to strategies to reduce child growth failure (CGF), improve water, sanitation, and hygiene (WASH), and increase access to oral rehydration therapy and vaccines. Several studies have recorded substantial between-country variation in both the likelihood of a child experiencing a diarrhoea episode and that episode resulting in death. To reduce the burden of childhood diarrhoea, the remaining subnational regions with the highest prevalence and those with the lowest levels of interventions should be identified.

Added value of this study

We present the first high-resolution subnational estimates of diarrhoeal morbidity and mortality from 2000 to 2017 in LMICs. We used Bayesian model-based geostatistics and an extensive geolocated dataset in combination with established methods from GBD 2017 for both burden estimation and risk factor association. We did a systematic assessment of local variation to estimate the distribution of diarrhoea prevalence, incidence, and mortality. Our estimates show considerable subnational variation in the diarrhoeal burden for children younger than 5 years. We synthesised new subnational estimates of the key risk factors of diarrhoea to discern averted deaths attributable to improvements in these drivers of diarrhoeal morbidity and mortality. Finally, when focusing on subnational regions with the highest remaining burden, we identified not only which regions of the world have the highest diarrhoeal burden and continued geographical inequalities but also the subnational risk factors that require targeted interventions to alleviate this burden.

Implications of all the available evidence

By providing estimates of remaining diarrhoeal burden at various spatial scales, we have identified countries and locations that are still most in need of preventive and protective measures. Our results indicate that regions with the highest burden had varied exposure to select risk factors; however, similar to previous studies, most high-burden areas showed some combination of poor WASH, high CGF, and low oral rehydration solution coverage. In view of the limited resources in many LMICs, quantification of both the local burden of diarrhoea and its drivers is important to maximise impact.

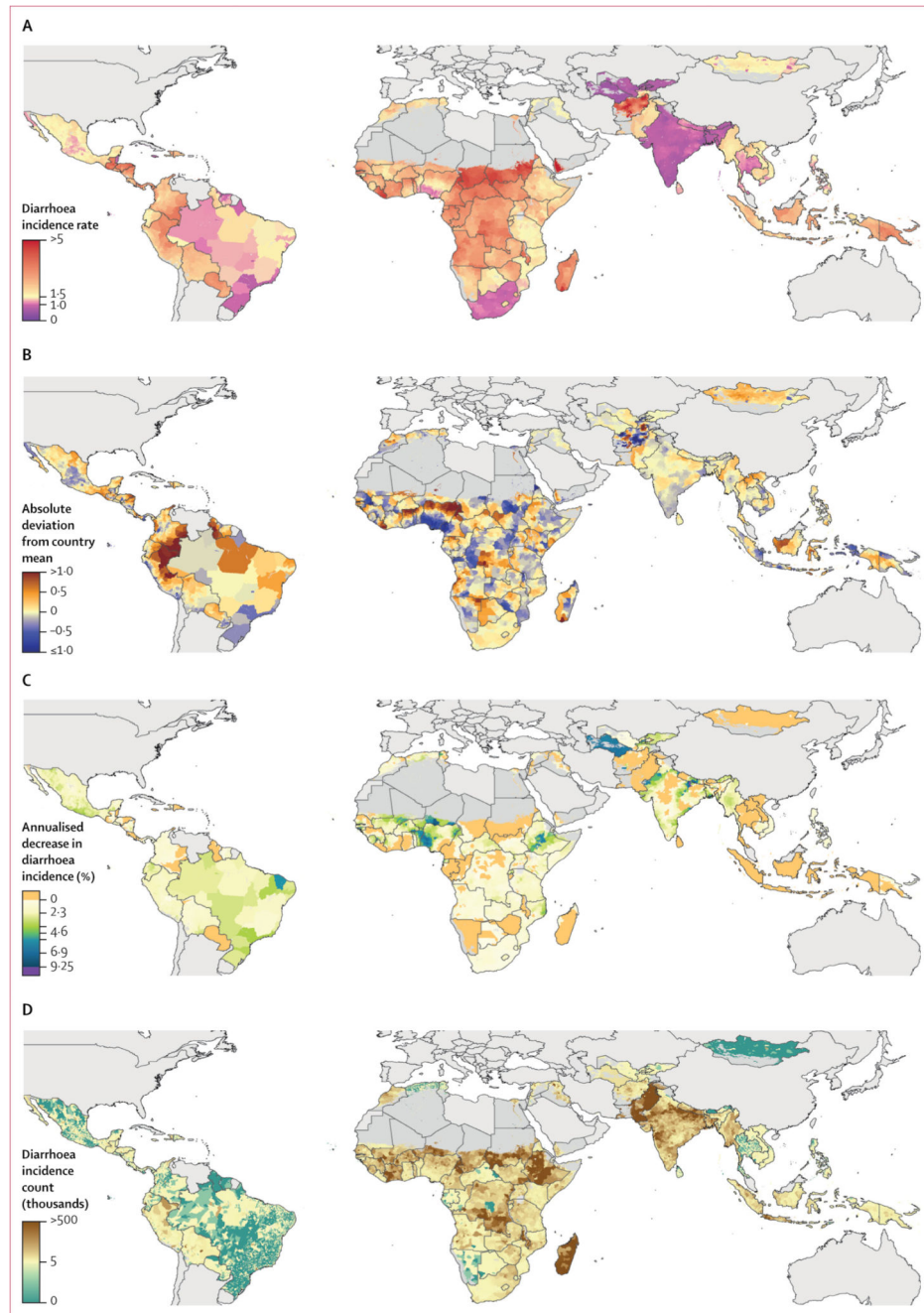


Figure 1. Mapping of diarrhoea incidence among children younger than 5 years in low-income and middle-income countries by second administrative-level unit, 2017

Estimated mean incidence rate per 1000 children in 2017 (A). Absolute deviation from mean incidence rate by country in 2017 (B). Annualised decrease in diarrhoea incidence rate from 2000 to 2017 (C). Estimated mean number of cases of diarrhoea among children in 2017 (D). All panels are aggregated to the second administrative-level unit. Maps reflect administrative boundaries, land cover, lakes, and population; grey-coloured grid cells were classified as barren or sparsely vegetated and had fewer than ten people per 1×1 km grid cell, or were not included in these analyses.^{33–38}

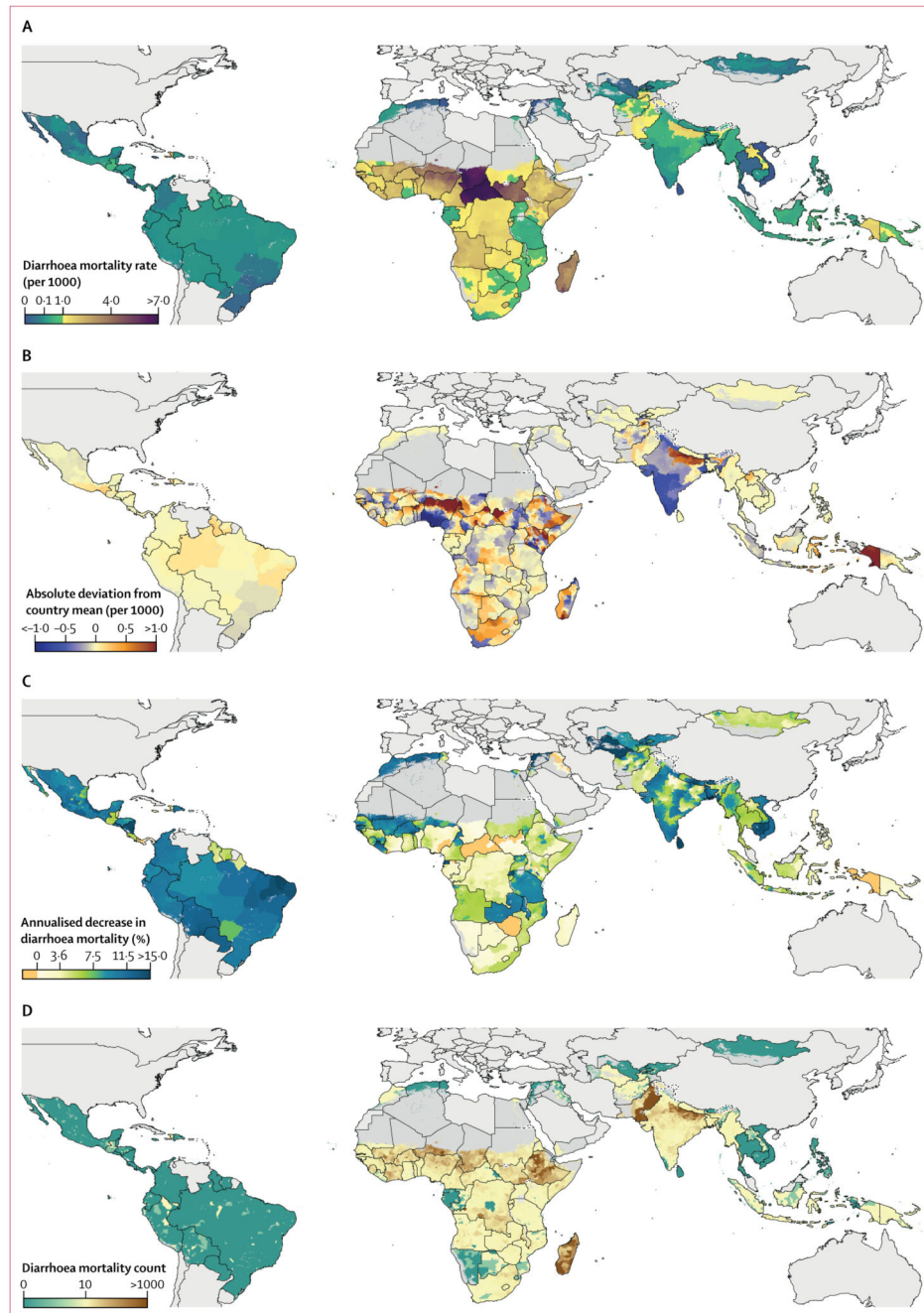


Figure 2. Mapping of diarrhoeal mortality among children younger than 5 years in low-income and middle-income countries by second administrative-level unit, 2017

Estimated mean mortality rate per 1000 children in 2017 (A). Absolute deviation from the mean mortality rate by country in 2017 (B). Annualised decrease in diarrhoeal mortality rate from 2000 to 2017 (C). Estimated mean number of diarrhoeal deaths among children in 2017 (D). All panels are aggregated to the second administrative-level unit. Maps reflect administrative boundaries, land cover, lakes, and population; grey-coloured grid cells were classified as barren or sparsely vegetated and had fewer than ten people per 1×1 km grid cell, or were not included in these analyses.^{33–38}

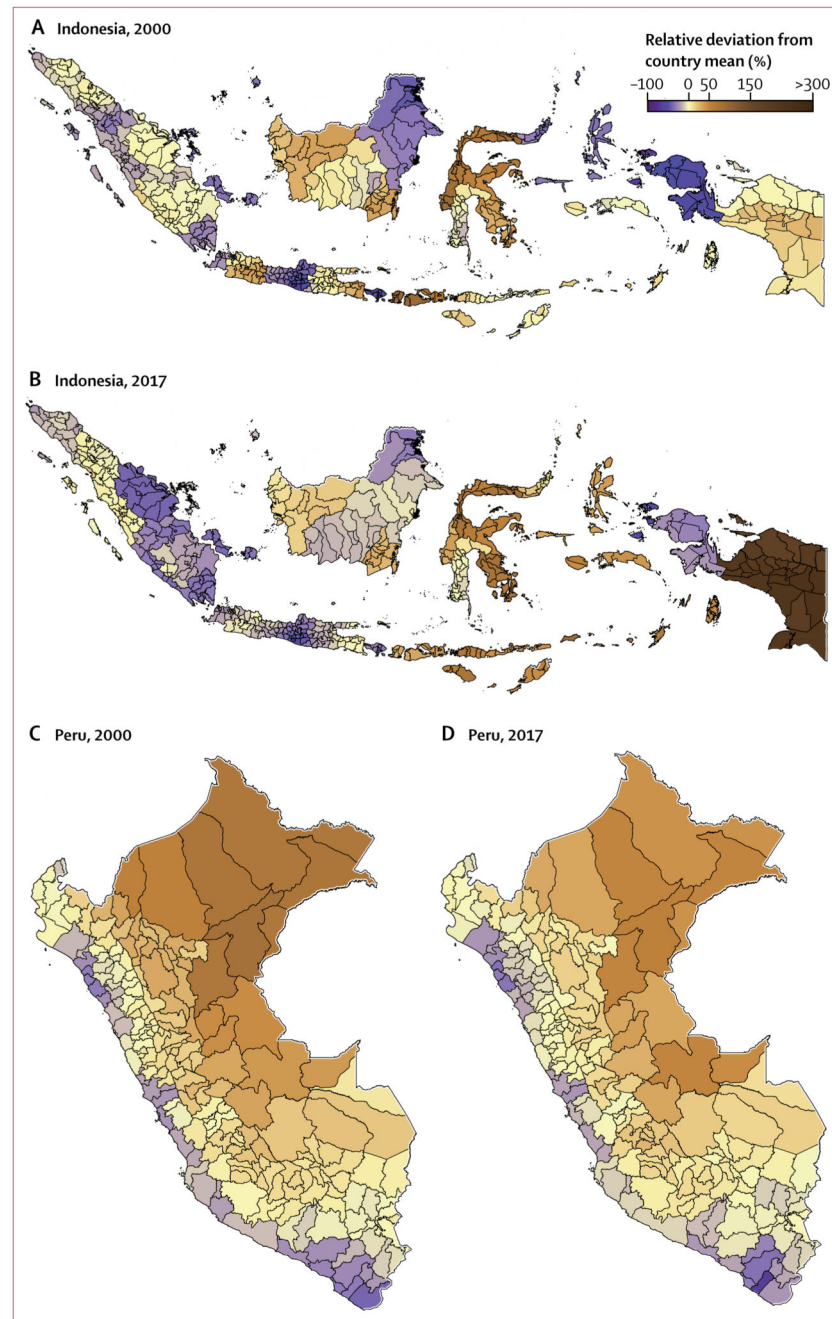


Figure 3. Relative geographical inequality of childhood diarrhoeal mortality in Indonesia and Peru in 2000 and 2017

Relative deviation of second administrative-level units from country mean for Indonesia in 2000 (A), Indonesia in 2017 (B), Peru in 2000 (C), and Peru in 2017 (D). Maps reflect administrative boundaries, land cover, lakes, and population; grey-coloured grid cells were classified as barren or sparsely vegetated and had fewer than ten people per 1×1 km grid cell, or were not included in these analyses.^{33–38}

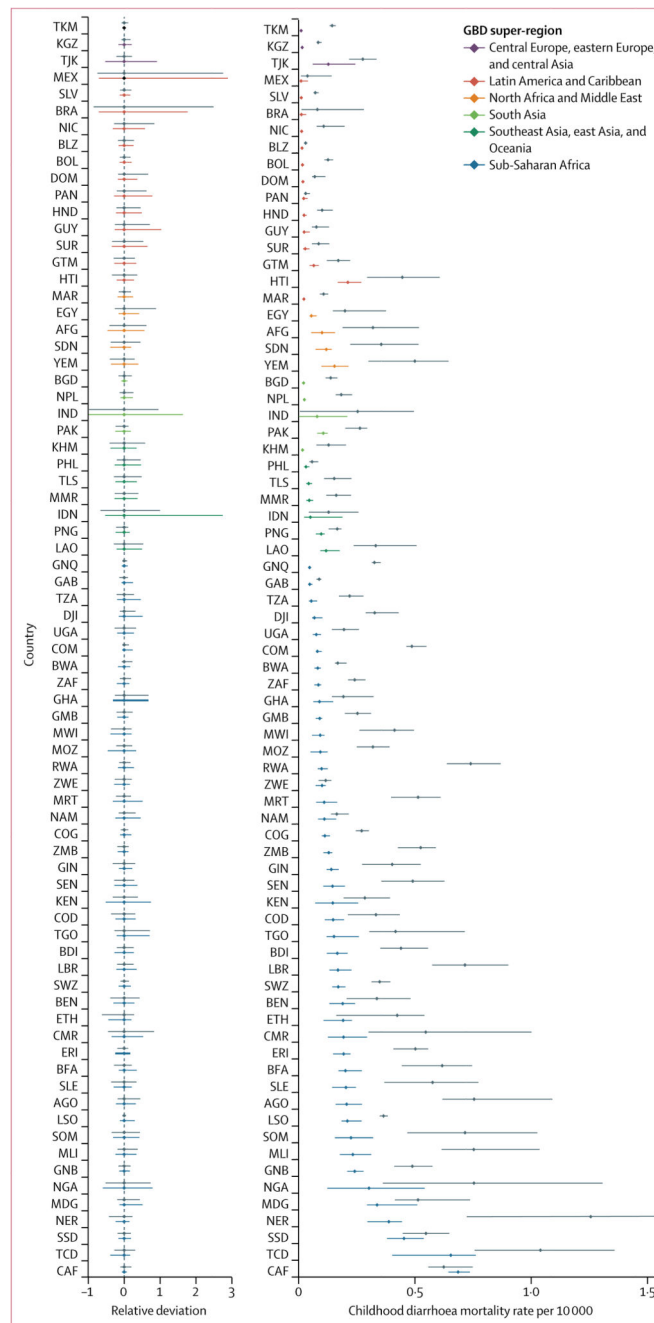


Figure 4. Geographical inequality of childhood diarrhoeal mortality at the second administrative-level unit

The left panel shows the range of relative deviation from the country mean diarrhoea mortality rate for each country in 2000 (upper bar) and 2017 (lower bar, coloured by GBD super-region). Each bar represents the range from the lowest to highest second administrative-level unit deviation for each country. The right panel shows LMICs with at least one death from diarrhoea per 10 000 children at the second administrative-level unit ranked by childhood diarrhoea mortality rate in 2017. Mean mortality rates are shown as dark grey dots and are national-level aggregations that correspond to the results shown in

figure 3. Each bar represents the range from the lowest to highest second administrative-level unit childhood diarrhoeal mortality rate for each country in 2000 (upper bar) and 2017 (lower bar, coloured by GBD super-region). Country names in both panels are the designated ISO 3166-1 alpha-3 codes. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. LMICs=low-income and middle-income countries.

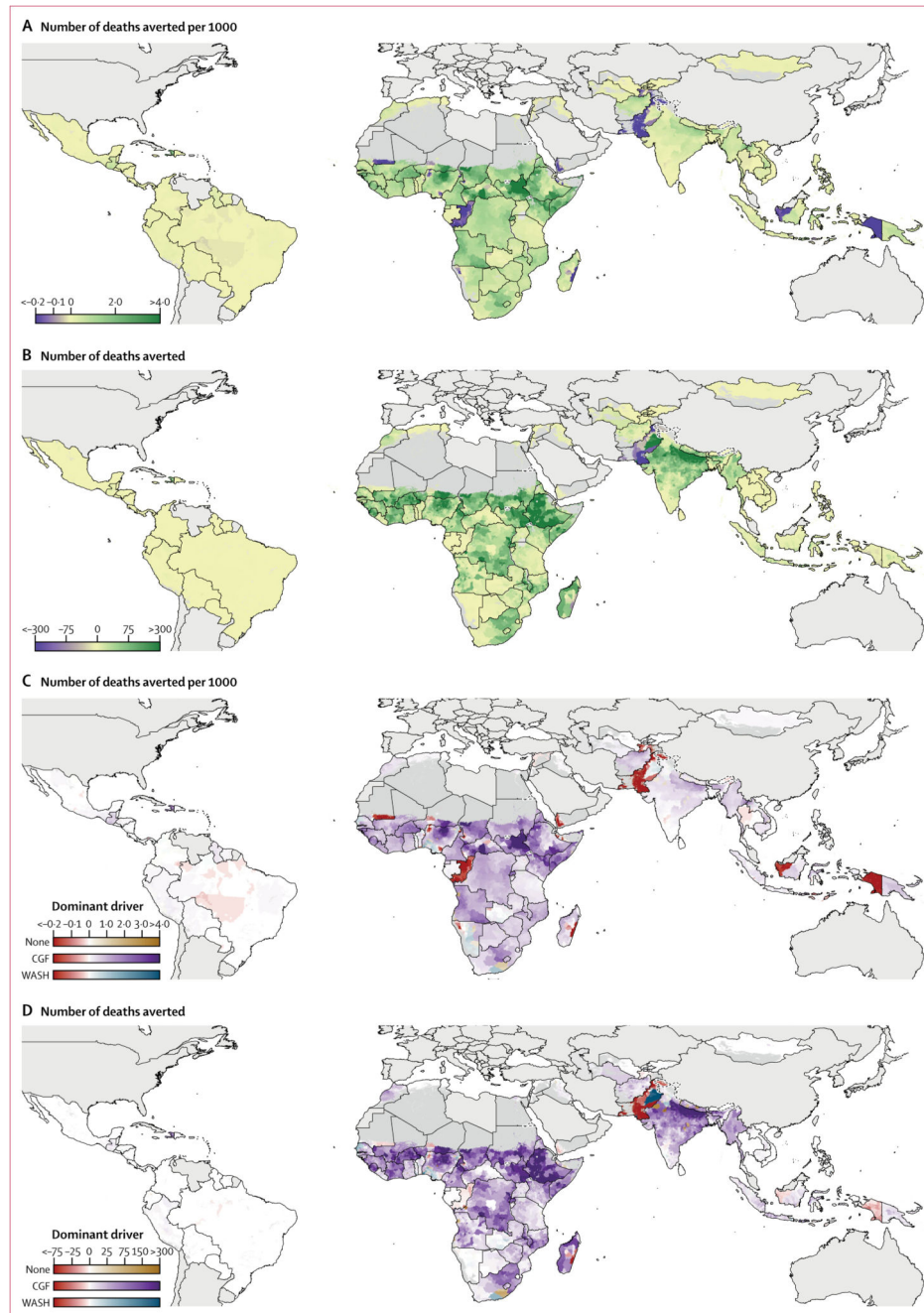


Figure 5. Averted diarrhoeal deaths in 2017 attributable to improvements in key risk factors implemented from 2000 to 2017

Number of deaths averted per 1000 children (A). Number of total deaths averted (B). Number of deaths averted per 1000 children with colour scale driven by dominant driver (C). Number of total deaths averted with colour scale driven by dominant driver (D). The risk factor contributing most of the reduction is indicated as either WASH (blue), CGF (purple), and none (gold), in which none represents locations where neither risk factor is dominant. Maps reflect administrative boundaries, land cover, lakes, and population; grey-coloured grid cells were classified as barren or sparsely vegetated and had fewer than ten people per 1

× 1 km grid cell, or were not included in these analyses.^{33–38} WASH water, sanitation, and hygiene. CGF=child growth failure.

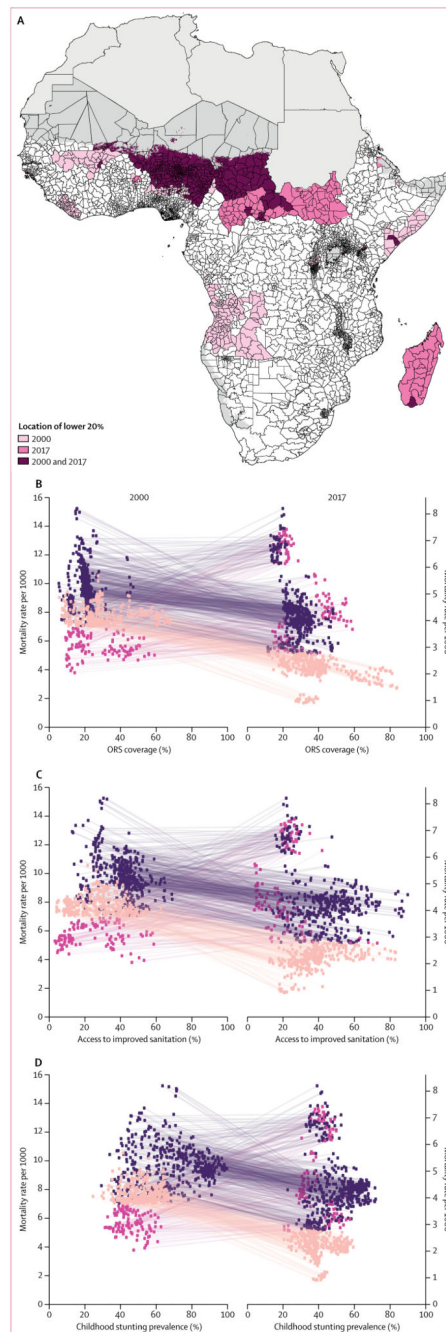


Figure 6. Second administrative-level units in sub-Saharan Africa with childhood mortality rates in the lower 20%

Second administrative units are coloured according to where children are most likely to die of diarrhoea, or the lower 20% (A). Scatter plots of mortality rates against ORS coverage (B),²¹ access to improved sanitation (C), and childhood stunting prevalence (D). The left axes are based on 2000 values whereas the right axes are based on 2017 values. The scale change in the y axis is due to substantial decline in mortality rates across most of sub-Saharan Africa. Because lower 20% is itself a relative distinction, scales are adjusted accordingly. Maps reflect administrative boundaries, land cover, lakes, and population; grey-

coloured grid cells were classified as barren or sparsely vegetated and had fewer than ten people per 1×1 km grid cell, or were not included in these analyses.^{33–38} ORS=oral rehydration solution.