A War Not Easily Won:

Curbing Infectious Diseases in Developing Countries

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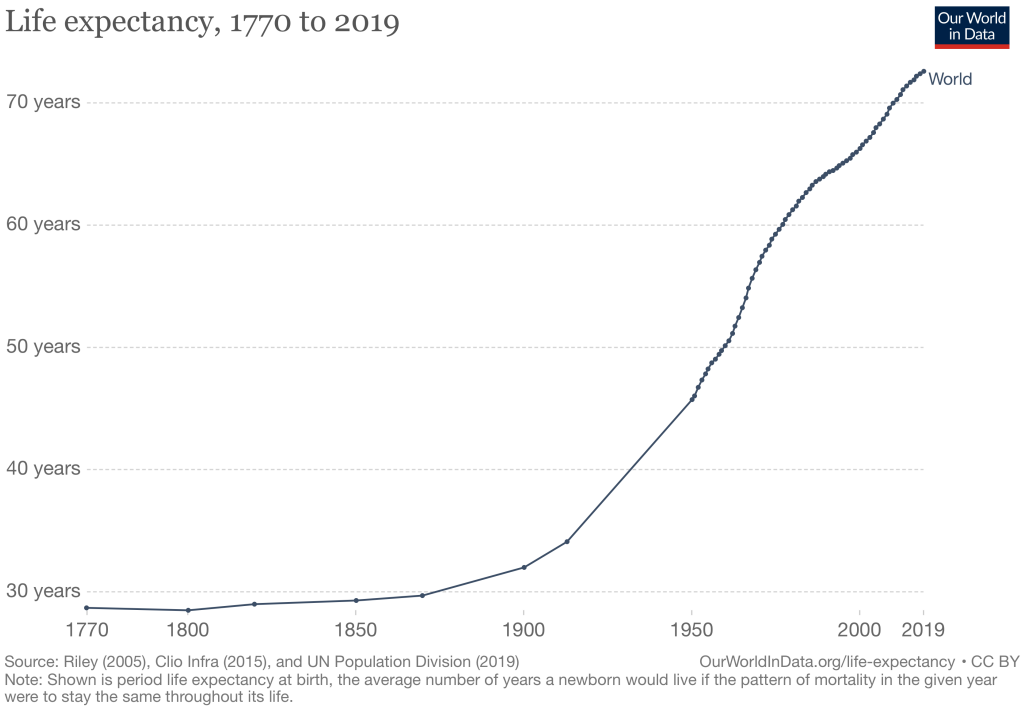
Introduction

By one crucial measure, the earth is becoming a healthier place for humans. Until the nineteenth century, the life expectancy of the average person born on the planet was between 20 and 30 years. As late as 1820, it was approximately 26 years. It then began to increase, first slowly, then rapidly, then more slowly. Today, the number is roughly 73 years and still rising.[1] Figure 1 shows how far we have come.



[1] The figures set forth in this paragraph were culled from the following sources: Samuel H. Preston, "Human Mortality Throughout History and Prehistory," in *The State of Humanity*, ed. Julian L. Simon, E. Calvin Beisner, and John Phelps (Cambridge, MA: Blackwell, 1995); James C. Riley, *Rising Life Expectancy: A Global History* (Cambridge: Cambridge University Press, 2001), 1, 33.; Indur M. Goklany, *The Improving State of the World* (Washington, D.C.: Cato Institute, 2007), 31-34.; WHO, "World Health Statistics 2014," http://www.who.int/gho/publications/world_health_statistics/en/.;"World Health Statistics 2019: Monitoring Health for the Sustainable Development Goals," (2019), https://www.who.int/gho/publications/world_health_statistics/2019/en/. Riley, *Life Expectancy*, Chapter 1.; WHO, "Life Expectancy," http://www.deathreference.com/Ke-Ma/Life-Expectancy.html#b.; C.J.L. Murray, Mohsen Naghavi, and Alan Lopez, "Global, Regional, and National Age–Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013," *Lancet* 385 (2015). Where the data supplied by different sources have diverged, we have tried to locate the median, but have given extra weight to sources that seem to us especially reliable.

All of these numbers are potentially misleading in one respect: they presume that health conditions would not change during the person's lifetime. Because health conditions were improving during the nineteenth and twentieth centuries, the average person in fact lived somewhat longer.

Whether we are now approaching an asymptote is contested. Some scientists believe that the human life span cannot be extended indefinitely – and thus that average life expectancy will never rise higher than somewhere between 85 and 100 years. Others believe that scientific advances will continue to raise the ceiling. Because this debate has little to do with the issues addressed in this book, we will not pursue it further.

Buried in these averages, however, are persistent disparities among the countries of the world. To see them, we will use data gathered by the World Health Organization (WHO) for 2019, the most recent year from which such numbers are currently available. As of that year, life expectancy at birth in the United States was 78.5 years. Many developed countries had attained even higher levels. In Japan, for instance, life expectancy was 84.3 years. By contrast, in Somalia, it was 56.5 years. The situation in the rest of sub-Saharan Africa was only modestly better; in most countries in the region, life expectancies were in the 50s or low 60s. Conditions in Latin America were better, but still substantially worse than in North America or Western Europe. For example, life expectancy in Bolivia was 72.1 years. Many countries in Southeast Asia had similar numbers.[2] Figure 2 shows the ranges into which all of the major countries in the world currently fall.

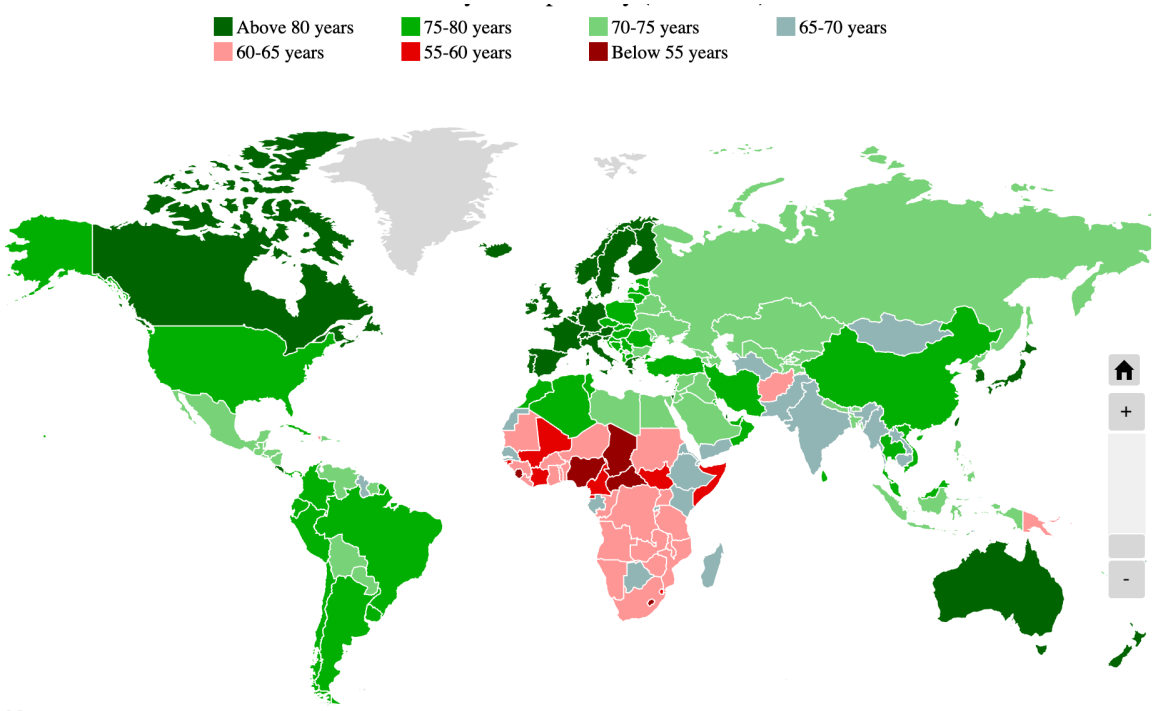


Figure 2: Life Expectancy at Birth (2019)

To be sure, some of the countries on the lower end of this spectrum had recently experienced improvements – indeed, were closing the gap between themselves and the countries at the top. For example, while life expectancy in the United States rose by only 1.8 years between 2000 and 2019, in Bolivia, it rose by 6.2 years; in India by 8.7 years; in China, by 5.8 years. Many other countries on the lower end, however, stagnated during that period.[3]

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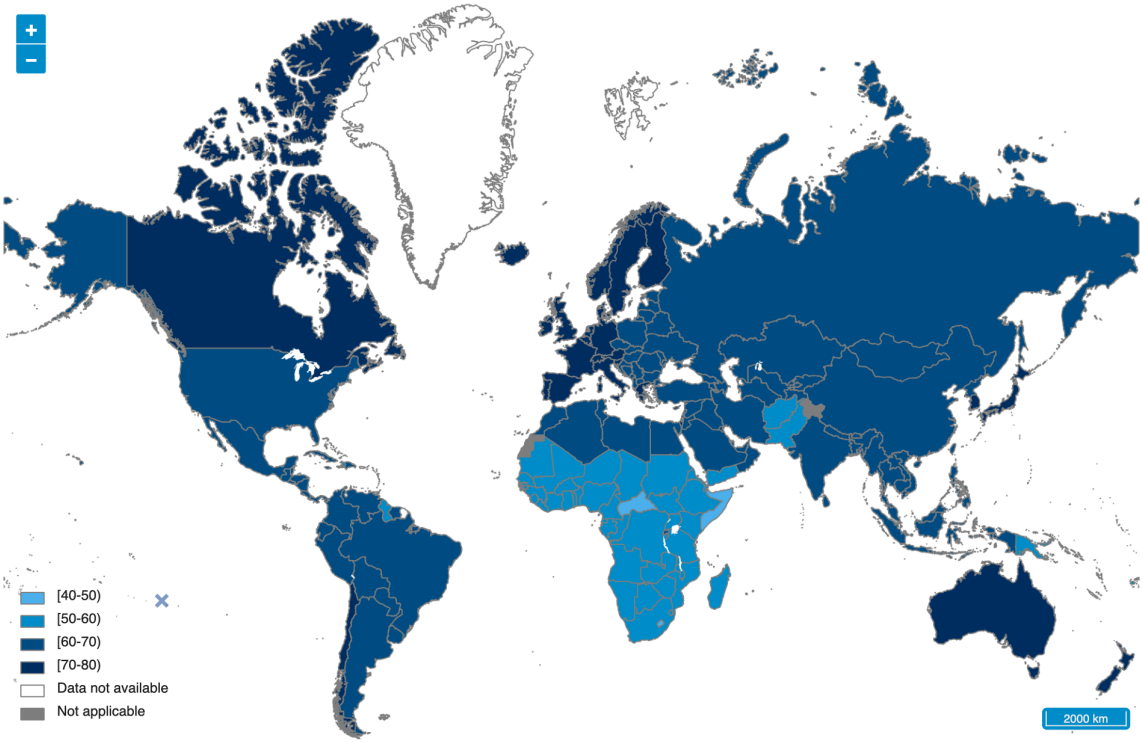
[2] See WHO, "Global Health Observatory Data Repository (last updated 2020-12-04), available at https://apps.who.int/gho/data/node.main.688. The numbers provided by the World Bank are slightly different. Because we will be relying on other data collected by the WHO, for consistency we will continue to use its life-expectancy numbers throughout this book.

[3] All of these numbers are derived from the WHO's "Global Health Observatory Data Repository Cf. Goklany, *The Improving State of the World*, 38. ("Of the 176 entities for which the World Bank's online database had data, 39 had lower life expectancy in 2003 than in 1990. Of those, 25 were in sub-Saharan Africa, 9 were part of the former Soviet Union, 4 were from Latin America and the Caribbean, and 1 was North Korea.")

The disparity between rich and poor countries becomes even sharper when one considers, not merely how long the typical resident lives, but also the amount of time he or she is sick. The WHO has developed a metric for comparing countries and regions on this basis. "Healthy Life Expectancy" (HALE) measures life expectancy at birth, adjusted (downward) for time spent in ill health. "It is most easily understood as the equivalent number of years in full health that a newborn can expect to live based on current rates of ill-health and mortality."[4] The map set forth below compares the HALEs of the countries of the world, using the most recent data collected by the WHO.

Figure 3: Healthy Life Expectancy (HALE) at Birth (2019)[5]



As the map makes clear, the divergence among countries is extreme. As of 2019, HALE in Japan was 74.1; in the United States, 66.1. In parts of sub-Saharan Africa, it was under 50.[6]

These data demand our attention for two independent reasons. First, radical disparity in access to a condition as fundamental as health should outrage us. Second, the data provide

[4] WHO, "The World Health Report 2004: Changing History," (2004): 96. The Report goes on to explain: "The measurement of time spent in poor health is based on combining condition-specific estimates from the Global Burden of Disease study with estimates of the prevalence of different health states by age and sex derived from the MCSS [Multi-Country Survey Study], and weighted using health state valuations." The methodology that the WHO employs to "weight" – in other words, to compare the severity of – different afflictions is controversial. We will examine the controversy and its implications in Chapter 9. The controversy has little relevance, however, for the gross comparisons with which we are presently concerned.

[5] Source: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-hale-healthy-life-expectancy-at-birth (2021).

[6] See WHO, "Global Health Observatory Data Repository.

an antidote to fatalism. The high levels of health in some parts of the world make it plain that the low levels in other parts are not inevitable. Collectively, we could do much better – and we should.

The first step in determining how we might change these conditions is, of course, to determine what causes them. Why are conditions so good in some regions and so bad in others? As one might imagine, many factors are at work. For example, countries at war have lower life expectancies than countries at peace.[7] Both suicide and homicide rates vary sharply by country.[8] The prevalence of smoking in each country affects the incidence of lung cancer (and related diseases), which in turn affects life expectancy.[9] Countries where swimming is taught and water hazards are guarded have lower rates of death from drowning than countries that lack such protections.[10] The incidence of fatal traffic accidents varies with the number of vehicles per capita, the frequency with which drivers consume alcohol or drugs, the strength of traffic safety regulations, and so forth.[11] But among the many causal factors, one looms largest. The principal determinant of the inequality reflected in Figures 2 and 3 is the incidence of infectious and parasitic diseases.

The easiest way to discern the importance of this variable is to compare the magnitude of the causes of morbidity and mortality in different parts of the world. For this purpose (and for many other purposes throughout this book), we will use yet another metric developed by the World Health Organization, known as Disability Adjusted Life Years (DALYs). That index is designed to measure the losses caused by a particular disease or condition both through premature deaths and through ill health. One DALY "can be thought of as one lost year of 'healthy' life."[12] For reasons we will explore later, this metric is far from perfect, but it is the only relevant index for which we currently have good comparative data – and is adequate for present purposes.

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[7] See [United Nations Development Programme], "The Human Impact of War: Life Expectancy in Selected Countries," http://www.undp.org/cpr/content/economic_recovery/Key_data_1.shtml.

[8] See World Health Organization, Preventing Suicide: A Global Imperative, http://www.who.int/mental_health/suicide-prevention/en/. A few examples show the disparity in suicide rates: Republic of Korea: 41.7 per 100,000 for males, 18 for females; Japan: 26.9 for males, 10.1 for females; France: 19.3 for males, 6 for females; Peru: 4.4 for males, 2.1 for females. An interactive map showing the rates in each country can be found at http://gamapserver.who.int/gho/interactive_charts/mental_health/suicide_rates/atlas.html. For the equally sharp divergence in homicide rates, see World Bank, Intentional Homicides (per 100,000 people): http://data.worldbank.org/indicator/VC.IHR.PSRC.P5.

[9] See Samuel H. Preston, Dana A. Glei, and John R. Wilmoth, "Contribution of Smoking to International Differences in Life Expectancy," in *International Differences in Mortality at Older Ages: Dimensions and Sources*, ed. Eileen M. Crimmins, Samuel H. Preston, and Barney Cohen (Washington, D.C.: National Academies Press, 2010).

[10] See Jeremy N. Smith, "Fatal Accidents as a Global Health Crisis," New York Times, Feb. 16, 2015.

[11] See, for example, J. R. M. Ameen and J. A. Naji, "Causal Models for Road Accident Fatalities in Yemen," *Accident Analysis and Prevention* 33, no. 4 (2001); Siem Oppe, "The Development of Traffic and Traffic Safety in Six Developed Countries," ibid.23, no. 5 (1991).

[12] WORLD HEALTH ORGANIZATION, THE WORLD HEALTH REPORT at 137 (2003).

Figure 4, below, compares the numbers of DALYs incurred annually in different parts of the world by each of the principal causes of death or disability – using the most recent data collected by the WHO.

Figure 4: Mortality and Morbidity (DALYs) by Region (2019)[13]
(all numbers in thousands)

	A	B	C	D	E	F
1		**Low Income Countries**	**Lower Middle Income Countries**	**Upper Middle Income Countries**	**High Income Countries**	**All countries**
2	Population	668455 (8.7%)	2913534 (37.8%)	2902542 (37.7%)	1223729 (15.9%)	7708261
3	Infectious and Parasitic Diseases	82989 (26.7%) 12415	182400 (58.6%) 6260	40117 (12.9%) 1382	5812 (1.9%) 475	311318 4039
4	Respiratory Infections	27212 (23.8%) 4071	60336 (52.7%) 2071	20058 (17.5%) 691	6825 (6.0%) 558	114431 2200
5	Maternal Conditions	4333 (34.3%) 648	6903 (54.6%) 237	1276 (10.1%) 44	137 (0.1%) 11	12649 164
6	Neonatal Conditions	48277 (23.9%) 7222	123036 (60.1%) 4223	26134 (12.9%) 900	4374 (2.2%) 357	201821 2618
7	Nutritional Deficiencies	9351 (19.4%) 1399	28883 (60.0%) 991	7979 (16.6%) 275	1912 (4.0%) 156	48125 624
8	Noncommunicable Conditions	105219 (6.6%) 15741	559850 (35.4%) 19215	622356 (39.3%) 21442	295231 (18.7%) 24126	1582657 20532
9	Injuries	34034 (13.1%) 5091	105188 (40.3%) 3610	88065 (33.8%) 3034	33423 (12.8%) 2731	260710 3382
10	**All Causes**	**311416 (12.3%) 46587**	**1066596 (42.1%) 36608**	**805985 (31.8%) 27768**	**347714 (13.7%) 28414**	**2531710 32844**

The numbers in the cells in Row 2 indicate the number of persons and the percentage of the global population that lives in each region. In all of the other cells in the table, the first number indicates (in thousands) the total number of DALYs caused annually in that region

[13] All data are derived from WHO, "Global Health Estimates 2019: Dalys by Age, Sex and Cause," (Geneva2020). A description of the methods and data sources used by the WHO in assembling this data is available at http://terrance.who.int/mediacentre/data/ghe/GlobalCOD_method_2000_2016.pdf?ua=1. The four income groups used in this chart were derived (by the WHO) from the World Bank's classification of countries. See http://data.worldbank.org/about/country-and-lending-groups.

by diseases or conditions of the type at issue, the second number shows the percentage borne by countries in that region of the total number of DALYs caused by that disease or condition globally, and the third number indicates the number of DALYs per 100,000 population suffered annually in that region as a result of the disease or condition. So, for example, cell E9 informs us that, in 2019, injuries (both intentional and unintentional) resulted in a loss of 33,423,000 DALYs in high-income countries (which represented 12.8% of the global DALY burden from injuries) and those same injuries caused a loss of 2731 DALYs for every 100,000 people in high-income countries.

Some of the conclusions that can be derived from this table are unsurprising. For example, by comparing E9 to the other cells in Row 9, we learn that losses per person due to injuries are higher in poorer countries. Indeed, that rate is roughly twice as high in low-income countries as in high-income countries. Rows 5 and 6 confirm the common expectation that losses due to maternal and neonatal conditions are also much higher in poor countries that in rich countries.

Other conclusions are more intriguing. For example, we learn from Row 8 that noncommunicable diseases now cause by far the largest number of lost DALYs throughout the world. (Within this group, the most burdensome subcategories are, in order, cardiovascular disease [including heart disease and stroke], cancer, mental and behavioral disorders, respiratory diseases, and musculoskeletal diseases [arthritis, back pain, and so forth].) However, the losses per person from such ailments are significantly lower in poorer countries than in richer countries.

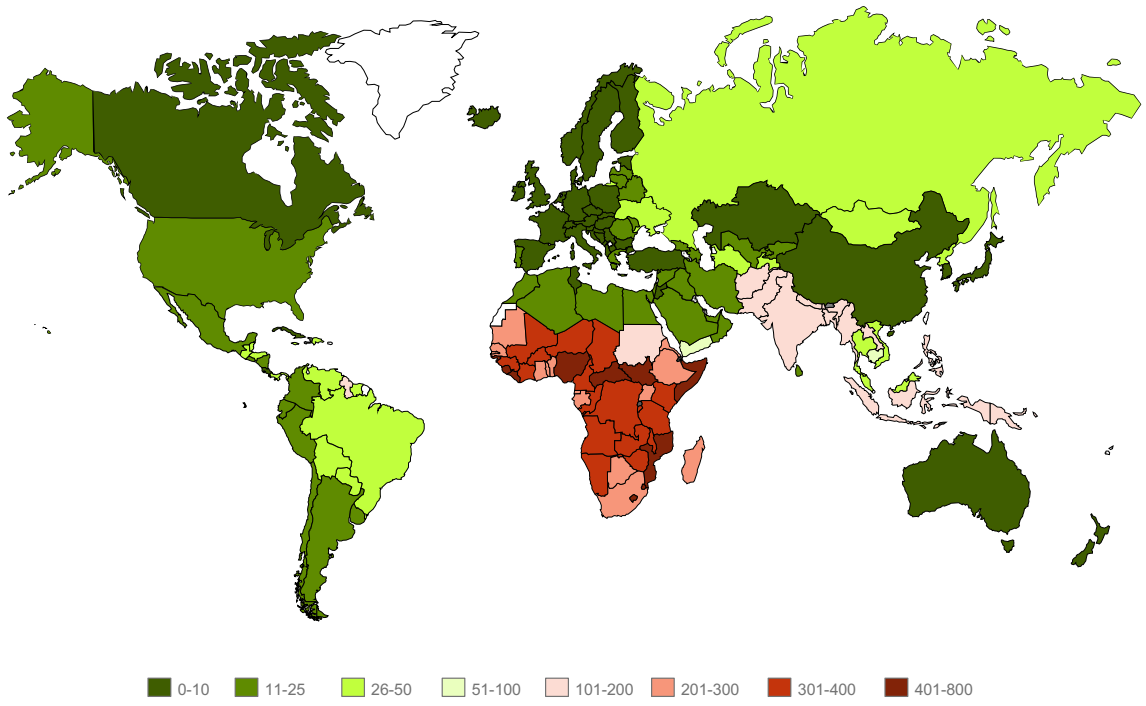
Most striking of all are the numbers in Row 3. Infectious and parasitic diseases, we can see, are vastly more common in low-income and lower-middle-income countries than in the upper tiers. The number of DALYs lost per person from these causes in low-income countries is three times the global average and 26 times the rate in high-income countries. The number of DALYs lost per person in lower-middle-income countries is roughly 1.5 times the global average and 13 times the rate in high-income countries. Equally important, the total number of DALYs forfeited in poor countries through the prevalence of such diseases is enormous: 83 million per year in low-income countries and 182 million in lower-middle-income countries – much larger numbers than result from any other cause except noncommunicable diseases. When one recalls that those noncommunicable diseases are <u>less</u> burdensome in poor countries than in rich countries, it becomes apparent that the principal cause of the global health disparity is inequality in the prevalence of infectious and parasitic diseases. (Henceforth in this book, we will refer to this category simply as "infectious diseases.")

If we put morbidity to one side and focus exclusively on mortality data, the picture changes slightly, but not fundamentally. In 2019, 1,123,442 people died from infectious and parasitic diseases in low-income countries (168 per 100,000 population). In lower-middle-income countries, the numbers were 3,054,139 (105 per 100,000 population). In upper-middle-income countries, the numbers were 699,860 (24 per 100,000 population). And in

high-income countries, the numbers were 223,759 (18 per 100,000 population – 11% of the rate in low-income countries).[14]

The map in Figure 5, below, provides a finer-grained look at mortality data, showing the differences among the countries of the world in age-standardized mortality[15] from infectious diseases.[16]

Figure 5: Mortality from Infectious and Parasitic Diseases (2019)
(per 100,000 population)



These data provide a good picture of the health disparities in the world on the eve of the COVID-19 pandemic. The World Health Organization has not yet made available data that would enable a similarly comprehensive comparison of the ways in which that pandemic has altered the picture. However, we already have enough information to make an overall assessment of its impact: The early stages of the pandemic resulted (to the surprise of many observers) in a diminution in the disparity between developed and developing countries. The reason is that, for complex reasons, the most serious of the "hotspots" of the disease during 2020 were in developed countries: the United States and most of the countries in western Europe. Both the morality rates and the suffering associated with notfatal infections in those

[14] All data are from "Global Health Estimates 2019: Estimated Deaths by Age, Sex, and Cause," (Geneva2020).

[15] The way in which age adjustment of mortality rates works is well explained in http://www.health.ny.gov/diseases/chronic/ageadj.htm.

[16] All of the data embodied in this map have been derived from WHO, "Global Health Estimates 2019 Summary Tables," (Geneva 2020). [Cite-check coding of each country.]

countries were extremely high. By contrast, most developing countries initially experienced only modest rates of infection. In 2021, however, the pattern began to reverse. The increasing availability of COVID vaccines in most developed countries, combined with increasingly sophisticated public-health and treatment practices, began to ease burdens in most of those countries. Developing countries, by contrast, lacked similar resources to combat accelerating infection rates. The result: The shares of the COVID cases and deaths borne by low-income and lower-middle-income countries are rapidly rising.[17] Much more detail concerning the origins and impact of the pandemic will be provided in Chaper 1. For now, it suffices to observe that, although COVID-19 briefly reduced the disparity between the damage done by infectious diseases in poor countries and the damage done in rich countries, that anomaly will almost certainly be short-lived.

To summarize: people in developing countries die sooner and suffer more than their counterparts in developed countries – in large part because of the higher prevalence in developing countries of infectious diseases. How the prevalence of those diseases might be reduced – and the lives of the residents of the developing world correspondingly improved – is the focus of this book.

We do not mean to suggest, of course, that noncommunicable diseases do not represent a serious problem in developing countries. Heart disease, cancer, diabetes and the like are just as deadly in sub-Saharan Africa as they are in North America and Western Europe. Indeed, as one might expect, in the subset of developing countries where people are living longer, noncommunicable diseases are becoming more common, not less.[18] Nor should a focus on infectious diseases deflect attention from the problem of mental illness in the developing world. The misery associated with depression, for example, certainly rivals that associated with most physical ailments, and depression is distressingly common everywhere.[19]

For three reasons, however, we will concentrate on infectious diseases. First, as indicated above, the disparity in the incidence of those diseases is the principal cause of the health gap between the developed and the developing world.[20] Second, and related, the fact

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[17] See, e.g., Indermit Gill and Philip Schellekens, "Covid-19 Is a Developing Country Pandemic," *Brookings* (2021), https://www.brookings.edu/blog/future-development/2021/05/27/covid-19-is-a-developing-country-pandemic/.

[18] See WHO, "The Global Burden of Disease: 2004 Update," http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. 47-48.; "Noncommunicable Diseases: Country Profiles, 2011," (2011), http://whqlibdoc.who.int/publications/2011/9789241502283_eng.pdf.; Sheri Fink and Rebecca Rabinowitz, "The Un's Battle with Ncds," *Foreign Affairs*.

[19] See Steve Hyman et al., "Mental Disorders," in *Disease Control Priorities in Developing Countries*, ed. Dean Jamison (New York: Oxford University Press, 2006); Vikram Patel et al., "Depression in Developing Countries: Lessons from Zimbabwe," *BMJ* 322; WHO, "Depression," http://www.who.int/mental_health/management/depression/definition/en/.("Depression is the leading cause of disability as measured by YLDs and the 4th leading contributor to the global burden of disease (DALYs) in 2000. By the year 2020, depression is projected to reach 2nd place of the ranking of DALYs calcuated for all ages, both sexes.")

[20] By contrast, the incidence of mental disorders in general is not substantially higher in the developing world than in the developed world. Depression, by far the most common of those disorders, causes the loss of 9,054 DALYs per year per million population in high-income countries – slightly above the global average of 8,431. The corresponding numbers for developing regions are 4,905 in Sub-Saharan Africa; 9,919 in Latin American

that the prevalence of infectious diseases is so low in the developed world gives us confidence that there is no insurmountable technological impediment to reducing their prevalence in the developing world. In other words, the problem is tractable. Finally, as will soon become apparent, solving the problems associated with infectious diseases is hard enough; we leave to others the different challenges presented by noncommunicable diseases, injuries, and mental disorders.

We pause for a moment to consider a common objection to the second of these three reasons. Some participants in the various lectures and seminars in which we have discussed the arguments that appear in this book have suggested that the unequal distribution of infectious diseases may be more resistant to change than we think. In particular, they contend that such diseases thrive in warm climates. It is no accident, they suggest, that the countries colored pink and red in Figure 5 are clustered around the equator. At least until climate change fundamentally alters global temperatures, they argue, inequality among regions is inevitable. Perhaps, but other data cast doubt on this pessimism. For example, Singapore, which straddles the equator, has a communicable-disease mortality rate of 3.9 per 100,000 inhabitants, while the rate in adjacent Malaysia is 25.5. Even within Sub-Saharan Africa, the mortality rates associated with infectious diseases vary widely. The number in Nigeria (the most populous country in Africa) is 302.2; in Benin (located immediately to the east of Nigeria), the number is 195.2. The contrast between the two countries on the Korean peninsula provides another illustration of the limited significance of climate. The infectious-disease mortality rate in South Korea is 10.1; in North Korea, it's 64.3. Cuba's rate is 8.1 (below that of the United States – 12.6); nearby island countries with similar climates include Jamaica (28.8); the Dominican Republic (30.8); and Haiti (81.8). In short, climate surely matters, but not as much as is often supposed.

For these reasons, most of our attention from here on will be devoted to infectious illnesses. What, then, are those illnesses? There are many, it turns out, but the 28 most important are set forth in the chart below. The list, the clusters in which they are organized, and the data concerning their impacts are all taken from the most recent reports by the World Health Organization.[21]

and the Caribbean; 6,544 in the Middle East and North Africa; 8,944 in Europe and Central Asia; 10,507 in South Asia; and 7,594 in East Asia and the Pacific. Hyman et al., "Mental Disorders," 606.

[21] The two reports from which these data are gleaned are: WHO, "Global Health Estimates 2019: Dalys by Age, Sex and Cause."; "Global Health Estimates 2019: Estimated Deaths by Age, Sex, and Cause."

Figure 8: Infectious Diseases (2019) (in thousands)

	Global Deaths	Global DALYs
HIV/AIDS	675	40,147
Tuberculosis*	1,208	66,024
Malaria*	411	33,398
STDs (excluding HIV/AIDS)		
Syphilis	43	3,814
Chlamydia	1	324
Gonorrhoea	2	231
Trichomoniasis	0	282
Genital herpes	0	250
Other STDs	3	352
Diarrhoeal Diseases	1,519	79,311
Childhood Diseases		
Pertussis ("whooping cough")	111	9,839
Diphtheria	5	420
Measles	165	14,528
Tetanus	47	3,474
Meningitis	233	16,314
Encephalitis	78	4,174
Hepatitis		
A	40	2,102
B	36	1,633
C	22	655
E	2	123
Parasitic and vector diseases (excluding Malaria)		
Trypanosomiasis*	2	102
Chagas*	8	217
Schistosomiasis	12	1,628
Leishmaniasis*	6	722
Lymphatic filariasis (elephantiasis)	0	1,616
Onchocerciasis (river blindness)	0	1,210
Cysticercosis	7	988
Echinococcosis	9	461
Dengue	30	1,952
Trachoma (infectious blindness)	0	194
Yellow fever	6	413
Rabies	47	2,634
Intestinal nematode infections		
Ascariasis	2	749
Trichuriasis	0	232
Hookworm	0	962
Food-bourne trematodes	0	805
Leprosy	13	36
Other infectious diseases	370	19,000
Totals	**5,101**	**311,318**

A note about terminology: The WHO has, influentially, classified diseases as Type I, II, and III, corresponding to global, developing-country, and neglected diseases.[22] All of the diseases included in this chart fall into the second category, meaning that the burdens associated with them are borne overwhelmingly by developing countries.[23] All except HIV/AIDS (and, perhaps, TB) are also "neglected diseases,"[24] so called for reasons that should be obvious and will become more so in the remainder of this book. Finally, the diseases marked with asterisks were identified by a joint roundtable of the WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFMPA) as the ailments most in need of additional research – and consequently have come to be known as "priority diseases."[25] We will try to use these labels consistently in the book.

The most striking number in Figure 8 is of course the total number of deaths. Together, these diseases kill roughly 5.1 million people in a typical year – 82% of them in low-income or lower-middle-income countries. But that number, horrific as it is, seriously understates the problem. Several of these diseases – Chlamydia, Gonorrhoea, Diphtheria, Lymphatic filariasis, Onchocerciasis, and all of the intestinal infections – kill few people, but cause the loss of large numbers of DALYs. When those figures are added to the DALY losses associated with the major killers, the total is staggering: the equivalent, annually, of 311 million years of lost human life – 85% of them in low-income or lower-middle-income countries.

How might we reduce these numbers? A natural place to start when looking for answers would be a survey of the techniques that developed countries have already employed to cut sharply the incidence of infectious diseases in their territories. For these purposes, the United States is representative. Beginning in the late nineteenth century, three main strategies enabled the United States to lower dramatically both mortality and morbidity associated with such diseases.

The first of those strategies consisted of improvements in sanitation and hygiene. The principal initiatives were: cleaning up food-supply systems (for example, the widespread

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[22] WHO, Investing in Health for Economic Development – Report of the Commission on Macroeconomics and Health 78 (2001) ("*Type I diseases* are incident in both rich and poor countries"; "*Type II diseases* are incident in both rich and poor countries, but with a substantial proportion of the cases in the poor countries [...] HIV/AIDS and tuberculosis are examples"; "*Type III diseases* are those that are overwhelmingly or exclusively incident in the developing countries.").

[23] See Lanjouw & Cockburn 1999, defining "developing country diseases" in similar terms.

[24] Among the sources using these terms – although not always identically – are Medecins Sans Frontieres, *Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases* (2001); Patrice Trouiller et al., *Drug Development for Neglected Diseases: A Deficient Market and a Public-Health Policy Failure*, 359 LANCET 2188 (2002); WHO, World Health Report 2003; and EFPIA, *infra*, note 25.

[25] Cited in European Federation of Pharmaceutical Industries and Associations, *Research & Development (R&D) and Diseases Prevalent in Developing Countries*, available at http://www.efpia.org/4_pos/access/RDdevecountries.pdf. The criteria used to determine which diseases were in greatest need of further R&D included the toll taken by the disease, the adequacy of currently available treatments, the presence of scientifically tractable targets, and whether or not substantial R&D was already underway. A similar list of diseases has been devised by the Medecins Sans Frontieres Campaign for Access to Essential Medicines; *see* http://www.accessmed-msf.org/ (identifying the Campaign's "Target Diseases" as HIV/AIDS, tuberculosis, malaria, leishmaniasis, trypanosomiasis, trachoma and meningitis, the last of which, while technically not a developing-country disease, does have roughly 90% of its global deaths and DALYs toll occur in the developing world).

adoption of milk pasteurization and meat inspections); improvements in consumer behavior (for example, habits of personal hygiene, care in food preparation, and breast feeding); and improvements in the water supply (principally through filtration and chlorination).[26] The impact of the last of these innovations was especially large. Between 1900 and 1937, the infectious-disease mortality rate in the United States fell from 797 per 100,000 population (a number roughly comparable to the rate in sub-Saharan Africa today) to 283 – an average decline of 2.8% per year.[27] Almost half of that reduction can be traced to the deployment of municipal water-supply systems.[28]

The science used to justify these public-health initiatives evolved in a halting, complicated way. In the early nineteenth century, diseases were commonly thought to be caused by "miasmas," poisonous vapors that emanated from contaminated water and filth. By the early twentieth century, that belief had been largely displaced (in the United States) by what came to be known as germ theory, the heart of which is recognition of the crucial roles played by microorganisms in contagious diseases. The stages in this transition were intricate.[29] But fortunately, most of the theories deployed during this trajectory pointed toward a common set of precautions and innovations.

Germ theory also provided an important catalyst for the second of the three strategies: immunization through vaccines. Whereas the public-health initiatives of the first third of the century reduced the exposure of people to pathogens, either by killing those pathogens or by blocking their transmission to humans, immunization altered people's bodies so they did not contract infectious diseases (or were protected against the toxins they produced) even when they were exposed to the pathogens.[30]

The first important vaccine was for smallpox. Developed in 1798, it was used increasingly widely in the United States in the early nineteenth century – and eventually succeeded in eradicating the disease altogether.[31] The next major wave of vaccine development began in the 1920s. Soon thereafter, federally funded vaccination programs made these

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[26] See John W. Sanders et al., "The Epidemiological Transition: The Current Status of Infectious Diseases in the Developed Versus the Developing World," *Science Progress* 9, no. 1 (2008): 7-8.

[27] See Gregory L. Armstrong, Laura A. Conn, and Robert W. Pinner, "Trends in Infectious Disease Mortality in the United States During the 20th Century," *Journal of the American Medical Association* 281, no. 1 (1999): 63.

[28] See D. Cutler and G. Miller, "The Role of Public Health Improvements in Health Advances: The Twentieth-Century United States," *Demography* 42 (2005).

[29] See Howard D. Kramer, "The Germ Theory and the Early Public Health Program in the United States," *Bulletin of the History of Medicine* 22, no. 3 (1948); Nancy J. Tomes, "American Attitudes toward the Germ Theory of Disease: Phyllis Allen Richmond Revisited," *Journal of the History of Medicine and Allied Sciences* 61, no. 3 (1997); "The Private Side of Health: Sanitary Science, Domestic Hygiene, and the Germ Theory, 1870-1900," *Bulletin of the History of Medicine* 64, no. 4 (1990); Riley, *Life Expectancy*, 60-68; Andrea Patterson, "Germs and Jim Crow: The Impact of Microbiology on Public Health Policies in Progressive Era American South," *Journal of the History of Biology* 42 (2009).

[30] For a detailed explanation of the ways in which different types of vaccines work, see Anita M. Loughlin and Steffanie A. Strathdee, "Vaccines: Past, Present, and Future," in *Infectious Disease Epidemiology: Theory and Practice*, ed. Kenrad E. Nelson and Carolyn F. Masters (Boston: Jones and Bartlett, 2007).

[31] See F. Fenner et al., *Vaccines* (Philadephia: W.B. Saunders Company, 1994); Loughlin and Strathdee, "Vaccines," 374-77.

innovations available to almost all children in the United States. The key innovations and the pace at which they were disseminated are illustrated by the following chart:

Figure 9: First-Generation Vaccines in the United States

Disease	First Vaccine	Developed	First widely distributed in US
Tuberculosis	Bacillus Calmette-Guerin (BCG) vaccine[32]	1921	1949
Diptheria	toxoid (inactivated toxin) vaccine[33]	1923	mid-1940s
Pertussis ("Whooping Cough")	Whole-cell vaccine[34]	1926	mid-1940s
Tetanus	toxoid (inactivated toxin) vaccine[35]	1927	mid-1940s
Yellow Fever	17D vaccine[36]	1932	1941
Influenza	Inactivated vaccine for types A and B[37]	1942	mid-1940s
Polio	Salk inactivated vaccine[38]	1952	late-1950s
Measles	Edmonston B strain live vaccine[39]	1964	1974
Mumps	"Jeryl Lynn" strain[40]	1967	1977
Rubella	Live non-human attenuated vaccines[41]	1969	1970
Hepatitis B	Heptavax vaccine[42]	1981	1980s
Varicella-zoster ("chicken pox")	Varivax	1984	1989
Haemophilus Influenzae type b	Bacterium capsular polysaccharide Hib vaccine	1985	1985
Rotavirus	Rotashield	1998	1998

[32] See Jaqueline S. Coberly and Richard E. Chaisson, "Tuberculosis," in *Infectious Disease Epidemiology*, ed. Kenrad E. Nelson and Carolyn F. Masters (Boston: Jones and Bartlett, 2007), 683-85.

[33] See http://www.immunizationinfo.org/vaccines/diphtheria#history-of-the-vaccine.

[34] See http://www.immunizationinfo.org/vaccines/pertussis-whooping-cough#history-of-the-vaccine.

[35] See http://www.immunizationinfo.org/vaccines/tetanus.

[36] See J. Gordon Frierson, "The Yellow Fever Vaccine: A History," *Yale Journal of Biology and Medicine* 83, no. 2 (2010).

[37] See I. Barberis et al., "History and Evolution of Influenza Control through Vaccination: From the First Monovalent Vaccine to Universal Vaccines," *Journal of Preventive Medicine and Hygiene* 57, no. 3 (2016): 116-17.

[38] See Bonnie A. Maybury Okonek and Linda Morganstein, "Development of Polio Vaccines," http://www.accessexcellence.org/AE/AEC/CC/polio.php.

[39] See Loughlin and Strathdee, "Vaccines," 370-71.

[40] See "Measles, Mumps, Rubella: History of the Vaccine," National Network for Immunization Information, April 22, 2010: http://www.immunizationinfo.org/vaccines/mumps#history-of-the-vaccine.

[41] See Stanley A. Plotkin, "The History of Rubella and Rubella Vaccination Leading to Elimination," *Clinical Infectious Diseases* 43 (2006).

[42] See Hepatitis B Foundation, "Hepatitis B Vaccine History," October 21, 2009: http://www.hepb.org/professionals/hepatitis_b_vaccine.htm.

In several cases, these first-generation vaccines proved imperfect, either because their effectiveness was limited or because they had bad side-effects, but they were soon followed by improved versions. Widespread administration of these vaccines quickly resulted in precipitous declines in all of the diseases at issue.[43] The only infectious disease with a substantial footprint in the United States for which there is not yet an effective preventive vaccine is HIV/AIDS – and at least partial success on that front now appears to be within reach.[44]

The third strategy overlapped the second. During the same period in which vaccines were being developed and deployed, other researchers were developing new medicines that could cure people who had become infected. The most revolutionary of them were antibiotics. Of those, the most famous were penicillin and streptomycin, both developed in the early 1940s. They were followed by a host of other more specialized antimicrobials. These proved to have seemingly miraculous powers in suppressing previously uncontrollable infections: pneumonia, meningitis, tuberculosis, malaria, and fungal infections. More recently, the same strategy has led to drugs that can suppress viral infections, such as HIV.[45]

The effect of the second and third strategies, in combination, was an even more dramatic drop in infectious-disease mortality rates. Between 1937 and 1952, the rate declined from 283 to 75 – an average reduction of 8.2% per year. Between 1953 and 1980, it kept dropping, but more slowly – specifically, at an average rate of 2.3%. By 1980, the number was 36 – less than 5% of the number in 1900. These trends stand out sharply in the following graph.

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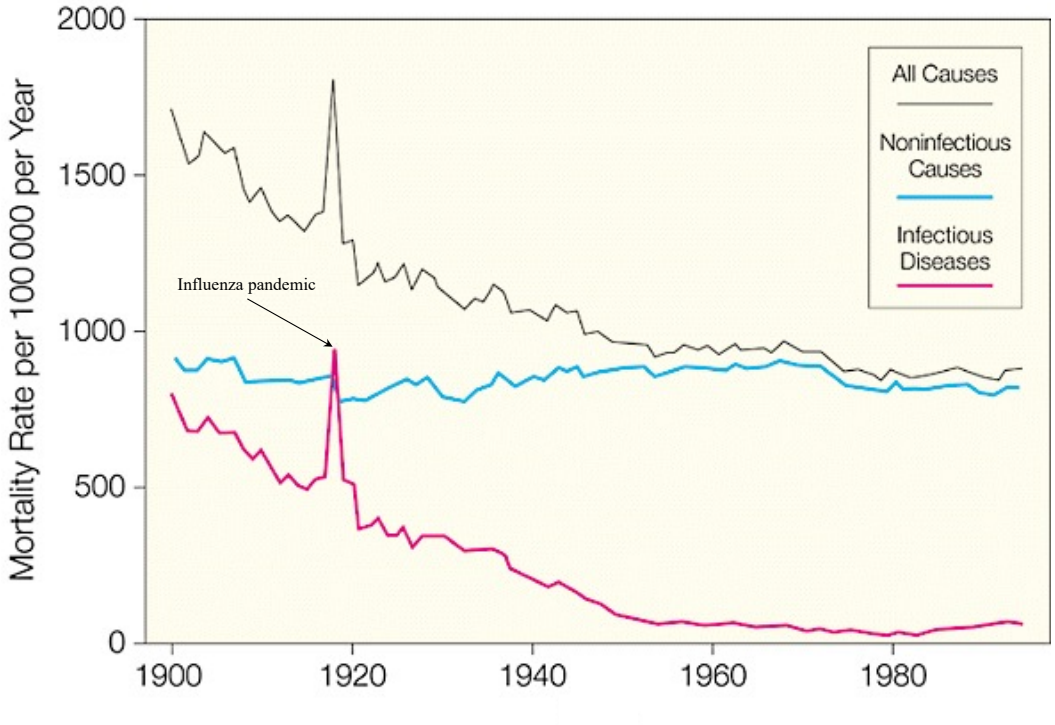
[43] See Sanders et al., "Epidemiological Transition," 9-10. For graphs showing the declines in selected diseases, see: Loughlin and Strathdee, "Vaccines," 369-70, 71, 73.(polio, measles, and Haemophilus influenza type b); http://www.healthsentinel.com/joomla/images/stories/graphs/us-diphtheria-1900-1967.jpg (diphtheria); http://www.healthsentinel.com/joomla/images/stories/graphs/us-pertussis-1900-1967.jpg (pertussis); http://www.healthsentinel.com/joomla/images/stories/graphs/us-measles.jpg (measles).

[44] See AIDS Vaccine Advocacy Coalition, "Hiv Vaccines: An Introductory Factsheet," (2019).

[45] See Sanders et al., "Epidemiological Transition," 10.

Figure 10: U.S. Crude Mortality Rates, 1900-1996



adapted from Armstrong et al., "Trends in Infectious Diseases," Journal of the American Medical Association 281 (1999): 61.

Notice the tight linkage between the mortality rate for infectious diseases and the overall mortality rate. The huge drop in the latter during the twentieth century (and the corresponding increase in life expectancy in the United States) is largely attributable to the progress we have made in controlling infectious diseases.[46] These remarkable gains, to repeat, were due primarily to the success of the three interlocking initiatives: public-health programs, which limit Americans' exposure to bacteria and viruses; immunization programs; and medicines capable of curing people of the diseases we fail to prevent.[47]

(Also noteworthy is the severity – and brevity – of the impact of the 1918 influenza pandemic. The impact of COVID-19 is likely to be similar.)

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[46] Note that these are "raw" or "crude" mortality rates, not age-adjusted mortality rates. That makes a difference when interpreting the stability over time of the mortality rate associated with noninfectious causes. One should not infer from its constancy that we have made no progress in controlling heart disease, cancer, industrial accidents, and so forth. On the contrary, we have made considerable progress – the main effect of which is that these things are catching up to us at later ages.

[47] For the most part, these three strategies were complementary. In particular, the public-health initiatives reduced the need for vaccines and medicines, by limiting the set of pathogens to which people were exposed. But occasionally the effect was reversed. The most important case involved polio. Prior to the installation of modern water and sanitation systems, infants were often exposed to the three polio viruses. However – either because they were receiving antibodies from their mothers through breast milk or because the receptors necessary for an infection to pass from the gastrointestinal tract to neurons are not expressed until later in childhood – the babies rarely contracted the paralytic form of polio, but instead developed their own antibodies, which then protected them throughout their lives. The public-health initiatives, by reducing the frequency with which infants were exposed to the viruses, increased the incidence of the disease and intensified the need for a vaccine. See Okonek and Morganstein, "Development of Polio Vaccines".; Loughlin and Strathdee, "Vaccines," 369.

When combating infectious diseases in developing countries, we can and should rely on the same three approaches that proved so effective in the United States. The first of the three initiatives is already well underway. In recent years, developing countries have gone far to institute the same public-health reforms that proved so important in the United States. 71% of the global population now use what the WHO classifies as "safely managed drinking-water sources" (up from 52% in 1990), and 37% of the populations in those countries now use "safely managed sanitation services." The only continent that lags behind is Africa, where the percentage of the population with safe drinking water is still only 26%. However, large amounts of development assistance (currently $2.4 billion per year) are currently being allocated to overcome this gap.[48] The health benefits of these initiatives have been large, and we should certainly complete the process.

Unfortunately, it is already apparent that these public-health initiatives will not, by themselves, solve the problem. Indeed, they appear to be less efficacious in curbing infectious diseases than they were in the United States – in part because most of the diseases that currently ravage developing countries are less dependent upon drinking water for transmission than were the major killers in the United States.

Effectively curbing infectious diseases in the developing world thus requires us also to deploy the second and third strategies – just as we did in the United States. We need to immunize residents (preferably while they are children) against the diseases that are transmitted in ways we can't block, and we need to provide infected people with medicines that will save their lives or at least make their lives bearable.

Again, substantial progress on these fronts has been made in recent years. All of the vaccines originally developed to combat diseases endemic in the United States and Europe are now (or will soon be) available in developing countries. Figure 11, below, (provided by the Centers for Disease Control) shows the global and regional coverage of the major vaccines. Plainly, there are some gaps, particularly in Africa, but the progress to date has been impressive.

[48] All numbers from WHO, "World Health Statistics 2019". [Update with 2021 report]

Figure 11: Vaccination Coverage (2017)[49]

Vaccine	No. (%) countries with vaccine in schedule	Coverage* (%)						
		Global	African	Americas	Eastern Mediterranean	European	South-East Asia	Western Pacific
BCG	158 (81)	88	80	92	86	92	91	97
HepB BD	105 (54)	43	10	69	34	41	44	85
HepB3	188 (97)	84	72	90	81	82	88	93
DTP3	194 (100)	85	72	91	81	94	88	97
Hib3	191 (98)	72	72	91	81	76	86	28
Pol3	194 (100)	85	71	90	81	93	88	97
Rota_last	96 (49)	28	46	68	30	24	9	1
PCV3	139 (72)	44	68	82	52	70	12	16
MCV1	194 (100)	85	70	92	81	95	87	97
RCV1	162 (84)	52	26	92	46	95	21	97
MCV2	167 (86)	67	25	74	67	90	77	94

Abbreviations: BCG = Bacille Calmette-Guérin vaccine; DTP3 = third dose of diphtheria and tetanus toxoids and pertussis-containing vaccine; HepB BD = birth dose of hepatitis B vaccine; HepB3 = third dose of hepatitis B vaccine; Hib3 = third dose of *Haemophilus influenzae* type b vaccine; MCV1 = first dose of measles-containing vaccine; MCV2 = second dose of MCV; PCV3 = third dose of pneumococcal conjugate vaccine; Pol3 = third dose of polio vaccine; RCV1 = first dose of rubella-containing vaccine; Rota_last = final dose of rotavirus vaccine series (number of doses to complete the series varies among vaccine products).

The only major exception to the widespread distribution of existing vaccines in developing countries involves COVID-19. The disparity to date in the distribution of COVID vaccines is stark – and will likely remain so for the foreseeable future.[50]

Less well known but equally serious is the absence of any effective vaccines for many of the infectious diseases endemic in developing countries. For example, there exists no reliable vaccine for malaria, which kills half a million people a year, most of them young children. For tuberculosis, there does exist a vaccine: the venerable BCG vaccine, originally developed from the cousin of the TB bacterium that afflicts cattle. BCG remains effective against some forms of TB – specifically, tuberculous meningitis and miliary tuberculosis – as well as against some unrelated diseases, such as leprosy. But in tropical climates (particularly rural areas), it has little power to prevent pulmonary tuberculosis among adults.[51] No vaccine

[49] Source: Kristin VanderEnde et al., "Global Routine Vaccination Coverage — 2017," (2018), https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a2.htm.

[50] More detail concerning the origins and implications of this inequality are provided in Chapter 1, Section F, below.

[51] See Frank Shann, "Bcg Vaccination in Developing Countries," *BMJ* 340. Additional details concerning the limitations of the BCG vaccine are provided in Chapter 1.

of any sort is available for any of the "tropical diseases" – Trypanosomiasis,[52] Chagas,[53] Schistosomiasis,[54] Leishmaniasis,[55] Lymphatic filariasis, and Onchocerciasis. The same is true for Trachoma,[56] Ascariasis,[57] Trichuriasis,[58] Hookworm, [59] and (with a partial exception) Dengue.[60]

Why? Are these diseases that much more difficult than measles and polio to understand and combat? In a few cases, perhaps. But in most cases, no. Indeed, for the majority of the neglected diseases, promising avenues for the development of vaccines were identified long ago. But we have not, as yet, invested in these projects the resources necessary to generate and test the vaccines we need.

What about medicines? Do we at least have ways of controlling the diseases once people have contracted them? The answer varies. For a few of the diseases, there are no cures. Dengue, for example, infects roughly 40 million people a year, 30,000 of whom die. The only treatments for the disease are symptomatic.[61]

For most of the diseases, therapies do exist, but many are outdated, limited in their effectiveness, or poorly adapted for use in developing countries. For example, the available treatments for Chagas disease (which currently afflicts roughly 10 million people) are almost always effective if initiated during the very early stages of the disease, but are much less potent if (as is common) they are not applied until the chronic stage.[62] The recent development of nifurtimox-eflornithine combination therapy (NECT) has sharply increased the effectiveness of responses to late-stage sleeping sickness, but detection is still difficult (requiring a lumbar puncture), and the treatment "remains labour-intensive, requiring 7 days of infusions of eflornithine twice a day, plus 10 days of oral nifurtimox tablets 3 times a day, … a minimum of 4 nurses, … and a doctor, to prescribe treatment and manage potential adverse events."[63]

The area of most dramatic recent progress concerns treatments for HIV/AIDS. The development of anti-retroviral therapies (ARVs) has sharply reduced the mortality rate

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[52] See S Magez et al., "Current Status of Vaccination against African Trypanosomiasis," *Parasitology* 137, no. 14 (2010).

[53] See Mary Ann Roser, "Baylor Doctor Working on Chagas Vaccine," *Statesman*, October 7, 2011.

[54] http://www.who.int/vaccine_research/diseases/soa_parasitic/en/index5.html.

[55] See Lukasz Kedzierski, "Leismaniasis Vaccine: Where Are We Today?," *Journal of Infectious Diseases* 2 (2010).

[56] See http://www.medindia.net/news/Experimental-Trachoma-Vaccine-Protects-Monkeys-91825-1.htm.

[57] See http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer/Diseases/cid/ViewDetails/ItemID/20.aspx.

[58] See http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer/Diseases/cid/ViewDetails/ItemID/20.aspx.

[59] See http://www.sabin.org/vaccine-development/vaccines/hookworm.

[60] "Planning for the Introduction of Dengue Vaccines," Hanoi, April 19, 2011, http://www.denguevaccines.org/sites/default/files/APDPBReport_Hanoi_April2011_Highlights.pdf.

[61] See WHO, Neglected Tropical Diseases, (2009), http://whqlibdoc.who.int/publications/2009/9789241598705_eng.pdf. 33.

[62] See ibid., 18.

[63] See Jacqueline Tong et al., "Challenges of Controlling Sleeping Sickness in Areas of Violent Conflict: Experience in the Democratic Republic of Congo," *Conflict and Health* 5, no. 7 (2011).

associated with the disease, not just in developed countries, but also in the developing world.[64] However, ARVs suppress the infection; they do not cure it. And they often become less effective over time, forcing patients to move from first-generation to second-generation to third-generation drugs.[65] In short, some medicines capable of curing or ameliorating developing-country diseases certainly do exist, but they are far from ideal.

The medicines that are available often are very expensive. A few examples:

- Roughly 3.5% of the 9 million new cases of active tuberculosis reported each year involve variants of the disease that are resistant to the standard course of antibiotics. Patients who contract those variants require special treatments – so-called DR-TB drugs. Whereas the costs of the standard TB treatments are now modest, the cost of a DR-TB regimen is not.[66]

- A combination of legal reforms and philanthropic initiatives (which we will discuss in due course) has led recently to significant reductions in the prices of the ARVs for HIV/AIDS, especially in low-income countries. That, in turn, has made possible a sharp increase in the number of infected people able to get the medicines. Unfortunately, the price reductions have been largest with respect to first-generation therapies. Second-generation ARVs are substantially more expensive, and the prices of third-generation drugs are higher still.[67]

- It is not merely in the high-profile contexts of TB and AIDS that one finds prohibitively high drug prices. In many other settings, run-of-the-mill drugs, long free of patent protection, are still expensive. A simple course of antibiotics, for

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[64] See Hillary Rodham Clinton, "Creating and AIDS-Free Generation," November 8, 2011, available at http://www.state.gov/secretary/rm/2011/11/176810.htm; USAID, "HIV/AIDS Health Profile: Sub-Saharan Africa," March 2011, available at http://www.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf. [Update.]

[65] See MSF, "Hiv/Aids Treatment in Developing Countries: The Battle for Long-Term Survival Has Just Begun," (2009), http://www.doctorswithoutborders.org/publications/reports/2009/msf_hiv-aids-treatment_battle-for-long-term-survival.pdf.

[66] See Lindsay McKenna, "The Price of Bedaquiline," (Treatment Action Group, 2018).; MSF, "Dr-Tb Drugs under the Microscope," (2011), http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_UndertheMicro_ENG_2011.pdf. Cf. UN, "Report of the United Nations Secretary General's High-Level Panel on Access to Medicines: Promoting Innovation and Access to Health Technologies," (2016), 15.(describing the effects of the high price of an XTDR drug)

[67] See Frontline AIDS, "The Problem with Patents: Access to Affordable Hiv Treatment in Middle-Income Countries," (2019), 6. (reporting that "The lowest prices (ppy) for third-line drugs that are widely patented were $664 ppy for darunavir, $439 for etravirine and $553 for raltegravir; the lowest combined prices were still in excess of $1500. Outside sub-Saharan Africa, median prices for darunavir were $5180. For salvage therapy (when standard treatment options no longer work), countries reported paying $6072 for tipranavir, $5190 for maraviroc and $17,700 for enfuvirtide."); Ellen 't Hoen et al., "Driving a Decade of Change: Hiv/Aids, Patents and Access to Medicine for All," *Journal of the International AIDS Society* 14, no. 15 (2011).

example, can cost in developing country more than the aveage resident earns in a month.[68]

In countries where the costs of drugs are borne by patients directly, these prices are often prohibitive; most residents simply cannot afford to buy the medicines they need. In countries where government agencies purchase and then distribute drugs, these prices place severe loads on their finances and frequently limit the sets of medicines (or the portfolios of other health services) that they can provide residents.

Finally, in many developing countries, the medicines even when they are affordable are often of poor quality. In part, this problem derives from inadequate storage conditions and insufficient monitoring of distribution chains – which increase the likelihood that, by the time the drugs are consumed by patients, they have degraded. And in part it derives from unscrupulous behavior by manufacturers and distributors, who deliberately supply drugs that do not contain any (or enough) of the active ingredients they purport to contain.

The data concerning the scale of this problem is chilling. In 2017, the World Health Organization, after aggregating many studies, estimated that the 10.5% of the drugs distributed in low-income countries were either falisifed or substandard. In middle-income countries, the number was barely lower: 10.4%.[69] An even more recent and comprehensive study found the overall rate in low and middle-income countries to be 13.6% -- and the rate in Africa to be 18.7%.[70]

The rates vary by type of drug. Least likely to be falsified or substandard are ARVs, because most of them are supplied through channels closely monitored by international donors. The rates for tuberculosis drugs and antibiotics are higher – somewhere between 6 and 17%.[71] Most likely to be falsified or substandard are anti-malarial drugs.[72]

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[68] See WHO, "Equitable Access to Essential Medicines: A Framework for Collective Action," (2004), http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.4.pdf. Cf. Dilara Inan et al., "Daily Antibiotic Cost of Nosocomial Infections in a Turkish University Hospital," *BMC Infectious Diseases* 5, no. 5 (2005).

[69] See WHO, "A Study of the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products," (2017), 7. The WHO defines these two terms as follows: Falsified medical products are those "that deliberately/fraudulently misrepresent their identity, composition or source"; substandard medical products are "authorized medical products that fail to meet either their quality standards or their specifications, or both." Ibid., at 1.

[70] See Sachiko Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis," *JAMA Network Open* 1, no. 4 (2018).

[71] See R. Bate et al., "Substandard and Falsified Anti-Tuberculosis Drugs: A Preliminary Field Analysis," *International Journal of Tuberculoisis and Lung Disease* 17, no. 3 (2013); Theodoros Kelesidis and Matthew E. Falagas, "Substandard/Counterfeit Antimicrobial Drugs," *Clinical Microbiology Reviews* 28, no. 2 (2015): 451; K.F. Laerson et al., "Substandard Tuberculosis Drugs on the Global Market and Their Simple Detection," *The International Journal of Tuberculosis and Lung Disease* 5, no. 5 (2001); O Moses, V Patrick, and N Muhammad, "Substandard Rifampicin Based Anti-Tuberculosis Drugs Common in Ugandan Drug Market," *African Journal of Pharmacy and Pharmacology* 7, no. 34 (2013); UNITAID, "Tuberculosis Medicines: Technology and Market Landscape," (2014), 32; WHO, "Impact of Substandard and Falsified Products," 17.

[72] See "Impact of Substandard and Falsified Products," 7.; Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis."

The presence in the market of falsified and substandard drugs has three bad effects. First and most obviously, patients who consume such drugs obtain either zero or reduced therapeutic benefit. The context in which this impact is especially severe is the administration of anti-malarial drugs to young children, who are especially vulnerable to the disease. The most comprehensive study estimates that, globally, 122,350 children under the age of five die each year in subSaharan Africa alone as a result of consuming falsified or substandard anti-malarials.[73] As the authors of the study concede, a good deal of uncertainty surrounds these numbers. But there is little doubt that the number of deaths is appalling.[74]

Second, when patients consume drugs that are supposed to cure them and fail to do so, they (and their neighbors) lose faith in western medicine. In settings where such faith is already shaky, this can diminish their willingness to consult doctors in the future.[75]

Last but not least, consumption of degraded medicines (or a course of treatment in which legitimate and falsified drugs are mixed) accelerates the emergence and spread of drug-resistant strains of all of the diseases with which we are concerned.[76] As we will see, such drug-resistant strains pose an enormous long-term threat to global health.

Analytically, these various impediments to efficient use of pharmaceutical products to reduce the incidence of infectious diseases in developing countries can be separated into three clusters. The best known of the three is commonly known as the "access problem." In brief, we already possess some of the drugs necessary to resolve the global health crisis – "possess" in the senses that we know how to produce those drugs, have confirmed their efficacy, and could manufacture them cheaply. The residents of the developing world desperately need them. But we are unable or unwilling to make the drugs available at prices they or their governments could pay. As a result, people suffer and die, needlessly.

The access problem is notorious, not just because of its scale, but because it is easily grasped. It calls to mind the most memorable scene in *The Grapes of Wrath*, Steinbeck's widely read depiction of the Great Depression in the United States. As Steinbeck tells the tale, starving migrants from the drought-stricken center of the country have arrived in California, desperate for both work and food. Fruit is abundant there, in part because of the success of scientists in developing fecund and blight-resistant plant varieties. But to give the fruit to the migrants would corrode the market for it. So the fruit is burned – to the dismay both of the

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[73] See John P. Renschler et al., "Estimated under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa," *American Journal of Tropical Medical Hygiene* 92, no. 6 (2015).

[74] Cf. Sarah M. Beargie et al., "The Economic Impact of Substandard and Falsified Antimalarial Medications in Nigeria," *PLoS ONE* 14, no. 8 (2019). (estimating the consumption of poor-quality antimalarials causes 12,300 deaths a year in Nigeria).

[75] See Kelesidis and Falagas, "Substandard/Counterfeit Antimicrobial Drugs," 458.

[76] See Bate et al., "Substandard and Falsified Anti-Tuberculosis Drugs: A Preliminary Field Analysis."; Kelesidis and Falagas, "Substandard/Counterfeit Antimicrobial Drugs," 458 ; WHO, "Global Surveillance and Monitoring System for Substandard and Falsified Medical Products," (2017), 6.; Sachiko Ozawa et al., "Modeling the Economic Impact of Substandard and Falsified Antimalarials in the Democratic Republic of the Congo," *American Journal of Tropical Medical Hygiene* 100, no. 5 (2019). The two factors emphasized in the text – failure to complete courses of treatment, and the presence of falsified and substandard drugs – are the most widely accepted explanations for the emergence of drug resistance in TB. Some scientists, however, contend the causes are more complex. See Keertan Dheda et al., "Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis," *Lancet Respiratory Medicine* 2 (2014): 324ff.

scientists whose work and genius made it possible and of the people who are eager to consume it.[77] The handling of some pharmaceutical products in developing countries today is similar.

Less well known is what we will call the "incentive problem." As shown above, we have thus far failed to stimulate the development of the arsenals of drugs and vaccines that we would need to address fully the global health crisis. Indeed, with respect to *infectious* diseases, the incentive problem is presently more serious than the access problem. Because *noncommunicable* diseases are common in rich countries, substantial financial resources have been – and will continue to be – deployed to develop the drugs we need to fight them. But, with the important exceptions of HIV/AIDS and COVID-19, the infectious diseases that currently ravage developing countries are rare in rich countries. The result, as we will see, is that, relatively few resources have been deployed to address them.

Least well known is the "quality problem." As just explained, distressingly high numbers of medicines distributed in poor countries do not work – either because they have deteriorated or because producers have deliberately omitted some or all of the active ingredients they are supposed to contain. Large numbers of people suffer or die as a result. And strains of these diseases capable of overwhelming all of our defenses are proliferating.

The ambition of this book is to identify ways in which we might solve these three problems simultaneously. More specifically, our goal is to determine how the laws and institutions that manage pharmaceutical products might be reformed first to generate more vaccines and drugs aimed at neglected infectious diseases, then to make those vaccines and drugs available to the people who need them at prices that they (or their governments) can afford, and finally to prevent the distribution of drugs that do more harm than good.

In undertaking this task, we are surely not writing on a blank slate. Much excellent work has already been done on these issues – by economists, physicians, legal scholars, and public-health activists. Our ambition is to distill the best ideas from the existing literature, add some new proposals of our own, and then bind them into a coherent whole that has a realistic chance of adoption in the foreseeable future.

Our argument will proceed in the following stages: Part I lays the foundation for the analysis. It begins with a chapter that examines in more detail the most devastating of the infectious diseases that are currently rampant in developing countries and discusses some ways in which those diseases might be controlled. The second chapter then describes the complex combination of governmental and nongovernmental institutions that currently determine the pace and direction of drug development and deployment.

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[77] See John Steinbeck, *The Grapes of Wrath* (1930), chapter 25. The key passage merits quotation:

> Men who can graft the trees and make the seed fertile and big can find no way to let the hungry people eat their produce. Men who have created new fruits in the world cannot create a system whereby their fruits may be eaten. And the failure hangs over the State like a great sorrow. The works of the roots of the vines, of the trees, must be destroyed to keep up the price, and this is the saddest, bitterest thing of all. Carloads of oranges dumped on the ground. The people came for miles to take the fruit, but this could not be. How would they buy oranges at twenty cents a dozen if they could drive out and pick them up? And men with hoses squirt kerosene on the oranges, and they are angry at the crime, angry at the people who have come to take the fruit. A million people hungry, needing the fruit – and kerosene sprayed over the golden mountains.

The heart of the book is Part II, which examines a wide variety of strategies that might be used to reduce the scourge of infectious diseases in the developing world. Our thesis is that no one approach is likely, on its own, to do the job. Rather, a cocktail of interdependent initiatives would be both most effective and most politically palatable. Somewhat more specifically, we advocate a combination of:

- modifications of intellectual-property laws – some involving the laws of developed countries, others involving the laws of developing countries, still others involving the treaties that bind both developed and developing countries (Chapter 3);
- legal and political reforms that would both enhance the power of pharmaceutical firms to engage in differential pricing of their products and discipline their exercise of that power (Chapter 4);
- more sophisticated use of financial carrots (both grants and prize systems) by governments, universities, and NGOs to induce the creation of kinds of drugs the patent system neglects and then maximize their availability (Chapter 5);
- a new regulatory system that would require all pharmaceutical firms selling drugs in the United States to achieve each year a minimum ratio between the health benefits of their products and their revenues (Chapter 6); and
- a combination of legal reforms, business practices, and technological initiatives that would increase the quantities of vaccines and drugs available to the residents of developing countries, while simultaneously reducing the percentage of those drugs that are falsified or substandard (Chapter 7).

Adoption of this set of reforms would impose costs on the residents of developed countries. Some of those costs would take the form of increased taxes, others of increased prices for drugs or increased insurance premiums. The financial burdens would not be overwhelming, but they would not be trivial either. In view of the skepticism many Americans – and, to a lesser extent, many residents of other developed countries – harbor toward foreign aid of any sort, the imposition of those burdens requires justification. Part III of the book takes up that task. Chapter 8 identifies an overlapping set of moral arguments that support the assumption by residents of developed countries of duties to their counterparts in the developing world. Chapter 9 rebuts some common objections to those arguments.

The conclusion summarizes our recommendations.

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