Rethinking Global Pharmaceutical Policy

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Chapter 2: The Potential Power of Drugs

(version 2.1, January 4, 2025)

Pharmaceutical products could help enormously in overcoming the current global health crisis. In the past, they have demonstrated their capacity to prevent or combat many diseases, and they could be even more effective in the future. However, several factors have thus far prevented us from fully exploiting the potential power of drugs. Unless they are removed those same factors will limit our ability to use these tools to address the crisis.

The first section of this chapter provides some illustrative examples of the extraordinary power of drugs. The bulk of the chapter then identifies and explores the factors that curtail that power. Much of the balance of the book will consider ways of mitigating those factors.

A. Achievements and Opportunities

A few brief narratives should be sufficient to remind readers of many contributions that pharmaceutical products have made to public health.

1. Infectious Diseases in the United States

Beginning in the late nineteenth century, three main strategies enabled the United States to lower dramatically both mortality and morbidity associated with infectious diseases. The first consisted of improvements in sanitation and hygiene. The principal initiatives were: cleaning up food-supply systems (for example, the widespread 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).[1] 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.[2] Almost half of that reduction can be traced to the deployment of municipal water-supply systems.[3]

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.

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[1] 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.

[2] 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.

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

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.[4] 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.[5]

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.[6] The next major wave of vaccine development began in the 1920s. Soon thereafter, federally funded vaccination programs made these 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:

First-Generation Vaccines in the United States

Disease	**First Vaccine**	**Developed**	**First widely distributed in US**
Tuberculosis	Bacillus Calmette-Guerin (BCG) vaccine[7]	1921	1949
Diptheria	toxoid (inactivated toxin) vaccine[8]	1923	mid-1940s

[4] 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); James C. Riley, *Rising Life Excpectancy: A Global History* (Cambridge: Cambridge University Press, 2001), 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).

[5] 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).

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

[7] 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.

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

Pertussis ("Whooping Cough")	Whole-cell vaccine[9]	1926	mid-1940s
Tetanus	toxoid (inactivated toxin) vaccine[10]	1927	mid-1940s
Yellow Fever	17D vaccine[11]	1932	1941
Influenza	Inactivated vaccine for types A and B[12]	1942	mid-1940s
Polio	Salk inactivated vaccine[13]	1952	late-1950s
Measles	Edmonston B strain live vaccine[14]	1964	1974
Mumps	"Jeryl Lynn" strain[15]	1967	1977
Rubella	Live non-human attenuated vaccines[16]	1969	1970
Hepatitis B	Heptavax vaccine[17]	1981	1980s
Varicella-zoster ("chicken pox")	Varivax	1984	1989
Haemophilus Influenzae type b	Bacterium capsular polysaccharide Hib vaccine	1985	1985
Rotavirus	Rotashield	1998	1998

In several cases, these first-generation vaccines proved imperfect, either because their effectiveness was limited or because they had harmful 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.[18]

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

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

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

[12] 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.

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

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

[15] 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.

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

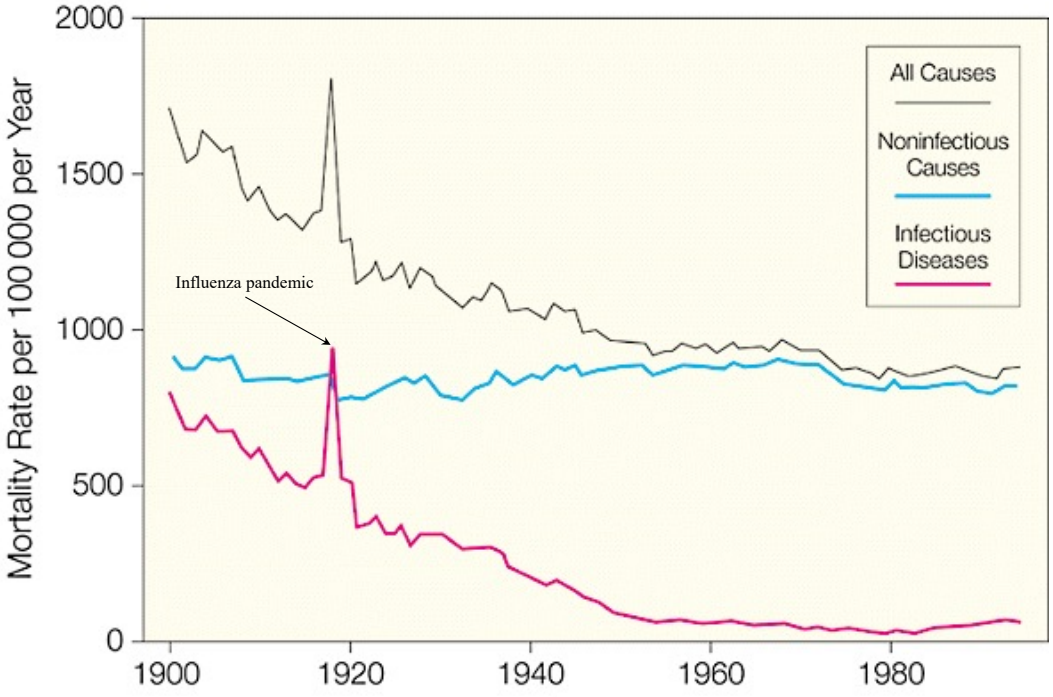
[17] See Hepatitis B Foundation, "Hepatitis B Vaccine History," October 21, 2009: http://www.hepb.org/professionals/hepatitis_b_vaccine.htm.

[18] 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).

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.[19]

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. [20]

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.

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

[20] A reminder: these are "crude" mortality rates, not age-adjusted 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.

2. AIDS in Africa

No cure for HIV/AIDS currently exists. However, since the early 1990s, medicines have become available that can slow or halt the progress of the disease. These medicines are commonly known as "anti-retroviral" drugs (ARVs), less commonly as "anti-retroviral therapies" (ARTs) or "highly active antiretroviral therapies" (HAARTs). The most effective are reverse transcriptase inhibitors, which impede the process by which modified DNA is generated from HIV RNA.[21] Inhibitors of this sort include zidovudine (AZT), tenofovir (TDF), lamivudine (3TC), staduvine (d4T), and emtricitabine (FTC).[22] Combinations ("cocktails") of these drugs have proven to be more effective than single drugs; typically, they are administered in combinations of three.[23]

Originally intended to be administered to people already infected with HIV, these drugs subsequently also proved to be effective when used prophylactically. Specifically, they have been administered increasingly often to the infected partners in serodiscordant couples and to infected pregnant women. The latter practice, if begun early enough, nearly eliminates transmission of the virus from mother to fetus.[24]

These drugs have transformed AIDS from a fatal disease to a manageable chronic ailment. As we saw in Chapter 1, before their deployment, many countries in Africa had extremely high death rates. After the drugs became widely available there, those rates fell sharply. In Chapter 6, we will examine in detail the initiatives that made their widespread availability possible. For the time being, our concern is with their remarkable net impact, which is effectively captured by the following figure:

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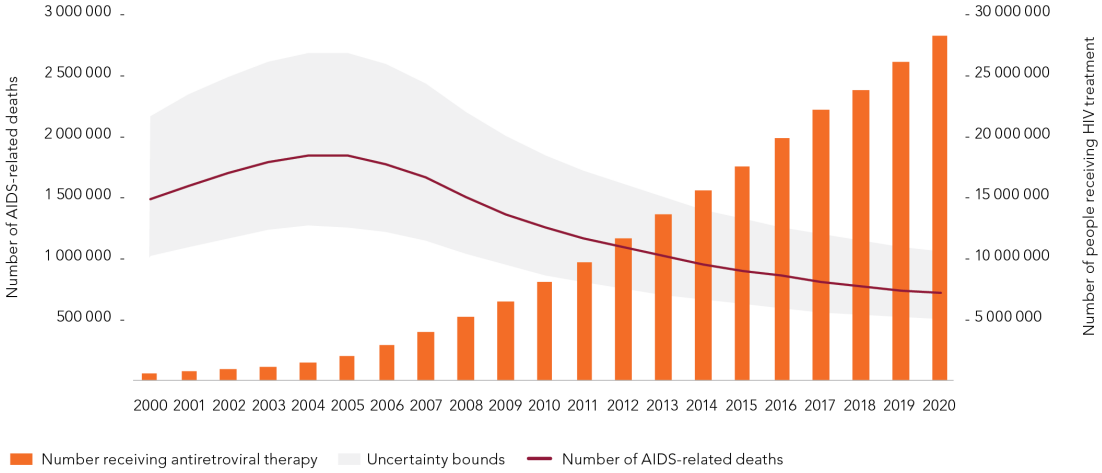
[21] See note ___, above.

[22] For a comprehensive catalogue of the ARVs used in developing countries, see MSF, Untangling the Web of Antiretroviral Price Reductions — 18th Ed., (2016), https://msfaccess.org/sites/default/files/HIV_report_Untangling-the-web-18thed_ENG_2016.pdf., pp. 16-46.

[23] For a catalogue of the principal combinations of ARVs, see ibid., pp. 47-69; Clinton Health Access Initiative, "Hiv Market Report: The State of Hiv Treatment, Testing, and Prevention in Low- and Middle-Income Countries," (2019).

[24] WHO, "Global Update on the Health Sector Response to Hiv, 2014," (2014)., Chpt. 3.

Numbers of AIDS-related deaths and people receiving HIV treatment, global, 2000–2020



Source: UNAIDS epidemiological estimates, 2021.

UNAIDS (from whom this figure has been drawn) estimates that, as of 2020, the deployment of these drugs had saved 16.5 million lives, the large majority of them in Africa.[25] To be sure, their increasingly widespread usage has not solved the AIDS crisis. As discussed in Chapter 1, the number of people infected each year by the HIV virus continues to rise, and the number killed each year remains at roughly 600,000. But the situation would be far worse in the absence of these products.

Recently, an even more efficacious drug has become available. In December 2022, the FDA approved lenacapavir (under the brand name "Sunlenca") for the treatment of HIV/AIDS. This new drug provides effective treatment for HIV that works for six months after each injection. Thus, patients receiving it will only have to visit a clinic twice a year. In addition, recent Phase 3 clinical trials have shown remarkable results in the use of lenacapavir for pre-exposure prophylaxis (PrEP). Gilead, the company that developed the drug, expects to receive approval for PrEP as soon as the end of 2024.[26] In the words of the lead researcher, lenacapavir brings us "as close as we've ever been to an HIV vaccine."[27] The potential for combatting the pandemic should be obvious.

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[25] UNAIDS, "Global Roll-out of Hiv Treatment Has Saved Millions of Lives," (2021).

[26] *Gilead Signs Royalty-Free Voluntary Licensing Agreements with Six Generic Manufacturers to Increase Access to Lenacapavir for HIV Prevention in High-Incidence, Resource-Limited Countries*, GILEAD (Oct. 2, 2024), https://www.gilead.com/news/news-details/2024/gilead-signs-royalty-free-voluntary-licensing-agreements-with-six-generic-manufacturers-to-increase-access-to-lenacapavir-for-hiv-prevention-in-high-incidence-resource-limited-countries [hereinafter Gilead Announcement].

[27] Kat Lay, HIV Drug Could be Made for Just $40 a Year for Every Patient, GUARDIAN (July 23, 2024), https://www.theguardian.com/global-development/article/2024/jul/23/hiv-aids-prevention-vaccine-lenacapavir-sunlenca-pharmaceuticals-gilead-generic-licensing.

3. Management of Diabetes

Until the early 20th century, there was no effective treatment for diabetes. The prognosis of patients with type-1 diabetes was especially bad. Most "remedies" did no good whatsoever. The only effective treatment – strictly restricting patients' diets – typically delayed only modestly the onset of complications and death.[28]

In 1921, a group of Canadian researchers, capitalizing on research that revealed the crucial role of the pancreas in diabetes, developed a technique for extracting insulin from the pancreas glands of animals (first dogs, later cattle and pigs). Regular injections of animal insulin radically improved the life prospects of type-1 sufferers. Since then, other researchers, nonprofit organizations, and pharmaceutical firms have refined insulin in myriad ways – reducing variations in its potency, improving its purity, prolonging its action, adjusting the speed with which it is absorbed by the body, and so forth. A major advance came in the late 1970s, when scientists at Genentech developed the first recombinant DNA human insulin, subsequently marketed by Eli Lilly under the brand name, "Humulin." The revolutionary technologies underlying Humulin subsequently enabled the development of insulin "analogs," such as Humalog and Lantus. By replacing or rearranging a few amino acids, these analogs have been able to tune the behavior of the hormone in ways that benefit many type-1 patients.[29]

During the same time period, type-2 diabetics benefitted, not just from the availability of increasingly effective and diverse forms of insulin and its analogs, but also from the development of a variety of other drugs. Major additions to the portfolio of substances used to treat type-2 diabetes included metformin (which increases the sensitivity of tissues to insulin, decreases the production of glucose by the liver, and facilitates weight loss), exenatide (which stimulates insulin secretion and suppresses glucagon production), and most recently semaglutide (whose operation is similar to that of exenatide).[30]

Perhaps the clearest indicator of the benefits of these innovations consists of the increase of diabetics' life expectancy in the countries where the drugs are readily available. For type-1 diabetes, the most revealing dataset comes from Finland, which has the highest prevalence rate in the world, but also a well-designed system for providing all patients access to insulin and its analogs. A recent study there found dramatic improvements in the life expectancies of type-1 diabetics between 1972 and 2017 – although they can still

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[28] See U.S. Food and Drug Administration, "100 Years of Insulin," (2022); Celeste C. Quianzon and Issam Cheikh, "History of Insulin," *Journal of community hospital internal medicine perspectives* 2, no. 2 (2012).

[29] See Marianna Karamanou et al., "Milestones in the History of Diabetes Mellitus: The Main Contributors," *World journal of diabetes* 7, no. 1 (2016); Administration, "100 Years of Insulin."

[30] See Andrew J. Ahmann et al., "Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide Er in Subjects with Type 2 Diabetes (Sustain 3): A 56-Week, Open-Label, Randomized Clinical Trial," *Diabetes care* 41, no. 2 (2018); Ralph A. Defronzo, "From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus," *Diabetes* 58, no. 4 (2009); Amisha Wallia and Mark E. Molitch, "Insulin Therapy for Type 2 Diabetes Mellitus," *JAMA : the journal of the American Medical Association* 311, no. 22 (2014); Simeon I. Taylor, "The High Cost of Diabetes Drugs: Disparate Impact on the Most Vulnerable Patients," *Diabetes Care* 43, no. 10 (2020).

expect to live, on average, approximately 10 fewer years than persons without diabetes.[31] Recent studies in other developed countries have found comparable gains with respect to type 1.[32]

The data with respect to type-2 diabetes is messier, because modern treatment regimens typically combine drugs with adjustments in other factors -- diet, lifestyle, weight, etc.. Distilling from life-expectancy data the benefit provided by the increasingly sophisticated drugs is thus more difficult. Certainly, type-2 diabetics in developed countries can expect to live much longer today than they could 50 years ago.[33] Almost as certainly, a substantial portion of the improved prospects is attributable to the availability in those countries of pharmaceutical products – but exactly how much is impossible to say.

4. COVID Vaccines

The last of the four examples is the best known. Starting in early 2020, when the magnitude of the threat posed by COVID-19 became apparent, governments and pharmaceutical firms throughout the world poured huge amounts of resources into the development of vaccines. This effort was remarkably successful. By June of 2021, seven COVID vaccines had been approved for emergency use by the WHO, and 19 had been approved by at least one national authority. Large quantities were quickly purchased by the governments of developed countries and made available to their residents.[34]

Many lives were saved as a result. A Lancet study sought to estimate the number just within the first year after vaccinations began, using two alternative methods. The first, which extrapolated from officially reported COVID deaths, suggested that 18.1 million additional deaths would have occurred worldwide had the vaccination programme not occurred. The second, using instead estimates of "predicted and reported excess mortality" caused by COVID, suggested that the number was 31.4 million.[35] The blue and green zones in the following graph represent the people who would have died according to the second model.

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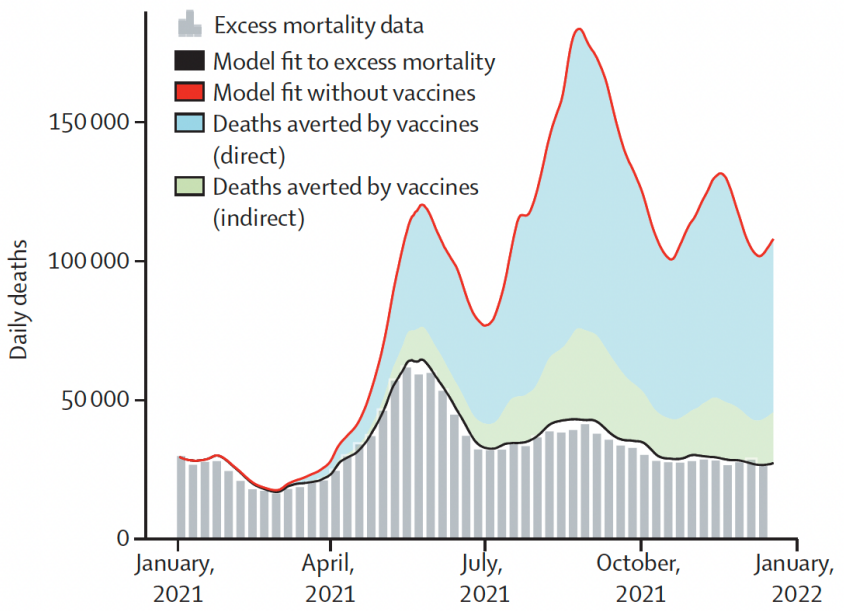
[31] See Martti Arffman et al., "Long-Term and Recent Trends in Survival and Life Expectancy for People with Type 1 Diabetes in Finland," *Diabetes research and clinical practice* 198 (2023).

[32] See, e.g., Rachel G. Miller et al., "Improvements in the Life Expectancy of Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study Cohort," *Diabetes (New York, N.Y.)* 61, no. 11 (2012): ("The life expectancy at birth for those diagnosed 1965–80 was ~15 years greater than participants diagnosed 50–64.").

[33] The relevant studies vary considerably, but all report large gains. See, for example, S. Kaptoge et al., "Life Expectancy Associated with Different Ages at Diagnosis of Type 2 Diabetes in High-Income Countries: 23 Million Person-Years of Observation," *The lancet. Diabetes & endocrinology* 11, no. 10 (2023).

[34] *See* UNICEF, "Covid-19 Vaccine Dashboard," https://www.unicef.org/supply/covid-19-vaccine-market-dashboard (last accessed 30 June 2021). The remarkable story of the rapid development of these vaccines can be traced in Florian Krammer, "Sars-Cov-2 Vaccines in Development," *Nature* 586 (2020).; L.A. Jackson et al., "An Mrna Vaccine against Sars-Cov-2 — Preliminary Report," *New England Journal of Medicine* 383, no. 20 (2020).; L.R. Baden et al., "Efficacy and Safety of the Mrna-1273 Sars-Cov-2 Vaccine," ibid.384, no. 5 (2021). The funding strategies that made this possible are described in Chapter 3.

[35] See Oliver J. Watson et al., "Global Impact of the First Year of Covid-19 Vaccination: A Mathematical Modelling Study," *Lancet. Infectious diseases/□The □Lancet. Infectious diseases* 22, no. 9 (2022).



Even if the magnitude of the counterfactual scenario is exaggerated, it is apparent that the expeditious development and distribution of the COVID vaccines resulted in a huge benefit to mankind.

These four narratives are far from unique. Analogous stories could be told with respect to many other diseases. They leave little doubt that, historically, the investment of substantial amounts of resources in the development, testing and distribution of new pharmaceutical products has paid enormous dividends. The implication: drugs could help a great deal to mitigate the current crisis.

To be sure, the same illustrative narratives also make clear the power of nonmedicinal public-health strategies. As we saw, suppression of most infectious diseases in the United States required more than vaccines and antibiotics; improvements in the food supply, water supply, and personal hygiene practices were also crucial. Similarly, mitigation of the AIDS pandemic in Africa was achieved by combining deployment of ARVs with other interventions: educational programs encouraging use of condoms;[36] male circumcision;[37] providing testing and medical services to sex workers;[38] providing similar services and sterile or disposable syringes to intravenous drug users;[39] testing blood

[36] See Johnson et al., "The Effect of Changes in Condom Usage and Antiretroviral Treatment Coverage on Human Immunodeficiency Virus Incidence in South Africa," 9 J R. Soc. Interface 1544 (2012). The current rates of condom use in the countries where HIV is most prevalent are reviewed in WHO, "Global Update on the Health Sector Response to Hiv, 2014.", pp. 11-12.

[37] See Auvert, Randomized Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk," 2 PLoS Med. E298 (2005); Gray, "Male Circumcision for HIV Prevention in Rakai, Uganda," 369 Lancet 657 (2007); Bailey, "Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya," 369 Lancet 643 (2007).

[38] See WHO, "Global Update on the Health Sector Response to Hiv, 2014.", Table 2.2.

[39] See WHO, "EFFECTIVENESS OF STERILE NEEDLE AND SYRINGE PROGRAMMING IN REDUCING HIV/AIDS AMONG INJECTING DRUG USERS" (2004),

supplies to prevent transmission through infusions;[40] and the use of various precautions by health-care workers to reduce transmissions from their patients. Likewise, educational programs encouraging exercise and dietary changes have been as helpful in limiting type-2 diabetes as have been drugs.[41] Finally, quarantines, social distancing, hand washing, and the use of masks (for adults, at least) were crucial in fight against COVID.[42] Thus, we certainly do not mean to suggest that, in combatting the current crisis, we should rely exclusively upon pharmaceutical products. Our claim, rather, is that those products could help a great deal.

To this claim, there is a natural retort: If pharmaceutical products are so powerful, why have they not already solved the problem? The balance of this chapter attempts to answer that question. It identifies four factors that thus far have limited the potential benefits to humankind of pharmaceutical products. Unless addressed, the same factors will prevent us from using drugs to address the crisis we now face.

B. Misalignment

The first of the factors is that the set of pharmaceutical products that, collectively, we are developing and distributing is not optimal – in other words, it is not well aligned with our health needs. Even if we confined our attention to the United States, this would be true. The misalignment would become even more stark if the criterion by which we evaluated the current portfolio of products were the health needs of the human race as a whole. Summarized below are the four most important forms of misalignment.

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http://www.who.int/hiv/pub/prev_care/effectivenesssterileneedle.pdf?ua=1; WHO, "Best Practices for Injections and Related Procedures ToolKit" (2010), http://www.who.int/injection_safety/toolbox/9789241599252/en/.

[40] WHO, Notes 58, 60.

[41] See, e.g., Hamed Kianmehr et al., "Potential Gains in Life Expectancy Associated with Achieving Treatment Goals in People with Type 2 Diabetes in the United States," *JAMA network open* 5, no. 4 (2022).

[42] See Kevin Escandón et al., "Covid-19 False Dichotomies and a Comprehensive Review of the Evidence Regarding Public Health, Covid-19 Symptomatology, Sars-Cov-2 Transmission, Mask Wearing, and Reinfection," *BMC Infectious Diseases* 21, no. 1 (2021); Hanna Grzybowska et al., "Safe Transport: Wearing Face Masks Significantly Reduces the Spread of Covid-19 on Trains," *BMC infectious diseases* 22, no. 1 (2022); Maryam Hajmohammadi, Amal Saki Malehi, and Elham Maraghi, "Effectiveness of Using Face Masks and Personal Protective Equipment to Reducing the Spread of Covid-19: A Systematic Review and Meta-Analysis of Case-Control Studies," *Advanced biomedical research* 12, no. 1 (2023); Isabelle J. Rao, Jacqueline J. Vallon, and Margaret L. Brandeau, "Effectiveness of Face Masks in Reducing the Spread of Covid-19: A Model-Based Analysis," *Medical Decision Making* 41, no. 8 (2021); Meenakshi Sharma et al., "Cost-Effectiveness Analysis of Surgical Masks, N95 Masks Compared to Wearing No Mask for the Prevention of Covid-19 among Health Care Workers: Evidence from the Public Health Care Setting in India," *PloS one* 19, no. 5 (2024); Stella Talic et al., "Effectiveness of Public Health Measures in Reducing the Incidence of Covid-19, Sars-Cov-2 Transmission, and Covid-19 Mortality: Systematic Review and Meta-Analysis," *BMJ* 375 (2021). But cf. Johanna Sandlund et al., "Face Masks and Protection against Covid-19 and Other Viral Respiratory Infections: Assessment of Benefits and Harms in Children," *Paediatric respiratory reviews* (2024).(arguing that mandating masks for young children is not net beneficial).

1. Vaccines v. Therapies

In a classic essay, Burton Weisbrod offered the following illustration of the relative merits of vaccines and therapies. In the early 20th century, he pointed out, we lacked any effective treatment for polio. The result was that the total health care costs associated with polio were low. "Many victims of the disease died quickly as a result of paralysis; for them, the effects were disastrous, but the attendant health care costs were small." The development and deployment of iron-lung technology "prolonged life, but at substantial cost." Those costs remained high, until the development of polio vaccines (Sabin and Salk), whose widespread distribution (in the United States) virtually eliminated the disease. (There were 38,000 cases in 1954; 5 cases in 1985.) The result is that we now devote virtually no resources to combatting polio.[43] The lesson is plain: vaccines have enormous potential both to alleviate suffering and to reduce costs.

The combination of pharmaceutical products that we are currently generating does not reflect that insight. Only 54 vaccines are currently licensed for use in the United States,[44] and the major pharmaceutical firms are investing discouragingly little money in research designed to develop new ones. As a result, the percentage of drugs approved each year by the FDA that consist of vaccines has been dropping in recent years. From a high of 14% in 2006-2008, it had fallen by 2018 to 5%.[45]

Why, then, are we neglecting vaccines? At least five factors seem to be at work. First, the methods by which vaccines have traditionally been produced are more expensive than the methods used to produce most medicines – and thus the potential profits they can generate are smaller. Second, some analysts think that, even after a modest adjustment of the relevant products-liability regime, the large potential damages to which vaccine producers are potentially exposed discourages entry into the industry.[46] Third, high-profile scandals involving impure vaccines have resulted in the imposition on vaccine producers of unusually tight and costly safety regulations. Fourth, two aspects of private markets for vaccines – the inability of sellers to monetize the positive externalities associated with vaccine consumption and the tendency of potential consumers to underestimate the risks of contacting the diseases to which they pertain – depress the prices that manufacturers can charge below the levels warranted by social value.[47] Finally, the understandable efforts of the administrators of vaccine procurement programs to use their bargaining power to drive down costs reduces incentives to hunt for new vaccines.

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[43] Burton Weisbrod, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature* 29, no. 2 (1991).

[44] FDA, "Vaccines Licensed for Use in the United States," https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states (current as of 11/27/2019) (counting identical vaccines manufactured by more than one company as one vaccine).

[45] See Jonathan J. Darrow, Michael S. Sinha, and Aaron S. Kesselheim, "When Markets Fail: Patents and Infectious Disease Products," *Food and Drug Law Journal* 73 (2018): 364.

[46] See Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* (2004).

[47] See Michael Kremer and Rachel Glennerster, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* (Princeton, N.J.: Princeton University Press, 2004), , 29ff.

In subsequent chapters, we will explore various ways in which we might seek to counteract these forces. For the time being, we wish merely to highlight the problem: too few resources are currently allocated to the development of vaccines.

2. Me-Toos

The pharmaceutical industry currently devotes too many resources to generating drugs that offer at best modest therapeutic advantages over existing drugs and devotes too few resources to pursuing genuine breakthroughs. Drugs of the first type are sometimes known as "me-too" drugs, a term that reflects the fact that they are frequently members of the same family as an existing drug and operate similarly. But it is more accurate to think of drugs as arrayed along a spectrum. At one extreme are those that, although safe and effective, are no better for any patient than existing drugs. At the opposite extreme are those that have enormous comparative advantages. To illustrate: Some of the follow-on statins (for heart disease) and tricyclic anti-depressants fall near the first end of the spectrum,[48] Sovaldi, the first drug to offer a permanent cure for hepatitis C, falls near the opposite end, and Harvoni, a successor to Sovaldi with significant advantages, falls near the middle.[49] The problem, then, is that the current system is tilted in favor of drugs that are closer to the first end of the spectrum.

One manifestation of this bias is the modest size of the subset of drugs that the FDA deems worthy of "priority review." To appreciate this indicator requires a bit of background: The FDA currently uses several procedural devices to accelerate evaluations of drugs that promise significant health benefits.[50] Of these, the differentiation of drugs according to "priority" is the most important. The agency describes its practice as follows:

> A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review). A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.
>
> Significant improvement may be demonstrated by the following examples:
> - evidence of increased effectiveness in treatment, prevention, or diagnosis of condition;

[48] See Jeffrey K. Aaronson and A. Richard Green, "Me-Too Pharmaceutical Products: History, Definitions, Examples, and Relevance to Drug Shortages and Essential Medicines Lists," *British Journal of Clinical Pharmacology* 86 (2020). Statins in general have large health benefits, see, e.g., Rory Collins et al., "Interpretation of the Evidence for the Efficacy and Safety of Statin Therapy," *The Lancet* 388 (2016)., but Crestor has not been shown to be significantly better than Lipitor, its major predecessor.

[49] See Laura Fegraus and Murray Ross, "Sovaldi, Harvoni, and Why It's Different This Time," *Health Affairs* (2014), https://www.healthaffairs.org/do/10.1377/hblog20141121.042908/full/.

[50] See U.S. Department of Health and Human Services, "Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics," (2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

- elimination or substantial reduction of a treatment-limiting drug reaction;
- documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or
- evidence of safety and effectiveness in a new subpopulation.[51]

For present purposes, the significance of this system is that it provides an indication of how many of the drugs presented for FDA review are considered by the agency to offer "significant improvements in the … treatment, diagnosis, or prevention of serious conditions." In 2019, 58% of the 48 novel drugs approved by the agency received priority review. This is a greater proportion than in years past,[52] but it still means that almost half of the approvals were for drugs that were not expected to have significant health benefits.[53] The other pertinent classifications used by the agency are even more worrisome: Only 35% of the approved drugs were designated "fast-track" (i.e., were deemed to have "the potential to address unmet medical needs") and only 27% were designated "breakthroughs" (i.e., were deemed "drugs for serious or life-threatening diseases for which there is unmet medical need and for which there is preliminary clinical evidence demonstrating that the drug may result in substantial improvement on a clinically significant endpoint … over other available therapies").[54] Most knowledgeable analysts of the pattern of drug development and approval in the United States come to the same conclusion: Too many resources are being devoted to the creation of drugs from which we benefit little.[55]

This judgment is not universally shared, however. Defenders of the current system point out that many of the so-called "me-too" drugs (such as the newer SSRIs for depression) are better than older drugs in the same family for modest groups of patients. And even when the newcomers are functionally equivalent to their predecessors, their presence in the market may lead to price competition, which would then make all drugs more affordable.[56]

These arguments have been persuasively rebutted by Aidan Hollis.[57] As he points out, me-too drugs can be approved only after surviving the standard three rounds of clinical testing. The substantial costs of those tests would surely produce greater benefits to public

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[51] U.S. Food and Drug Administration, "Priority Review," https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review.

[52] 59% of NMEs licensed in the United States between 1990 and 2004 consisted of "me-toos."

[53] Food and Drug Adminstration, "Advancing Health through Innovation: New Drug Therapy Approvals 2019," (2020), 22.

[54] Ibid., 21.

[55] See, e.g., Jerry Avorn; Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (New York: Random House, 2004); Mark Dugan and Fiona Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," *Quarterly Journal of Economics* 71, no. 1 (2006).

[56] See Joseph A. DiMasi and Cherie Paquette, "The Economics of Follow-on Drug Research and Innovation: Trends in Entry Rates and the Timing of Development," *Pharmacoeconomics* 22 (2004).

[57] Aidan Hollis, "Me-Too Drugs: Is There a Problem?," (2004), https://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf.

health had they been devoted to medical problems for which we do not yet have solutions. In addition, at least in the United States, the entry of a me-too drug into a market already occupied by a pioneer rarely results in significant price competition. Instead, the me-too is typically introduced at or near the price point of the original, and the price of the original does not significantly decline. To be sure, the arrival of the me-too typically does cut into the market share of the pioneer. But that's a bug, not a feature, because it corrodes incentives to develop pioneering drugs in the first instance. Even if one believes (as do the defenders of the current regime) that Hollis overstates the relevant evidence,[58] there is little doubt that the social benefits of resources devoted to drugs that fall into the same class as efficacious and safe existing drugs are lower than the social benefits of resources devoted to first-in-class drugs.

3. The Short-term Bias

The global burdens of noncommunicable diseases that afflict the central nervous system are increasing rapidly. Chapter 1 described the threats posed by three of those diseases: Parkinson's, dementia, and depression. Others include multiple sclerosis, schizophrenia, autism, migraine, and epilepsy. The annual losses, in DALYs caused by the diseases in this family are shown below.

	CNS Disorders	All Cancers
2000	208,118,297	206,516,669
2010	241,075,366	230,404,164
2015	261,559,160	246,667,765
2019	280,602,255	263,578,345
2020	297,641,031	260,746,081
2021	304,358,208	270,057,158

As can be seen, the losses associated with CNS disorders are higher than the losses associated with all forms of cancer – and are rising faster.

One might expect that the dangers posed by these disorders would prompt pharmaceutical firms to increase the resources they devote to research on drugs that would address them. Instead, during the period covered by this table, the opposite happened; the major pharmaceutical firms steadily reduced, rather than augmented, their investments in CNS.

In 2014, one of us joined a group of scholars attempting to sound the alarm on this front.[59] We pointed out that, in the preceding 5 years, the number of projects being pursued by the major firms had plummeted:

[58] See Joseph A. DiMasi, "Comment on "Me-Too Drugs: Is There a Problem?"," (2005), https://www.who.int/intellectualproperty/forum/HollisResponse.pdf.

[59] Dennis Choi et al., "Medicines for the Mind: Policy-Based "Pull" Incentives for Creating Breakthrough Cns Drugs," *Neuron* 84, no. 3 (2014).

Table 1. CNS Program Portfolios in Large Pharma: 2009 versus 2014

	2009	2014
Total Programs	267	129
Abbott/AbbVie	17	10
AstraZeneca	21	7
Bristol-Myers Squibb	12	2
GlaxoSmithKline	40	14
Johnson & Johnson	18	17
Lilly	16	9
Merck/Schering-Plough	32	7
Novartis	14	15
Pfizer/Wyeth	46	15
Roche/Genentech	22	21
Sanofi/Genzyme	29	12

Total number of discovery, preclinical, and clinical drug development programs addressing neurology or psychiatry disease targets, visible from publicly available sources including SEC filings, investor briefings, and company websites.

Our call to arms apparently did little good. In the following decade, the retreat continued.[60]

Very recently, there have been a few signs of recovery. Small biotech companies have shown renewed interest in CNS research, and venture-capital funding has increased.[61] But the share of resources that we devote to this sector remains modest – well below the share devoted to oncology, for example.[62]

There are two main causes of this bias. The better known is that the science underlying CNS disorders is more complex and has been less thoroughly explored than the science of most diseases. Consequently, the challenges to developing new drugs in the CNS field are higher. Less obvious is that the financial returns for a CNS are, on average, smaller. The main reason is that it takes substantially longer to conduct clinical tests on CNS drugs and thus to obtain regulatory approval. Because the period during which new

[60] See Jacob Bell, "Big Pharma Backed Away from Brain Drugs. Is a Return in Sight?," *Giopharma Dive* (2020); Kelly Bilodeau, "Neuro Drugs Are Still Faltering, Despite Rising Investment," *Pharmavoice* (2024), https://www.pharmavoice.com/news/neuro-drug-brain-chip-axosim-fda/722593/; Asher Mullard, "Pfizer Exits Neuroscience," *Nature Reviews: Drug Discovery* (2018), https://www.nature.com/articles/nrd.2018.16.

[61] See Damian Garde, "A 'Renaissance in Neuroscience' Could Deliver a Fresh Crop of Psychiatric Medicines," *Stat News* (2024); Michael Gibney, "Don't Call It a Comeback: Biotech's Cns Resurgence Forges Big Pharma Connections," *Pharmavoice* (2024), https://www.pharmavoice.com/news/neuroscience-bristol-myers-prothena-central-nervous-system-comeback-resurgence/719983/; Krzysztof Potempa, "Pharma Ins and Outs: Neuroscience," (2024), https://www.linkedin.com/pulse/pharma-ins-outs-neuroscience-krzysztof-potempa; Markus Gores and Stefan Lutzmayer, "Two Steps Forward, One Step Back: The Long Road to Success in Cns," (2023).

[62] See Ian Lloyd, "Pharma R&D Annual Review 2024," (2024), 19-20.

drugs enjoy intellectual property protection is limited, the window in which the developer of a CNS drug is shielded from competition is typically shorter than is true of other drugs.[63]

The general principle illustrated by the dire situation involving CNS drugs is that our current system is biased against pharmaceutical products that require long periods to develop and test.

The same bias can be seen in the pattern of product development within oncology. As Eric Budish and his colleagues have shown, pharmaceutical firms overinvest in drugs that, if successful, will extend modestly the lives of people with advanced or especially aggressive cancers and underinvest in drugs that, if successful, will prevent cancer altogether or result in longer extensions of the lives of people with less advanced or aggressive forms. At least one of the reasons is that clinical trials of the drugs in the first category can be performed more quickly and thus the periods in which their developers can enjoy monopoly profits are longer.[64]

4. Neglected Diseases

For the purposes of this book, the final dimension of misalignment is the most important. We currently direct an excessively large proportion of our resources toward research projects that promise to generate drugs for which there are large and lucrative markets, at the expense of projects that would have larger net health benefits but would generate fewer profits.[65] A market, to be lucrative, must include many people suffering from a particular ailment who have both the ability and the willingness to pay substantial sums for protection or relief. The large (and in most cases growing) sets of people suffering from noncommunicable diseases in high-income countries (above all, in the United States) means that lucrative markets for drugs that address all of those diseases exist. By contrast, the markets for the subset of infectious diseases that are concentrated in developing countries are much smaller.

The unfortunate impact on the patterns of health-related research and development has been dramatic. The shares of total investment and of clinical trials devoted to infectious diseases have long been well below the shares that would match the global disease burdens associated with those diseases.[66] Investment in the neglected tropical diseases have been especially low – less than 1% of the global total.[67] These biases are confirmed by other

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[63] See Choi et al., "Medicines for the Mind," 555 ("The total clinical trial plus FDA review time for CNS drugs approved between 1996 and 2010 averaged 32 months (35%) longer than for non-CNS drugs.").

[64] See Eric Budish, Benjamin N. Roin, and Heidi Williams, "Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials," *The American economic review* 105, no. 7 (2015). But cf. Vinay Prasad and Stephan Lindner, "Why Is Research in Early-Stage Cancer Research So Low?," *Journal of cancer policy* 17 (2018).(arguing that "technological barriers" may also contribute to this bias)

[65] Among the many sources exploring this problem are Kremer and Glennerster, *Strong Medicine*; Michael R. and Dranove Ward, David, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry* 33, no. 1 (1995).

[66] See Darrow, Sinha, and Kesselheim, "When Markets Fail."

[67] See John-Arne Rottingen et al., "Mapping of Available Health Research and Development Data: What's There, What's Missing, and What Role Is There for a Global Observatory," *Lancet* 382 (2013): 1303.

indicators: Of clinical trials, 89% focus on Type I diseases, 9.1% focus on Type II diseases, and 1.9% focus on Type III diseases.[68] And at the end of the research chain, the percentages of drug approvals that involve anti-microbial drugs are low – and have been declining since the 1980s.[69]

For obvious reasons, this bias helps to explain the high degree of inequality, discussed in Chapter 1, in the disease burdens born by rich and poor countries. Correcting it will be crucial if in the future we hope to use additional investment in pharmaceutical research and development to reduce that inequality.

C. Inaccessibility

The second of the four factors that currently limits the benefits of pharmaceutical products is that many of the drugs that we have managed to develop are inaccessible to many of the people who could benefit from them. The proportion who are deprived of access is substantial even in the United States and other rich countries; it is vastly higher in poor countries.

Sometimes, inaccessibility results from the fact that the drug at issue has not been approved for distribution in the country in question. A dated but still illuminating illustration of this problem is provided by a study, conducted by a group of scholars affiliated with the Gates Foundation, of the approval history of an AIDS drug in 20 sub-Saharan African countries.[70] In the chart below (reprinted from their paper), both the drug in question and the countries have been anonymized.[71] The two "SRAs" that appear at the top of the chart, are the Food and Drug Administration [FDA] in the United States, and the European Medicines Agency [EMA] in the European Union; the "NRAs" are the NMRAs in the African countries.

[68] See ibid. This categorization was discussed in Chapter 1. See pages ___, supra. For itemization of the diseases that fall into each category, see WHO Secretariat, "Defining Disease Types I, II, and III (2012), https://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf.

[69] Darrow, Sinha, and Kesselheim, "When Markets Fail."

[70] Vincent Ahonkhai et al., "Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization," *PLoS ONE* 11, no. 11 (2016).

[71] The reason for the anonymization is that the data at issue were shared with the Gates Foundation under confidentiality agreements.

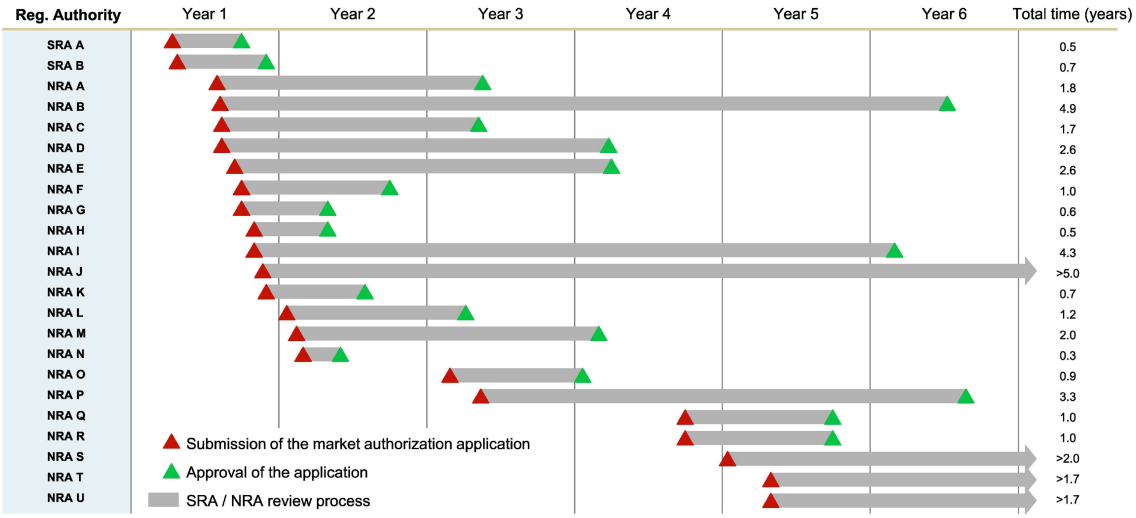


Fig 3. Registration Application Submissions and Approval in SSA for an anonymized antiretroviral drug, demonstrating 1) the variance in approval timelines across SSA countries and 2) the spread in manufacturer submissions. Red triangles represent the moment of dossier submission to the SRA or NRA, green triangles the market authorization approval by the NRA, and the grey arrows the review process.

As is apparent, in many of the African countries the drug was not submitted for approval until months or years after it had been submitted in the United States and Europe, and the approval process in those countries typically took substantially longer than in either the FDA or the EMA. Indeed, in four countries, it had not been completed by the time of the study.

A more recent example of this source of inaccessibility involves two vaccines for Respiratory Syncytial Virus (RSV). RSV is the most common cause of acute lower respiratory tract infection (LRTI) and hospitalization in children under 2 years of age. Each year, it causes more than 30 million cases of acute LRTI and over 100,000 deaths in young children. 97% of those deaths occur in low and middle-income countries.[72]

Several companies have been attempting for decades to develop a safe and efficacious vaccine for RSV. In the past few years, two especially promising candidates emerged from the pipeline. In clinical trials, nirsevimab (a monoclonal antibody developed by AstraZeneca) showed remarkable effectiveness when administered to infants, while RSVpreF (an RSV prefusion F maternal vaccine developed by Pfizer) showed similar power when administered to pregnant women.[73] Nirsevimab was approved by by the EMA on November 4, 2022[74] and by the FDA on July 17, 2023;[75] RSVpreF was approved by the

[72] See Tracy J. Ruckwardt, "The Road to Approved Vaccines for Respiratory Syncytial Virus," *npj vaccines* 8, no. 1 (2023).

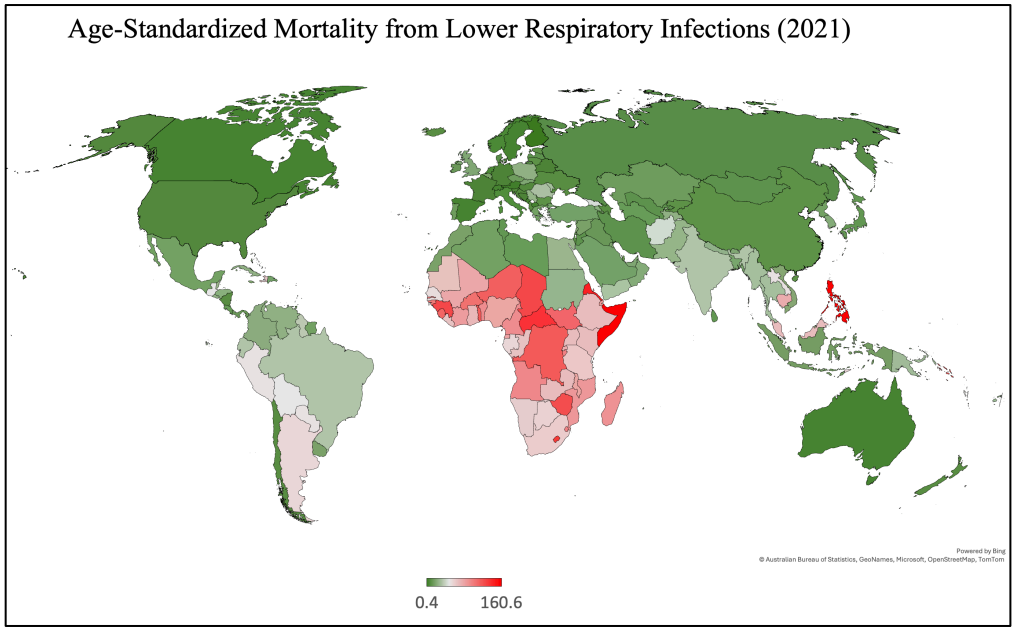
[73] See Clint Pecenka et al., "Respiratory Syncytial Virus Vaccination and Immunoprophylaxis: Realising the Potential for Protection of Young Children," *The Lancet (British edition)* 404, no. 10458 (2024).

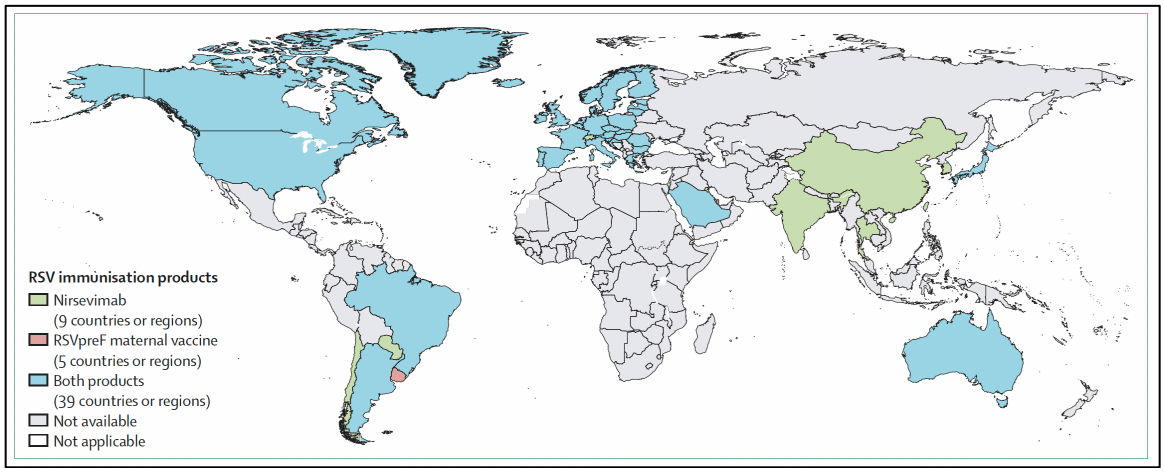
[74] See https://www.astrazeneca.com/media-centre/press-releases/2022/beyfortus-approved-in-the-eu-for-the-prevention-of-rsv-lower-respiratory-tract-disease-in-infants.html.

[75] See https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-prevent-rsv-babies-and-toddlers; https://www.astrazeneca.com/media-centre/press-releases/2023/beyfortus-approved-in-the-us-for-the-prevention-of-rsv-lower-respiratory-tract-disease-in-infants.html.

EMA on July 21, 2023[76] and by the FDA on August 21, 2023.[77] Approvals in other high-income countries and in upper-middle-income countries followed in short order. In the winter of 2023-2024, both drugs began to be deployed in several of those jurisdictions. Meanwhile, the regulatory approval process in poor countries languished.

On the opposite page appear two maps. The first shows the footprint of age-standardized mortality from LRTIs in general (the largest portion of which are caused by RSV). The second shows the pattern of regulatory approvals as of July 2024.[78] The contrast between the two is galling.





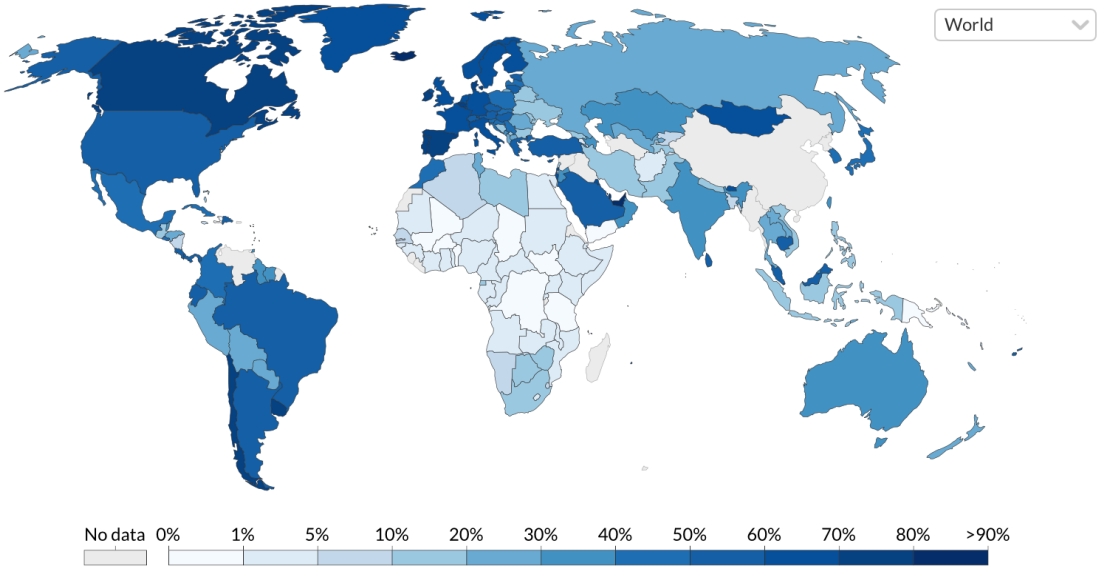
[76] See https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-and-older-adults.

[77] See https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants.

[78] Source: Pecenka et al., "Rsv Vaccination," 1158.

In other situations, inaccessibility arises, not from a lack of regulatory approval, but from the fact that supplies of the drug are insufficient to meet global demand, and the scarce supplies go to the residents of rich countries. The COVID vaccines provide the most notorious example. As indicated above, those vaccines were developed and tested at extraordinary speed starting in early 2020. But once approved, they were not then evenly distributed throughout the world. Rather, most batches in the first wave were purchased (typically well in advance of their manufacture) by developed countries, leaving little for the developing world.[79] In 2021, the supply of vaccines to developing countries slowly increased, in part because of efforts by the COVID-19 Vaccines Global Access Facility ("COVAX") to secure batches on their behalf and in part because of modest donations by developed countries of doses that they found they did not need. But the flow remained insufficient to meet demand. As one might expect, the net result (evident from the following map) was radical disparity among countries in the administration of vaccines.

Share of the Population that Had Received
at Least One COVID-19 Vaccine Dose as of August 14, 2021[80]



Source: Official data collated by Our World in Data – Last updated 15 August 2021, 10:20 (London time) OurWorldInData.org/coronavirus • CC BY
Note: This data is only available for countries which report the breakdown of doses administered by first and second doses.

Naturally, the effect of this imbalance was a shift during the course of the pandemic in the concentration of deaths from north to south.[81] The following maps, which contrast

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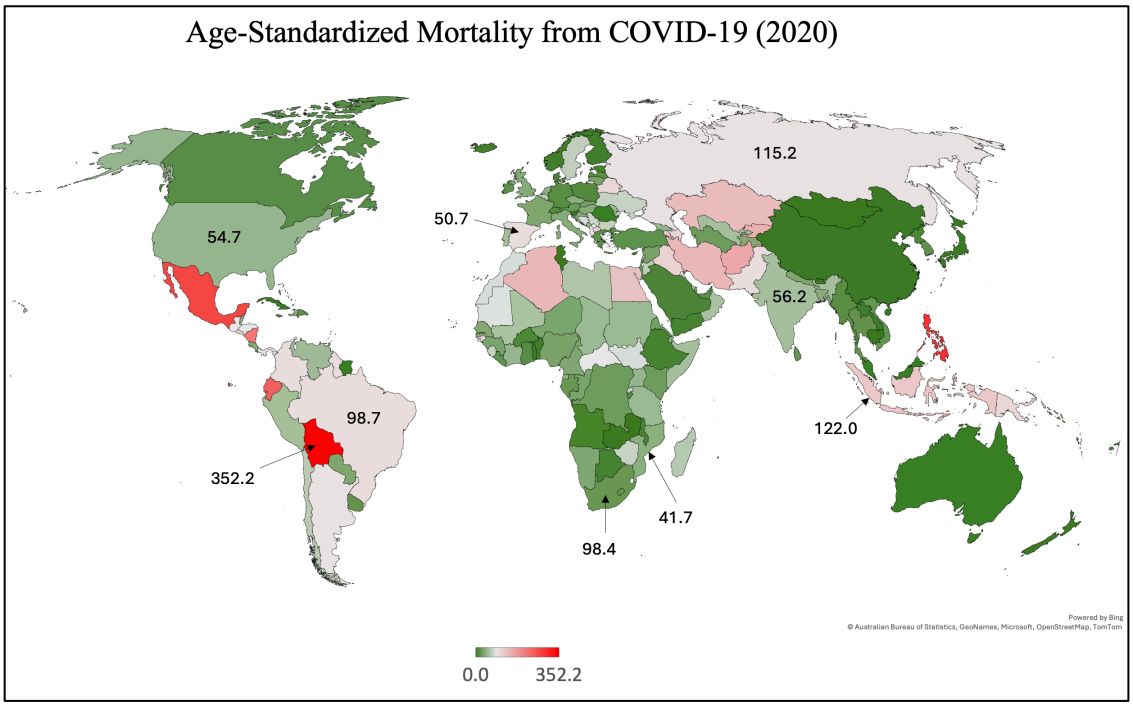
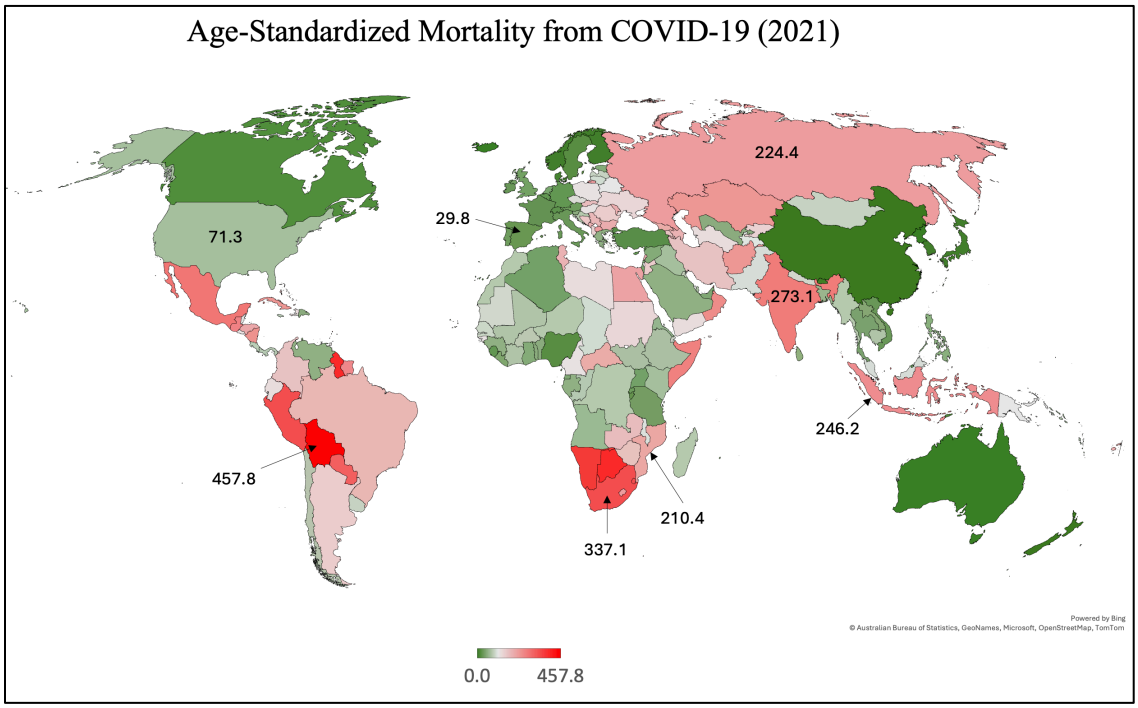
[79] *See* Megan Twohey, Keith Collins, and Katie Thomas, "With First Dibs on Vaccines, Rich Countries Have 'Cleared the Shelves'," *New York Times*.; Padmashree Gehl Sampath, "Covid-19 and the Need for a New Global Health Diplomacy, *Harvard Public Health Review, 2021 (29),* available at: https://harvardpublichealthreview.org/29-article-gehlsampath/#_ftn1

[80] Source: https://ourworldindata.org/covid-vaccinations. Note, in particular, the dire situation in Africa. In the United States, despite the resistance of many people to being vaccinated, over 60% of the population has already received at least one dose; in Africa, the number currently is under 2%. Ibid.

[81] See, e.g., Richard C. Paddock and Muktita Suhartono, "No Longer 'Hidden Victims,' Children Are Dying as Virus Surges in Indonesia," *New York Times*, July 31, 2021; OHRLLS, "Impact of Covid-19 and Responses in Landlocked Developing Countries," (2024); Andrew T. Levin et al., "Assessing the Burden of Covid-19 in Developing Countries: Systematic Review, Meta-Analysis and Public Policy Implications," *BMJ*

the age-standardized mortality rates in 2020 and 2021, provide a rough but nevertheless revealing view of the shift.





global health 7, no. 5 (2022).; Jinshan Hong, Randy Thanthong-Knight, and Jason Scott, "It's Not Just India: New Virus Waves Hit Developing Countries," *Bloomberg* (2021).

To be sure, the deterioration of the position of poor countries with respect to COVID deaths had other causes as well, including inferior health-care systems and urban population densities.[82] But limited access to vaccines was surely one of the factors.

The attitude underlying this particular source of inaccessibility is now commonly known as "vaccine nationalism" – the notion that each national government is primarily responsible for the health of its own citizens and thus should use all of the resources at its disposal to ensure that they are fully immunized as soon as possible, even if the result is to deprive vulnerable residents in other countries of similar protection.[83] This attitude is not new; it shaped the distribution of the smallpox vaccine, the polio vaccine, and most recently the vaccines that helped curb the 2009 H1N1 influenza pandemic.[84] But it seems to have intensified in recent years.

The primary resource employed by rich countries to provide their citizens privileged access to vaccines is of course money, but physical control also sometimes comes into play. For example, in January of 2021, the European Union imposed an export authorization requirement on "vaccines against SARS-related coronaviruses" and "active substances including master and working cell banks used for the manufacture of such vaccines." The regulation provided that such an authorization would be granted only when "the volume of exports is not such that it poses a threat to the execution of the Union Advanced Purchased Agreements concluded with vaccines manufacturers."[85] The United States adopted a similar policy.[86] Initially, the government of India adopted a more open posture. Capitalizing on that openness, in early 2021, the Serum Institute of India, a private company, entered into contracts with governments in several low and middle-income countries to provide them batches of the AstraZeneca vaccine – and then began shipping them millions of doses. However, when (in March of 2021) India experienced a surge in COVID cases, the Indian government immediately reversed course, imposing an (informal but nearly total) export ban on vaccines in order to increase supplies to its own residents. The result, of course, was to cut off other countries' access. Those in Africa were

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[82] See Matthew E Levison, "Covid-19 Challenges in Developing Countries," *Merck Manual* (2020); Levin et al., "Assessing the Burden of Covid-19 in Developing Countries: Systematic Review, Meta-Analysis and Public Policy Implications."; Terrence McCoy and Heloísa Traiano, "Brazil's Densely Packed Favelas Brace for Coronavirus: 'It Will Kill a Lot of People.'," *Washington Post*, Masrch 21, 2020.; Yasmeen Serhan, "Where the Pandemic Is Only Getting Worse," *The Atlantic* (2020).; Brett Walton, "Healthcare Facilities in Developing Countries a High Risk for Coronavirus Transmission," *New Security Beat* (2020).

[83] See, e.g., Niladri Chatterjee, Zaad Mahmood, and Eleonor Marcussen, "Politics of Vaccine Nationalism in India: Global and Domestic Implications," *Forum for development studies* 48, no. 2 (2021); Ingrid T. Katz et al., "From Vaccine Nationalism to Vaccine Equity — Finding a Path Forward," *New England Journal of Medicine* 384, no. 14 (2021).

[84] See World Economic Forum, "Vaccine Nationalism – and How It Could Affect Us All," (2021).

[85] Commission Implementing Regulation (EU) 2021/111 (Jan. 29, 2021) making the exportation of certain products subject to the production of an export authorization, art. 1(1-5), https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R0111&from=EN. See Imad Antoine Ibrahim, "Overview of Export Restrictions on Covid-19 Vaccines and Their Components," *Insights* 25, no. 10 (2021).

[86] See "American Export Controls Threaten to Hinder Global Vaccine Production," *The Ecnomist*, April 22, 2021.

especially dependent upon the deals with Serum Institute – and thus were especially hard hit.[87]

The third and perhaps most serious of the sources of inaccessibility is financial. All too often, the prices at which drugs are sold place them beyond the means of the people who could benefit from them. Many examples of this problem will surface in the course of this book. For the time being, a few should be sufficient to illustrate the severity of the issue:

- Sickle cell disease is a family of inherited blood disorders that primarily affect people of African descent. Its symptoms include joint pain, anemia, susceptibility to bacterial infections, dizziness, and stroke.[88] Roughly 7.7 million people suffer from it, 80% of whom reside in subSaharan Africa. In December of 2023, the FDA approved two innovative and effective treatments for the disease, which are now sold under the brand names, Lyfgenia and Casgevy. Bluebird Bio, the developer of the former, plans to focus its marketing on the United States, where reside roughly 100,000 people with the disease (less than 2% of the affected population). Vertex Pharmaceuticals, the developer of the latter, plans to focus on the United States and western Europe. The initial prices (specifically, "wholesale acquisition costs") of the drugs: $3.1 million for Lyfgenia and $2.2 million for Casgevy. As one might imagine, this places them well out of reach of almost all of the sufferers in Africa as well as most of the sufferers in the companies' primary markets who lack appropriate insurance.[89]

- Although, as indicated above, the prices in most countries for first-line HIV drugs are now modest, the prices of second-line drugs (i.e., those deployed when the first tier are no longer effective) are much higher, and the prices of third-line drugs are higher still.[90]

- The prices of insulin and its analogs vary considerably by country, but are high enough everywhere to force many diabetics to ration drugs – i.e., to use less than would be optimal to manage their conditions. The situation is

[87] See Jeffrey Gettleman, Emily Schmall, and Mujib Mashal, "India Cuts Back on Vaccine Exports as Infections Surge at Home," *New York Times*, March 25, 2021.

[88] See Gregory J. Kato et al., "Sickle Cell Disease," *Nature reviews. Disease primers* 4, no. 1 (2018).

[89] See Rebecca Robbins and Stephanie Nolen, "New Sickle Cell Therapies Will Be out of Reach Where They Are Needed Most," *New York Times*, December 8, 2023. The companies' announcements of the initial prices are available at

[90] See Frontline AIDS, "The Problem with Patents: Access to Affordable Hiv Treatment in Middle-Income Countries," (2019), 6. (reporting that "The lowest prices for third-line drugs that are widely patented were $664 [per person per year] 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).

especially harsh in developing countries. "To assess affordability of insulins in low- and middle-income countries, [a recent study] expressed the estimated median purchase price of a 1000 IU of insulin (approximately 30 days of insulin supply) as the number of wage-days of the lowest paid unskilled government worker. Their study showed that the lowest paid unskilled government worker in the 13 low- and middle-income countries studied needed to spend 6–8 days of wages to purchase 1000 IU insulin analogues in the public sector and 7–16 days of wages to purchase in the private sector. In contrast, human insulin were found to be more affordable, with an estimated 4 equivalent days of wages when purchased in the public sector and 2–4 days in the private sector."[91]

- A recent survey by the World Health Organization of 35 countries concerning the costs their residents faced for receiving tuberculosis care concluded: "The percentage of TB-affected households facing total costs that were catastrophic ranged from 13% … in El Salvador to 92% … in the Solomon Islands; the pooled average for all 35 countries, weighted for each country's number of notified cases, was 49%. Among 31 countries that reported disaggregated data, the percentage facing catastrophic total costs was much higher for drug-resistant TB, with a pooled average of 82%."[92] (The WHO defines "catastrophic" in this context as costs that exceed 20% of annual household income.). To be sure, these costs include many items other than those associated with the drugs themselves, but the price of the drugs is a substantial portion of the total. This is especially true with respect to the regimens necessary to overcome drug-resistant infections.[93]

In many instances, high prices of these sorts arise because the drugs are subject to patents or other forms of intellectual-property protection. (The role of the intellectual-property system will be considered in detail in Chapter 4.) But not always. Other causes (which we will also explore in due course) include limited competition among manufacturers, high margins charged by distributors, and (ironically) some of the ways in which national governments have sought to control prices.

In summary, the capacity of pharmaceutical products to curb diseases and to reduce global inequality in health outcomes is limited in three contexts: when they have not been

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[91] The study in question is Margaret Ewen et al., "Insulin Prices, Availability and Affordability in 13 Low-Income and Middle-Income Countries," *BMJ global health* 4, no. 3 (2019). The quotation in the text is from the WHO's summary of the study. See WHO, "Keeping the 100-Year-Old Promise: Making Insulin Access Universal," (2021), 16. Other studies of the problems associated with high insulin prices include [insert Sarpatwari, Global Diabetes Drugs Market, EMA Diabetes, Taylor 2020, Zhou 2020, Access to Medicine.]

[92] "Global Tuberculosis Report," (2024): 29.

[93] 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)

approved for distribution and use; when exercises of nationalism deprive residents of poor countries access to them; and when high prices place them out of reach of some of the people who need them.

D. SFMPs

All too often, pharmaceutical products, even when they are affordable, are of poor quality. Sometimes 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. More often it derives from unscrupulous behavior by manufacturers or distributors, who deliberately supply drugs that do not contain any (or enough) of the active ingredients they purport to contain. Low-quality drugs of these various sorts are now commonly referred to as "substandard or falsified medical products" – SFMPs, for short.[94]

All countries currently suffer from this problem, but its severity varies (roughly) with countries' wealth. 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 falsified or substandard. In middle-income countries, the number was barely lower: 10.4%.[95] 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%.[96] High-income countries are less severely affected, but even they are not immune; batches of counterfeit products on occasion evade regulators and conscientious distributors (often with tragic consequences).[97]

The rates also 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 –

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[94] The term, "substandard," typically means that they contain too little of the active ingredient. As a result, they are not as effective in addressing of the disease in question as they should be. "Falsified" means that they don't have any of the active ingredient. Such drugs are sometimes described as "counterfeit," but that's an ambiguous term. Counterfeit can mean that they're manufactured without the permission of patentees. Alternatively, it can mean that they do not contain the chemicals they purport to contain. For present purposes, we're primarily concerned with the second meaning – which is more clearly denoted by the term, "falsified."

[95] 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.

[96] 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).

[97] For examples, see Shabbir Imber Safdar, "Acting on the Drug Supply Chain Security Act," *Medicine Maker* (2022), https://themedicinemaker.com/business-regulation/acting-on-the-drug-supply-chain-security-act; Nahoko Uchiyama et al., "Chemical Analysis of Counterfeit Hepatitis C Drug Found in Japan," *YAKUGAKU ZASSHI* 137, no. 10 (2017).; Jennifer Kite-Powell, "Pharmasecure Uses Mobile Device and Id Codes to Take on Counterfeit Drug Problem," *Forbes*, February 16, 2012. (documenting the discovery of counterfeit Avastin, a cancer drug, in the United States).

somewhere between 6 and 17%.[98] Even more likely to be falsified or substandard are anti-malarial drugs.[99]

The supplies of cancer drugs also seem distressingly vulnerable to this problem. Some examples:

> In 2019, the World Health Organization was alerted to falsified versions of Iclusig tablets (ponatinib; Ariad Pharmaceuticals, Inc) for leukemia that were circulating in Europe, America, and Asia and contained paracetamol instead of ponatinib. An analysis of 31 generic docetaxel formulations [used to treat breast, lung, and prostate cancer] in Asia, Africa, the Middle East, and Latin America found wide variations in quality, with only 32% of products providing expected levels of docetaxel, thus putting patients at risk of receiving insufficient active drug and complications from higher levels of impurities.[100]

In our own testing of drugs in a major public hospital in Namibia, we also found a distressingly high number of boxes containing substandard versions of an important cancer drug.

Soon after the COVID vaccines became available, they too became targets for falsifiers. A recent report summarized the situation:

> China has been clamping down on counterfeit versions of its domestically produced vaccines, while Mexico and Poland have reported counterfeits of Pfizer vaccines being given to people for $1000 each. Mexican customs officials have also seized vials of fake Sputnik V vaccine destined for Honduras. An Interpol operation across southern Africa in July and August led to the identification of 179 suspects and the seizure of $3.5m worth of goods, including vaccines, face masks, and fake covid-19 test certificates.
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> "I've never seen such a dynamic situation before," Jürgen Stock, general secretary of Interpol, told *Time* magazine, "The liquid gold in 2021

[98] 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.

[99] See "Impact of Substandard and Falsified Products," 7.; Ozawa et al., "Prevalence and Burden of Sfmps."

[100] Javier Cortes et al., "Enhancing Global Access to Cancer Medicines," *CA: A Cancer Journal for Clinicians* 70, no. 2 (2020): 118.

is the vaccine, and already we are seeing that vaccine supply chains are targeted more and more [by counterfeiters]."[101]

When bad drugs reach unsuspecting consumers, almost everyone suffers. Most importantly, the consumers receive either zero or reduced therapeutic or immunological benefit. The context in which this impact is most 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.[102] As the authors of the study concede, a good deal of uncertainty surrounds these data. But there is little doubt that the number of deaths is appalling.[103] The WHO estimates that a similar problem with respect to substandard antibiotics results in roughly 100,000 deaths per year from pneumonia.

The long-term secondary effects of SFMPs are also serious. In many poor countries, faith in western medicine is weak and fragile. When what appear to be legitimate drugs do no good, that faith corrodes. The result, of course, is to reduce the inclination of person who contract diseases to seek professional help.[104]

Consumption of degraded medicines (or a course of treatment in which legitimate and falsified drugs are mixed) also accelerates the emergence and spread of drug-resistant strains.[105]

The pharmaceutical firms selling authentic versions of the drugs at issue also suffer. Some of their potential sales are displaced by fakes. More importantly, the reputations of the drugs and of the companies from which they purportedly emanate are damaged. Because, as we soon see, the firms depend in part on revenue from sales of their products

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[101] Kanchan Srivastava, "Fake Covid Vaccines Boost the Black Market for Counterfeit Medicines," *BMJ* 2021 (2021), https://www.bmj.com/content/375/bmj.n2754. See also Kerlijn Van Assche, Céline Caillet, and Paul Newton, "Medical Product Quality Report – Covid-19 Issues," (Medicine Quality Research Group, Centre of Tropical Medicine & Global Health, University of Oxford, 2021).; WHO, "Medical Product Alert N°7/2021: Falsified Covid-19 Vaccine Astrazeneca," (2021). (reporting distribution of falsified vaccines in Iran).

[102] 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).

[103] 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).

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

[105] See Bate et al., "Substandard and Falsified Tb Drugs."; 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.

to fund their R&D programs, all of the potential beneficiaries of as-yet undeveloped drugs are hurt.

Finally, in cases in which SFMPs are purchased by public-health services, the result is a waste of the countries' scarce financial resources, which in turn either drains the government's coffers or impairs their ability to address residents' needs.

To be sure, some people benefit: counterfeiters, corrupt government officials, and distributors who violate the guidelines for safe storage of products. Their stake in the practice largely explains its persistence. But their interests plainly do not merit our attention.

E. Hesitancy

Vaccines are only effective if people are willing to receive them. Since the invention of vaccines, significant numbers of people have refused to be inoculated. In the eighteenth and nineteenth centuries, such resistance was entirely understandable. The novelty of vaccines and the ways in which they were created (including the use of material taken directly from the sores of infected people) made many otherwise healthy people reluctant to accept inoculation. As their efficacy improved and became increasingly evident, resistance diminished. By the end of the twentieth century, in most parts of the world, hostility to vaccines had declined to modest levels. Since the turn of the century, however, hostility has rebounded. In most parts of the world, the percentage of people eligible for vaccines who refuse to take them is now higher than it was 25 years ago.[106]

This phenomenon has come to be known as "vaccine hesitancy" – defined by the World Health Organization as "the reluctance or refusal to vaccinate despite the availability of vaccines." The adjective, "hesitant," is unfortunate, because it obscures the subset of the people whose attitudes toward vaccines are better described as "opposed." But the term is now sufficiently ubiquitous in the public-health literature that we will follow suit.

As one might expect, the global resurgence of vaccine hesitancy has impeded efforts to suppress infectious diseases. For example, as we saw in Chapter 1, the incidence of measles is rising fast.[107] Polio, which had nearly been eliminated globally, is now re-emerging in several locations. Perhaps most important, vaccine hesitancy reduced the numbers of people who are vaccinated against COVID-19. In the United States alone, refusals of COVID vaccines during the height of the pandemic likely caused more than

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[106] See, e.g., Maya J. Goldenberg, *Vaccine Hesitancy : Public Trust, Expertise, and the War on Science* (Pittsburgh: University of Pittsburgh Press, 2021); Ana Santos Rutschman, "Vaccine Hesitancy across Time," *North Carolina Journal of Law and Technology* 23 (2022); M. Wiegand et al., "Global Declines in Vaccine Confidence from 2015 to 2022: A Largescale Retrospective Analysis," (2022).

[107] See WHO, "Measles cases spike globally due to gaps in vaccination coverage" (2018), https://www.who.int/news/item/29-11-2018-measles-cases-spike-globally-due-to-gaps-in-vaccination-coverage.

300,000 deaths.[108] Impacts of these sorts have prompted the WHO to include vaccine hesitancy in its list of "ten threats to global health."

Although vaccine hesitancy currently exists in all parts of the world and in all demographic groups, its salience is uneven. It varies significantly by region. For example, an aggregation of many studies reported that, while the "pooled acceptance rate" of COVID vaccines globally was 62%, the acceptance rates varied as follows:[109]

African Region:	42%
Eastern Mediterranean Region	41%
European Region	65%
Region of the Americas	67%
South-East Asia Region	66%
Western Pacific Region	71%

When the rates are broken down by country, the divergence is even more dramatic. With respect to COVID vaccines in particular, willingness to accept vaccines was especially high in India, China, and Tunisia -- and especially low in Russia. Egypt, and South Africa.[110]

Even within a country, there are sometimes sharp geographic variations. The US is the country where geographic differences have been best documented,[111] but similar

[108] See Katherine M. Jia et al., "Estimated Preventable Covid-19-Associated Deaths Due to Non-Vaccination in the United States," *European Journal of Epidemiology* 38 (2023).

[109] Sultan Mahmud et al., "The Acceptance of Covid-19 Vaccine: A Global Rapid Systematic Review and Meta-Analysis," (2022).

[110] See Wiegand et al., "Global Declines in Vaccine Confidence."; Kazi Abdul Mannan and Khandaker Mursheda Farhana, "Knowledge, Attitude and Acceptance of a Covid-19 Vaccine: A Global Cross-Sectional Study," *International Research Journal of Business and Social Science* 6 (2020); Yana Roshchina, Sergey Roshchin, and Ksenia Rozhkova, "Determinants of Covid-19 Vaccine Hesitancy and Resistance in Russia," (National Research University Higher School of Economics, 2021); Mohamed Masoud et al., "Acceptance of Covid-19 Vaccination and Associated Factors in Middle East Countries: A Multinational Study," *Alexandria Journal of Medicine* 60 (2023).

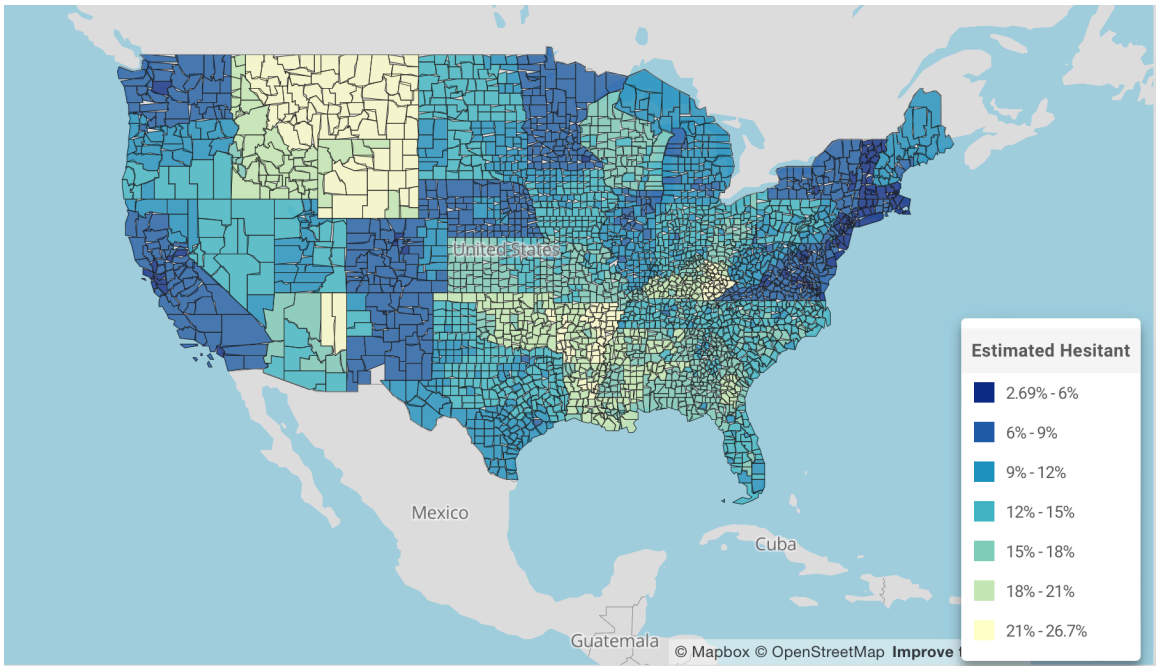
[111] The following map, prepared that the Centers for Disease Control, shows variations in COVID-19 vaccine hesitancy rates as of May 2021:

variations can be found elsewhere. For example, whereas the acceptance rate for Nigeria as a whole was 58%, in the northwest part of the country, it was 29%.[112]

Hesitancy varies significantly along other axes as well. For example, in most countries, it is higher among men than among women,[113] higher among young adults than among older adults,[114] and higher among the members of historically disadvantaged groups.[115] Finally, the rates vary significantly across time. For example, in some countries, hesitancy dropped during the pandemic, while in others it rose.

So what causes vaccine hesitancy in general – and these variations in particular? The reasons that hesitant people report as the bases for their resistance are only moderately helpful in answering this question. Most often, they point to:

- doubts concerning the severity of the disease that a vaccine is designed to prevent;
- doubts concerning the probability that they will contract that disease;
- doubts about the safety or efficacy of the vaccine;
- fear of side-effects; or
- the inconvenience of obtaining inoculation.



Source: https://data.cdc.gov/stories/s/Vaccine-Hesitancy-for-COVID-19/cnd2-a6zw/

[112] Mahmud et al., "The Acceptance of Covid-19 Vaccine: A Global Rapid Systematic Review and Meta-Analysis."

[113] See, e.g., Masoud et al., "Acceptance of Covid-19 Vaccination and Associated Factors in Middle East Countries: A Multinational Study."

[114] See, e.g., Sonika Sethi et al., "The Uptake Study: A Cross-Sectional Survey Examining the Insights and Beliefs of the Uk Population on Covid-19 Vaccine Uptake and Hesitancy," *BMJ Open* 11 (2021).

[115] See, e.g., Wiegand et al., "Global Declines in Vaccine Confidence."

These sentiments are surely genuine, but to address this problem, we will need to look beneath them and identify the factors that give rise to these attitudes. From the large empirical literature, we can distill seven such factors.

(1) The least surprising is general distrust of government. Members of groups that have been subject to exploitative or discriminatory conduct by governments in the past tend to be skeptical of governmental assertions that vaccination is in their best interest. This factor is especially strong when the group at issue was previously subject to government-sponsored medical experimentation.[116]

(2) Next, the absence of accurate information concerning the diseases and vaccines at issue conduces to hesitancy. People who have not been provided information concerning the threats they face and the origins and effectiveness of the specific vaccines they are being asked to take tend to balk.[117]

(3) Misinformation and disinformation exacerbate the problem. Since the late eighteenth century, so-called "anti-vax" movements have been disseminating false or misleading information about vaccines. Some of these messages exaggerate the hazards of vaccines' side-effects; others underestimate the effectiveness of the vaccines; still others advance conspiracy theories concerning the motivations of the developers or distributors of the vaccines. In the nineteenth century, most of the messages were conveyed through print media. In the mid-twentieth century, television began to be employed more often. Since 2000, the channel that most anti-vax groups have found to be most effective is social media.[118] This problem is by no means limited to developed countries. Deliberate distribution of false information by anti-vax groups is at least as common in Africa as in the United States or Europe.[119]

(4) Recently, partisanship has contributed to vaccine hesitancy. In a growing set of countries, support for the use of vaccines has come to be associated with a particular political party – typically the one that enjoys power when a vaccination program is first initiated. Opponents then seek to discredit that party by characterizing the vaccine at issue (or vaccines in general) as ineffective or even pernicious. Once established, these associations prove durable. In the United States, for example, the left-leaning Democratic Party was in power when large-scale COVID vaccination programs began, and vaccine

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[116] See, e.g., Manase Kudzai Chiweshe and Gerald Dandah, "Social Media, Fake News and Covid-19 Vaccine Hesitancy in Zimbabwe," *Africa review (New Delhi)* 16, no. 1 (2024).; Rutschman, "Vaccine Hesitancy across Time," 19.;

[117] See, e.g., Jhoys Landicho-Guevarra et al., "Scared, Powerless, Insulted and Embarrassed: Hesitancy Towards Vaccines among Caregivers in Cavite Province, the Philippines," *BMJ global health* 6, no. 9 (2021): 5.

[118] See Rutschman, "Vaccine Hesitancy across Time," 20-25.

[119] See Juma James Masele, "Misinformation and Covid-19 Vaccine Uptake Hesitancy among Frontline Workers in Tanzania: Do Demographic Variables Matter?," *HUMAN VACCINES & IMMUNOTHERAPEUTICS* 20, no. 1 (2024); Mahama Tawat, "Fake News and Covid-19 Vaccine Hesitancy. A Study of Practices and Sociopolitical Implications in Cameroon," *SSRN eLibrary* (2024).

hesitancy soon became associated with the right-leaning Republicans.[120] That difference is unlikely to change when, soon, Republicans retake national political power. In Poland, the valence is reversed: The United Right coalition, currently in power, favors vaccination, while the left-leaning Confederation is the most vaccine hesitant.[121] The relationships among hesitancy, partisanship, and political power are more complex in China. There, nationalism is strongly associated with support for the ruling Communist Party – but also with "enthusiastic embrace of outgroup conspiracy theories regarding COVID-19 – those claiming that the SARS-CoV-2, the virus that causes the pandemic, first appeared outside China or was manufactured against China." Because conspiratorial thinking, in turn, correlates with vaccine hesitancy, people who strongly support the government tend to be more hesitant than average.[122]

(5) International political conflicts sometimes add to the problem. For instance, very recently, organizations based in Russia have become increasingly influential in spreading vaccine misinformation online in the United States.[123]

(6) Religious leaders also sometimes contribute to vaccine hesitancy. In Indonesia, for example, a sharp drop in vaccine confidence between 2015 and 2019 can be traced in part to a campaign mounted by Muslim leaders against the measles, mumps, and rubella (MMR) vaccine, arguing first that it was unsafe and later that it contained ingredients derived from pigs.[124] Studies of vaccine hesitancy in many other countries have found that it is positively correlated with intensity of religious beliefs.[125]

(7) Finally, the cognitive bias known as the "availability heuristic" is a common contributing factor. As economists and psychologists have long recognized, people in all cultures give disproportionate weight to data that they can easily recall. One major manifestation of this bias is that people exaggerate the probability of recurrence of phenomenon that is publicly prominent. The reason that the phenomenon matters in the present context is that adverse events associated with the distribution of vaccines – above all, incidents in which people who appear to suffer serious side-effects – tend to be covered by the press, which in turn causes the public at large to infer that such events are common.

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[120] See Alana Wise, "The Political Fight over Vaccine Mandates Deepens Despite Their Effectiveness," *National Public Radio* (2021), https://www.npr.org/2021/10/17/1046598351/the-political-fight-over-vaccine-mandates-deepens-despite-their-effectiveness.; Kimberly H. Nguyen et al., "Changes in General and Covid-19 Vaccine Hesitancy among U.S. Adults from 2021 to 2022," *Annals of medicine (Helsinki)* 56, no. 1 (2024).

[121] See Paweł Waszkiewicz et al., "Vaccines and Political Divisions: An Analysis of the Attitudes toward Vaccination and Political Preferences in Poland," *SSRN Electronic Journal*.

[122] See Ruifen Zhang et al., "Nationalism, Conspiracy Theories and Vaccine Mandates: Exploring the Statism Determinants for Attitudes to Covid-19 Control in China," *Vaccine. X* 13 (2023).

[123] See David A. Broniatowski et al., "Weaponized Health Communication: Twitter Bots and Russian Trolls Amplify the Vaccine Debate," *American Journal of Public Health* 108 (2018).

[124] See Dyna Rochmyaningsih, "Indonesian 'Vaccine Fatwa' Sends Measles Immunization Rates Plummeting," *Science (American Association for the Advancement of Science)* (2018).

[125] See Jamie Murphy et al., "Psychological Characteristics Associated with Covid-19 Vaccine Hesitancy and Resistance in Ireland and the United Kingdom," *Nature communications* 12, no. 1 (2021); G. Troiano and A. Nardi, "Vaccine Hesitancy in the Era of Covid-19," *Public health* 194 (2021).

The role of the press in this unfortunate dynamic need not be partisan or nefarious; it can arise simply from the natural need to capture viewers.[126]

Some of the ways in which these various factors can interact are illustrated by the troubling history of dengue vaccination in the Philippines. Understanding this episode requires a bit of background:

There are four closely related strains (or "serotypes") of the dengue virus.[127] Infection by one strain confers lifelong immunity to another infection by that strain, but only temporary (roughly two years) of immunity against infection by one of the other strains. A second infection is much more likely to lead to DHF or DSS than a first infection – apparently because of "antibody-dependent enhancement" (ADE), a poorly understood phenomenon.[128]

Efforts to develop a dengue vaccine have been hampered by several factors: the complex pathology of the disease; the necessity of addressing all four of the dengue serotypes; and the difficulty of protecting not just persons who have never been infected, but also persons who have already been infected by one of the four serotypes and thus are at especially high risk for DHF or DSS.[129] Despite these obstacles, several pharmaceutical firms have been working for decades to develop a vaccine. As of 2010, there were nine such ventures underway;[130] by 2015, the number had declined to six.[131]

The most promising of the candidates was "Dengvaxia," a live attenuated vaccine developed by Sanofi using a yellow-fever-vaccine backbone. Early on, it became clear

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[126] A grim illustration of the importance of this factor is provided by the recent history of the Human Papillomavirus (HPV) vaccine inoculation program in Japan. HPV causes cervical cancer, which in turn results in over 300,000 deaths per year worldwide. Effective HPV vaccines have been available since 2006. In April of 2013, the government of Japan, responding to alarming increases in the incidence of HPV, introduced the vaccines into the national immunization program and announced that they would be provided free to all girls between the ages of 12 and 16. The uptake was rapid; in some areas over 70% of eligible girls were inoculated. Unfortunately, soon thereafter, "unconfirmed reports of adverse events following immunization began to appear in the media and emotive images of girls having difficulty walking or controlling their movements were broadcast extensively on news programmes." The government responded by withdrawing its recommendation that girls be vaccinated. The percentage of eligible girls inoculated plunged – and has remained extremely low despite the subsequent discrediting of the reports of adverse events. One study estimates that over 5000 women will die prematurely as a resultSee Kate T. Simms et al., "Impact of Hpv Vaccine Hesitancy on Cervical Cancer in Japan: A Modelling Study," *The Lancet. Public health* 5, no. 4 (2020). See also Asami Yagi et al., "Potential for Cervical Cancer Incidence and Death Resulting from Japan's Current Policy of Prolonged Suspension of Its Governmental Recommendation of the Hpv Vaccine," *Scientific Reports* 10, no. 1 (2020).

[127] A fifth serotype may have been discovered recently. See Dennis Normile, "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts," *Science* 342, no. 6157 (2013).

[128] See Duane Gubler, "Dengue and Dengue Hemorrhagic Fever," *Clinical Microbiology Reviews* 11, no. 3 (1998): 487.

[129] See Maria G. Guzman et al., "Dengue: A Continuing Global Threat," *Nature Reviews Microbiology* (2010): S13.

[130] See ibid.

[131] See Lauren M. Schwatrz et al., "The Dengue Vaccine Pipeline: Implications for the Future of Dengue Control," *Vaccine* 33 (2015): 3294.

that Dengvaxia was not perfect. In stage III clinical trials, it prevented only 61% of infections (albeit a higher percentage of DHF cases) and was less effective in children under nine years old than in adults.[132] But it was sufficiently promising that it was quickly approved for use in Mexico, Brazil, Indonesia, and the Philippines.[133] Unfortunately, in practice, it proved to have a crucial drawback, which had not come to light in the trials: When administered to a "dengue-naïve" person (i.e., someone who had never been infected by any of the four dengue variants), it produced the ADE effect, mentioned above. In other words, although it shielded the person against the variant at which the vaccine was directed, it sharply increased the risk that the person would experience the potentially deadly dengue hemorrhagic fever if subsequently infected with a different variant.[134]

Dengue is endemic in the Philippines. Between 2008 and 2012, there were roughly 850,000 symptomatic cases of the diseases per year in the country. The direct medical costs associated with treating those cases were roughly $350 million per year.[135] Between 2012 and 2015, the number of cases and the associated costs rose sharply.[136]

In April of 2016, Sanofi, with the active support of the Philippine Department of Health, initiated a program of mass immunization of public-school children, using a three-dose course of the Dengvaxia vaccine.[137] Nineteen months later, Sanofi, having learned of the hazard that the vaccine posed to dengue-naïve people, announced that its administration would be limited to children who had already had one infection. By that point, roughly 830,000 children had received at least one dose, 415,000 had received two, and 365,000 had received all three. The number of those children who had not previously been infected and who suffered adverse medical events because they received the vaccine was as yet uncertain. However, press coverage of the change in policy was harsh and lurid, suggesting that injuries were widespread.

Midway through the initial vaccination program, the government of Benigno Aquino had been replaced by the government of Rodrigo Duterte. The new regime accused

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[132] See Makiko Kitamura, "World's First Dengue Vaccine Approved after 20 Years of Research," *Bloomberg Business*, December 9, 2015.; Monica Antonio, "Dengvaxia, World's First Dengue Vaccine, Gets Mexican Approval -- What You Need to Know," *Patent Herald*, December 11, 2015.

[133] See Rogerio Jelmayer, "Brazil Approves Sanofi's Dengue Vaccine," *Wall Street Journal*, December 28, 2015.; http://en.sanofi.com/NasdaQ_OMX/local/press_releases/dengvaxia_first_dengue_vaccine_1975899_28-12-2015!11_30_00.aspx; http://www.sanofipasteur.com/en/articles/sanofi-pasteur-dengue-vaccine-approved-in-the-philippines.aspx; http://www.scidev.net/asia-pacific/disease/news/philippines-licenses-dengue-vaccine-but-usage-on-hold.html.

[134] See Helen Branswell, "Fda Approves the First Vaccine for Dengue Fever, but with Major Restrictions," *STAT* (2019), https://www.statnews.com/2019/05/01/fda-dengue-vaccine-restrictions/.

[135] See Frances E. Edillo et al., "Economic Cost and Burden of Dengue in the Philippines," *The American Society of Tropical Medicine and Hygiene* 92, no. 2 (2015).

[136] See Heidi J. Larson, Kenneth Hartigan-Go, and Alexandre de Figueiredo, "Vaccine Confidence Plummets in the Philippines Following Dengue Vaccine Scare: Why It Matters to Pandemic Preparedness," *Human vaccines & immunotherapeutics* 15, no. 3 (2019).

[137] See Victoria White, "World's First Public Dengue Immunisation Programme Starts," *European Pharmaceutical Review* (2016), https://www.europeanpharmaceuticalreview.com/news/40215/dengue-immunisation-programme/.

the leaders of the Ministry of Health who had authorized the program of negligence – and fanned the flames of the critical press coverage. Government teams performed autopsies of dead children, sometimes before live television cameras, and then blamed those deaths on the vaccine.[138] Hearings before the Senate were attended by parents carrying photographs of children, claiming that they had been killed by the vaccine. Conspiracy theories bloomed on social media.[139] Prosecutors filed criminal charges -- for "reckless imprudence resulting [in] homicide" – against the former Minister of Health, several of her subordinates, former officials in the Philippine Food and Drug Administration, executives of Sanofi, and even an academic researcher who had published articles assessing the vaccine favorably.[140] (As of this writing, some of those cases are still pending.) The Ministry demanded that Sanofi return the $67 million that it had paid for the vaccine – eventually settling for roughly half that amount.[141]

Subsequent research established that, because of the prevalence of dengue in the Philippines, the number of children who, prior to vaccination, had had no previous encounter with the disease and thus were placed at risk was small. One assessment concluded that only 19 children likely died because of administration of the vaccine.[142] However, many parents were convinced that their vaccinated children were going to die.

Public confidence, not just in Dengvaxia, but in all vaccines, plummeted. One study found that, between 2015 and 2018, the percentage of respondents who "strongly agreed" that "vaccines are important for children to have" dropped from 93% to 32%; that "vaccines are safe" from 82% to 21%; and that "vaccines are effective" from 82% to 22%.[143] As one would expect, coverage for all types of vaccines declined sharply.[144] The diminution in the uptake of the measles vaccines was especially tragic. Data from the World Health Organization show a dramatic increase in reported measles cases in the Philippines immediately after the Dengvaxia controversy.[145] Hundreds of children died, the overwhelming majority of whom were unvaccinated.[146] The adverse impact on the

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[138] See Maria Angela A. Mabale et al., "Implications of Information Heard About Dengvaxia on Filipinos' Perception on Vaccination," *Vaccine* 42, no. 7 (2024).

[139] See Mark Donald C. Reñosa et al., ""Respect My Opinion and I'll Respect Yours!" : Exploring the Challenges, Concerns, and Informational Needs of Vaccine-Hesitant Caregivers and Pregnant Women in the Philippines," *Public health challenges* 2, no. 3 (2023).

[140] See Fatima Arkin, "Dengue Vaccine Fiasco Leads to Criminal Charges for Researcher in the Philippines," *Science (American Association for the Advancement of Science)* (2019).

[141] See Karim Atassi et al., "Did Dengvaxia-Associated Deaths Result in an Increase in Vaccine Hesitancy in the Philippines?," *McGill Journal of Global Health* 9, no. 1 (2020).

[142] See ibid.

[143] See Larson, Hartigan-Go, and de Figueiredo, "Vaccine Confidence Plummets in the Philippines."

[144] See Atassi et al., "Vaccine Hesitancy in the Philippines."

[145] These data were derived from WHO, "Measles reported cases and incidence" 2024, https://immunizationdata.who.int/global/wiise-detail-page/measles-reported-cases-and-incidence.

[146] See Fleurette M. Domai et al., "Measles Outbreak in the Philippines: Epidemiological and Clinical Characteristics of Hospitalized Children, 2016-2019," *The Lancet Regional Health - Western Pacific* 19 (2022).

acceptance of COVID vaccines in the Philippines is harder to measure, but all studies indicate that it was substantial.[147]

In retrospect, the surge in vaccine hesitancy in the Philippines triggered by the Dengvaxia affair seems attributable to a "perfect storm" of several of the factors catalogued above: a background condition of general distrust of government, especially strong in the southern provinces; misinformation distributed in many fora exaggerating the hazards of the Dengvaxia vaccine; intense partisanship, in which the new administration used the affair to discredit its predecessor; a modest boost in resistance caused by Muslim leaders' accusations of impurities in the vaccine (again concentrated in the southern regions); all reinforced by the universal human tendency to assign disproportionate weight to highly visible current events when estimating the likelihood of future, similar hazards.

[147] See, e.g., Landicho-Guevarra et al., "Hesitancy Towards Vaccines among Caregivers in Cavite Province."; Reñosa et al., "Vaccine-Hesitant Caregivers."; Ma Leslie Ulmido et al., "Conflicting and Complementary Notions of Responsibility in Caregiver's and Health Care Workers' Vaccination Narratives in the Philippines," *Journal of global health* 14 (2024).

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