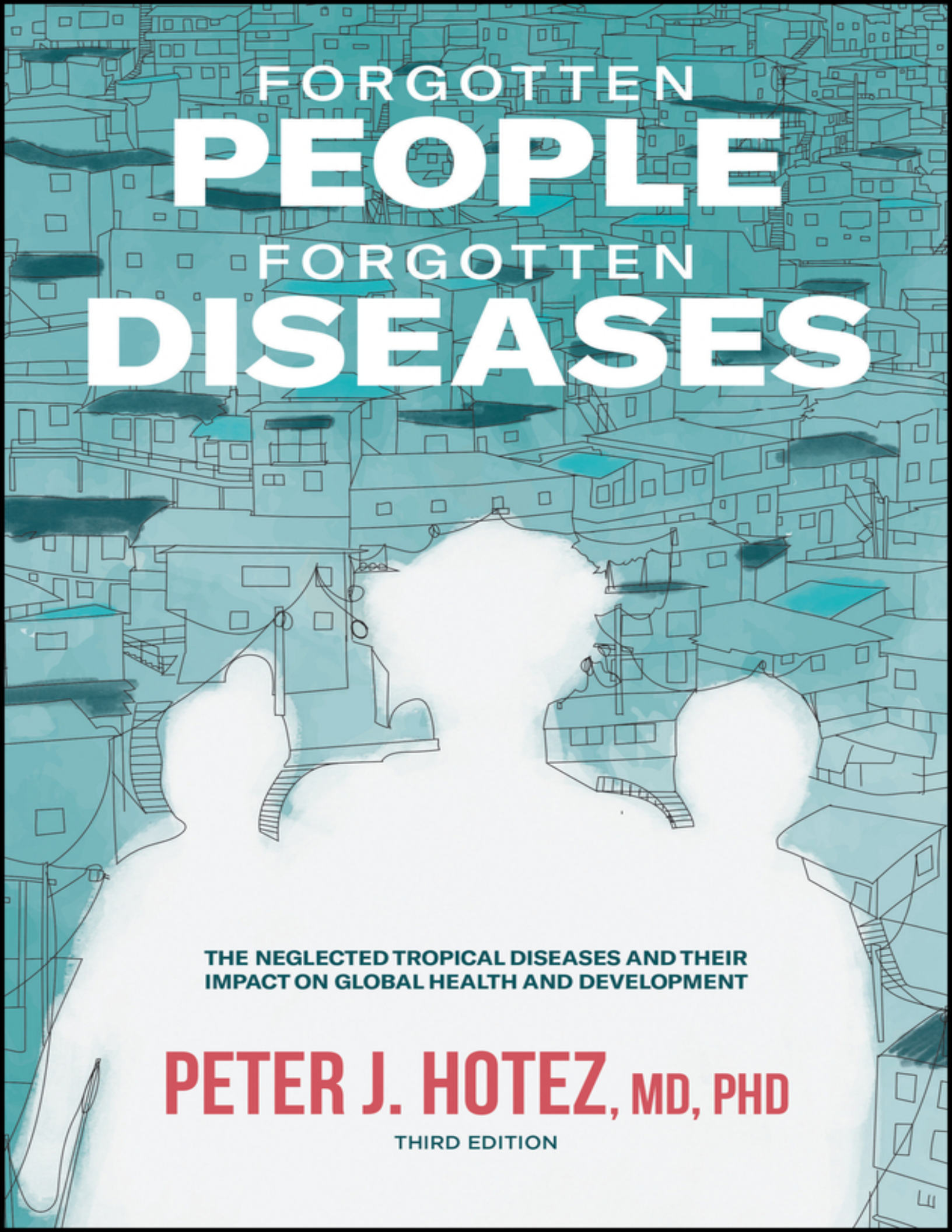
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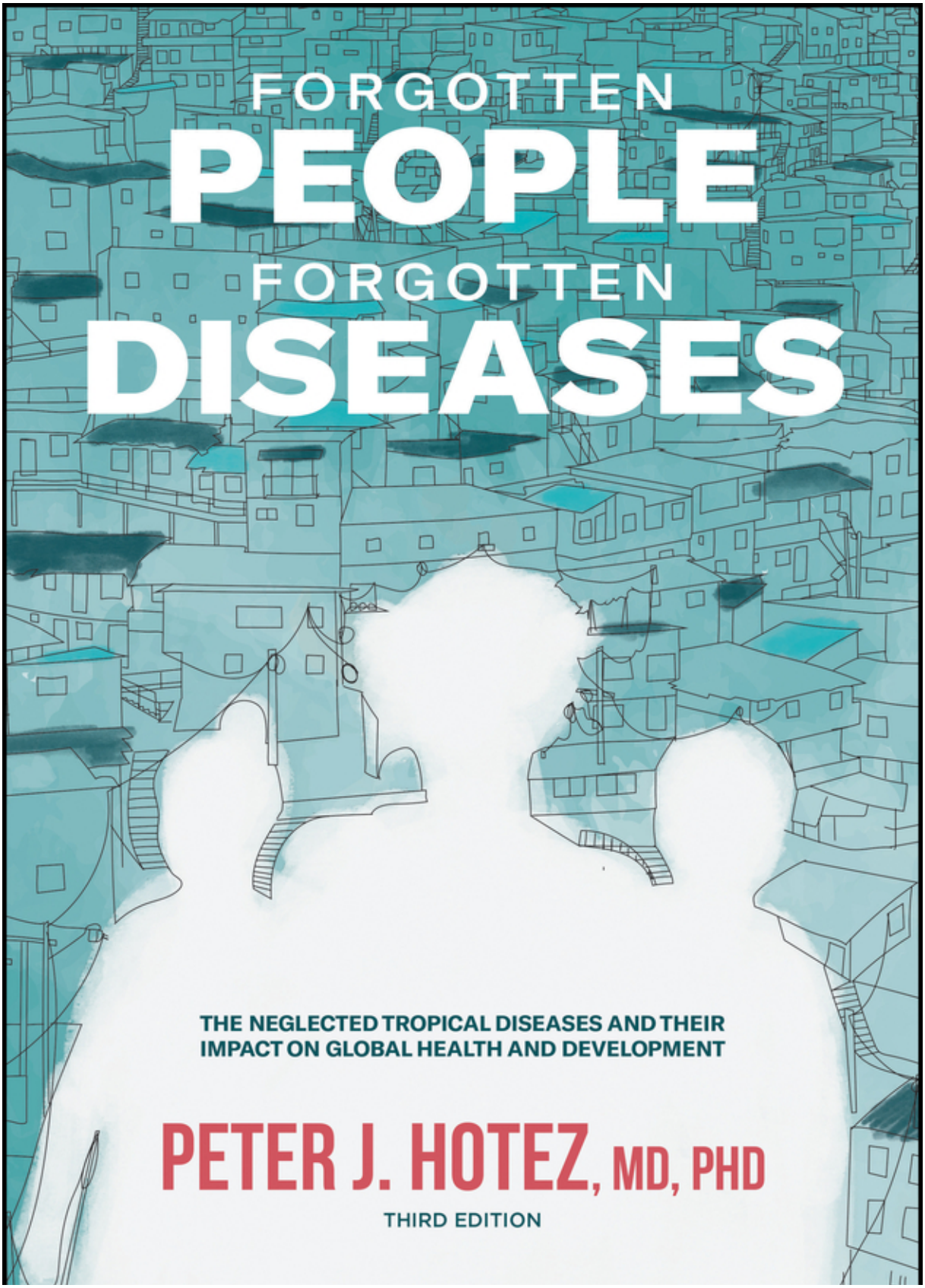
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Forgotten People, Forgotten Diseases

The Neglected Tropical Diseases and Their Impact on Global Health and Development

Third Edition

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Dedicated to my wife, Ann Hotez, and my four adult kids, Matthew Hotez, Emily Hotez, Rachel Hotez, and Daniel Hotez

To my mother, Jean Hotez, and brother and sister, Lawrence Hotes, M.D., and Elizabeth Kirshenbaum, J.D., and their families

To the memory of my brother and father, Richard Hotes, M.D. Edward Joseph Hotez

To Mark Wallace and Paul Klotman, M.D., and the leadership of Texas Children's Hospital and Baylor College of Medicine

And to the Bill & Melinda Gates Foundation, the U.S. National Institutes of Health, and the Kleberg Foundation for the opportunity to devote my life to the Neglected Tropical Diseases

Preface

Ever since junior high school, I have been fascinated by the application of scientific knowledge for solving tropical public health problems of global importance. Starting with an M.D.-Ph.D. dissertation begun in 1980, my adult life has been a quest to develop experimental vaccines for diseases of the poor, beginning with human hookworm infection. More than 20 years ago, thanks to the support of the Bill & Melinda Gates Foundation, I had the opportunity and good fortune to head a multidisciplinary team to develop and manufacture those vaccines and test them in areas of Brazil and Gabon and where hookworm was endemic. Since then our group, now co-headed by my science partner for the last 20 years, Dr. Maria Elena Bottazzi, has led the development of vaccines against schistosomiasis, Chagas disease, and other neglected tropical diseases (NTDs). Starting in 2011 we began using this same approach to develop coronavirus vaccines, including vaccines against SARS and MERS, and beginning in 2020 we turned our attention to COVID-19. As a result a new low-cost recombinant protein, COVID-19 vaccine is being scaled up for production in India, with the hope that it will fill a troubling gap in terms of COVID-19 vaccines for Africa and Latin America. While that work was intensely satisfying on both a professional and personal level, I realized that completing early-stage development of a new product for an NTD such as hookworm was in many ways the easy part! It was apparent that unless there was greater general awareness about the public health and economic importance of NTDs there would never be the political will and large-scale financial investment necessary to ensure global access to a hookworm vaccine, or indeed any other product for the diseases of poverty.

The first edition of *Forgotten People, Forgotten Diseases* focused on summarizing in mostly nontechnical language the major concepts about NTDs and how they cause human suffering, as well as their global importance and the unique and unusual opportunity we had to lift the world's poorest people out of poverty through low-cost and highly cost-effective control measures. Along with Professor David H. Molyneux of the Liverpool School of Tropical Medicine, Professor Alan Fenwick from Imperial College London, Dr. Lorenzo Savioli from the World Health Organization (as well as some of his close colleagues there, including Drs. Dirk Engels and Jacob Kumaresan), Professor Jeffrey Sachs and Dr. Sonia Ehrlich Sachs of Columbia's Earth Institute, and Dr. Eric Ottesen (then at Emory University), I formed an informal NTD working group, and in a series of policy papers published in *PLoS* and the *New England Journal of Medicine*, we were able to articulate the concept of the NTDs and how we could control or eliminate them through a global scale-up of access to essential medicines. We also established a Global Network for NTDs to coordinate global advocacy and resource mobilization efforts for these conditions.

By the time of the second edition, published in 2013, much had already begun to change. In the area of public health control in developing countries, and through support from the United States Agency for International Development (USAID), approximately 250 million people had been treated with all or part of an integrated “rapid-impact package” of essential medicines for seven of the most common NTDs—ascariasis, hookworm infection, trichuriasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma. The World Health Organization estimated that more than 700 million people annually were receiving essential medicines against one or more NTDs—almost all of whom were living in the poorest

parts of Africa, Asia, and the Americas—representing some of the largest public health control efforts ever undertaken. The successes of both mass drug administration and product development activities rely heavily on a substantial alliance of private-public partnerships, including product development partnerships and nongovernmental development organizations, as well as international advocacy efforts to raise awareness about the NTDs (including the Global Network for Neglected Tropical Diseases) and parallel resource mobilization initiatives. Another major development was the realization that NTDs also occur among the poor living in wealthy countries, especially the United States and, to some extent, Europe. In 2011, I committed my life and work to this problem by relocating a group of more than a dozen scientists to Texas in order to establish the Texas Children's Hospital Center for Vaccine Development and the new National School of Tropical Medicine at Baylor College of Medicine. Through the hard work of our faculty and scientists, we uncovered an extraordinary disease burden from NTDs in Texas and adjacent Gulf Coast states, including Chagas disease, dengue, Zika virus infection, murine typhus, toxocariasis, trichomoniasis, and hookworm infection. NTDs and poverty are inextricably linked.

This third edition of *Forgotten People, Forgotten Diseases* coincides with the third decade of the NTDs movement and ecosystem that began in the early 2000s. Now mass drug administration/preventive chemotherapy is taken for granted as a recognized international standard for advancing global health and for addressing the plight of people who live in profound poverty. But this approach truly represents hard-fought efforts from our small group of tropical and parasitic disease experts, who included my “three musketeer” colleagues Alan Fenwick and David Molyneux, as well as the leaders of the WHO's Department

of NTDs Control—Lorenzo Savioli, Dirk Engels, Mwele Ntuli Malecela, and so many others.

Today, more than 1 billion people benefit from access to essential NTD medicines, and also the many collateral benefits in terms of therapeutic effects on diseases that we did not necessarily intend to target. This book tells the story of how the NTD space evolved and control was implemented on a global scale. It discusses some of the major non-governmental development organizations committed to NTDs and advocacy for the NTDs, and the important contributions of the U.S. and U.K. governments, as well as the Bill & Melinda Gates Foundation, as well as other organizations. It tells how we measured the health and economic impact of the NTDs through the Global Burden of Disease (GBD) Study of the Institute for Health Metrics and Evaluation at the University of Washington. It also highlights the role of innovation in the development of new treatments and vaccines for NTDs, and the role of important product development partnerships, including ours, and others such as DNDi, IDRI, IVI, and FIND, to name some. It explains how science and vaccine diplomacy ensures that a new generation of these biotechnologies reaches the world's poorest people. Most of all, it tells the story of the world's people who live in extreme poverty and what it means for them to live with NTDs.

PETER J. HOTEZ
Houston, Texas

Acknowledgments

This book and my career in tropical medicine owe so much, to so many people. I had the unique opportunity to thank many of them during my 2011 Presidential Address to the American Society of Tropical Medicine and Hygiene.[1] I again want to thank my bosses at Baylor College of Medicine and Texas Children's Hospital, Dr. Paul Klotman and Mark Wallace, respectively, and the boards of those two institutions. I also thank my long-standing colleagues and partners in battle against the neglected tropical diseases (NTDs), including Professors David Molyneux and Alan Fenwick; and Drs. Lorenzo Savioli, Dirk Engels, and Mwele Ntuli Malecela—past and current heads of the Department of Control of NTDs of the WHO. Also thanks to TDR, the Special Programme for Research and Training in Tropical Diseases, of the World Health Organization. I also thank my science partner for the last 20 years, Dr. Maria Elena Bottazzi, and our team of amazing scientists at the Texas Children's Center for Vaccine Development, and the heads and directors of the many organizations committed to NTDs, which include the areas of implementation, product development, and advocacy. Along those lines I want to thank the heads of the important non-governmental development organizations, public-private partnerships, and product development partnerships committed to the NTDs, and my good colleagues at *PLoS Neglected Tropical Diseases*. A special thank you to Drs. Patrick Soon-Shiong and Gary Michelson for their commitment and interest in NTDs. I also extend my appreciation to the work of the Institute for Health Metrics and Evaluation of the University of Washington for its Global Burden of Disease

Study (GBD) 2019. This book presents the results and mapping from the GBD 2019 for each of the major NTDs. I also want to thank Alyssa Milano for her long-standing commitment to NTDs and both Alyssa and Soledad O'Brien for their willingness to contribute forewords for the previous two editions. Many thanks to Nathaniel Wolf for his editorial assistance and insights and to Ashish Damania for his help with new maps and other related materials. I also thank Douglas Soriano Osejo for his help. Finally, many thanks to the donors and partners that made it possible for me to pursue a career in NTDs, including the Bill & Melinda Gates Foundation, the U.S. National Institutes of Health (especially the National Institute of Allergy and Infectious Diseases and the Fogarty International Center), the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation, the Carlos Slim Foundation, JPB Foundation, Tito's Vodka, Southwest Electronic Energy Medical Research Institute, Blavatnik Charitable Trust, Rebecca Marvil and Brian Smyth, Mendell Family Fund, MD Anderson Foundation, Rawley Foundation, John S. Dunn Foundation, Jay H. Newman and Newman Family Foundation, Jerold B. Katz Foundation, Jesse W. Couch Charitable Foundation, and others. Finally, I want to thank my wife Ann Hotez and my family for bearing with me through another edition of *Forgotten People, Forgotten Diseases*, and Christine Charlip for “rolling the dice” once again with me at ASM Press.

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Houston, Texas

Note

1. **Hotez PJ.** 2012. ASTMH Presidential Address. Four Horsemen of the Apocalypse. *Am J Trop Med Hyg* **87:** 3–10.

1 Introduction to the Neglected Tropical Diseases: the Ancient Afflictions of Stigma and Poverty

The age of hypocrisy has been succeeded by that of indifference, which is worse, for indifference corrupts and appeases: it kills the spirit before it kills the body. It has been stated before, it bears repeating: the opposite of love is not hate, but indifference.

ELIE WIESEL, *A JEW TODAY*, P. 17

It is a trite saying that one half the world knows not how the other lives. Who can say what sores might be healed, what hurts solved, were the doings of each half of the world's inhabitants understood and appreciated by the other?

MAHATMA GANDHI

Since the beginning of the 21st century, we have seen unfold a new sense of urgency about the plight of the world's poorest people in developing countries. Today, the average well-educated layperson living in “the North” (North America, Europe, and Japan) is far more aware than ever before about the suffering of the people living in “the South” (the developing countries of sub-Saharan Africa, Asia, and the Americas). Almost certainly, the human catastrophe of HIV/AIDS in sub-Saharan Africa, known as the “plague of the 21st century,” and epidemics or pandemics from Ebola virus and Zika virus infections, and most recently coronavirus disease 2019 (COVID-19), have helped to focus world attention on health threats from infectious diseases, especially problems in the world's low- and middle-income countries (LMICs).[1]

Simultaneously, an unprecedented and extraordinary advocacy effort led by some highly influential international leaders and celebrities has helped to fuel a 21st-century global health movement. Throughout the decade of the 2000s, Bono, Angelina Jolie, Brad Pitt, George Clooney, Oprah Winfrey, Annie Lennox, Bob Geldof, and other actors, celebrities, and musicians; Bill Gates, Melinda French Gates, Warren Buffett, Carlos Slim and his family, and other philanthropists; Jeffrey Sachs; Chelsea Clinton; Prime Ministers Tony Blair, Gordon Brown, David Cameron, Theresa May, and Boris Johnson of the United Kingdom; and Secretaries of State Hillary Clinton and John Kerry and Presidents Jimmy Carter, Bill Clinton, George W. Bush, and Barack Obama of the United States have donated their time and energy to advocate for the health of the world's poorest people. These efforts captivated world attention and have even infused an element of glamour into solving global health problems. Between 2005 and 2006 alone, Bono, Bill Gates, and Melinda Gates were named *Time* magazine Persons of the Year; the Time Global Health Summit in New York was branded the “Woodstock of global health”; Brad Pitt narrated a 6-hour-long documentary, *Rx for Survival, a Global Health Challenge*, for PBS; former President Clinton featured global health issues at his annual Clinton Global Initiative; and Bono and Bobby Shriver launched Product RED to support HIV/AIDS, malaria, and tuberculosis relief at the 2006 World Economic Forum in Davos, Switzerland.

As a university professor and now as a dean, I can attest that these activities stimulated an unprecedented level of interest in global health issues from both undergraduates and graduate public health and medical students. With the important exception of our 2020–2021 years of COVID-19, almost every week during the academic year I have been visited by one or more young persons who request advice on how they can help solve a health problem in an LMIC. I

am not the only faculty member to have this experience—today, new university-wide global health institutes are springing up at Duke, Baylor, Brown, Yale, Vanderbilt, Harvard, Emory, Washington University in St. Louis, the University of California campuses, University of Washington, and elsewhere, as university deans and presidents scramble to keep up with student interest.

Like any movement, the one in global health that I benchmark as beginning in 2000 was stimulated by a *manifesto*, which is defined by Webster as "a public declaration of motives and intentions by a government or by a person or group regarded as having some public importance."[1] For the global health movement, we can point to at least three landmark 21st-century policy documents that have effectively served as manifestos.

The first had its origins in January 2000, when then-World Health Organization (WHO) Director-General Gro Harlem Brundtland launched the Commission on Macroeconomics and Health (CMH) and appointed the international macroeconomist Jeffrey Sachs to serve as its chair. Jeff and his colleagues were charged with analyzing the impact of health on development. Their *Report of the CMH*, illustrated with examples of how health investments translate into economic development, elegantly articulated a profound relationship between disease and chronic poverty. As a result, the world's most influential finance ministers and policymakers began to regard improvements in global health as an important tool for poverty reduction. A second initiative was also launched in 2000 when the General Assembly of the United Nations convened in New York City to adopt a resolution known as the UN Millennium Declaration. The Declaration was a renewed call for sustainable development and for the eradication of poverty, and its core was a set of eight specific Millennium Development Goals (MDGs) along with a set of specific

targets for the year 2015. As shown in Table 1.1, three of the goals (MDGs 4, 5, and 6) specifically emphasize health. Finally, a third manifesto was *Our Common Interest: Report of the Commission for Africa*, commissioned by British Prime Minister Tony Blair to provide specific recommendations on how to accelerate development and reduce poverty in Africa. The report served as an important blueprint for commitments by the Group of Eight (G8) nations at their 2005 summit in Gleneagles, Scotland.

Table 1.1 The MDGs

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria, and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

Unlike many UN and international declarations, which too often are forgotten by the global community almost as soon as they are written, the CMH report, the MDGs, and the *Report of the Commission for Africa* continue to exert a major influence on global policymakers. Although the MDGs ended in 2015, they have since continued under a new set of Sustainable Development Goals (SDGs), sometimes just referred to as the “Global Goals”. Equally important, together with the new advocacy by leaders and celebrities, the global health manifestos have stimulated high-level efforts to invent innovative financial instruments for supporting disease control, including some very substantial funding initiatives from both the G7 nations and some prominent private philanthropic organizations such as the Bill & Melinda Gates Foundation.

MDG 6 (to “combat HIV/AIDS, malaria, and other diseases”) has been a particular target of these new funds, with approximately US$90 billion committed so far by the U.S. Congress for HIV/AIDS through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR),[2] together with more than US$6 billion for malaria through the U.S. President's Malaria Initiative (PMI). Internationally, the Global Fund to Fight AIDS, Tuberculosis, and Malaria now commits more than US$4 billion annually to support interventions against these infections (http://theglobalfund.org), while the Gates Foundation has also committed vast sums. Practically speaking, these extraordinary new financial commitments mean that unprecedented numbers of poor people in Africa and elsewhere are receiving lifesaving antiretroviral medications for the treatment of HIV/AIDS or drugs and bed nets for the treatment and prevention of malaria. Such interventions are producing significant positive changes to the global health landscape under the auspices of the SDGs.

Unfortunately, with the exception of some important support from the Gates Foundation, the flurry of global health advocacy and resource mobilization occurring over the past few years has, until recently, largely bypassed the third, “other diseases” component of the original MDG 6. This neglect is particularly true for a group of exotic-sounding tropical infections that represent a health and socioeconomic problem of extraordinary dimensions but one that world leaders and global health advocates are only now waking up to. Beginning in 2005, an original core group of the 13 major so-called neglected tropical diseases, or NTDs, was proposed,[3] which has since been expanded by the WHO to a list of 20 diseases and conditions (Table 1.2). They include the major parasitic worm infections of humans, such as the major soil-transmitted helminth infections, e.g., ascariasis (roundworm infection), hookworm infection, and trichuriasis (whipworm infection); and lymphatic filariasis (LF or elephantiasis), schistosomiasis (snail fever), onchocerciasis (river blindness), food-borne trematode infections (liver fluke, lung fluke, and intestinal fluke), cysticercosis, echinococcosis, and dracunculiasis (guinea worm infection). In addition, the NTDs include an important group of infections caused by single-celled protozoan parasites, such as Chagas disease, leishmaniasis, and human African trypanosomiasis (sleeping sickness). Several nonparasitic infections are also prominent, including some atypical bacterial infections, such as trachoma, yaws, and endemic treponematoses; the mycobacterial infections Buruli ulcer and leprosy; mycetoma and related fungal diseases; and selected viral infections, such as dengue and rabies. More recently, snake envenomation and ectoparasitic conditions, especially scabies, were added. Still other tropical infections can also be considered NTDs,