Rethinking Global Pharmaceutical Policy

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Appendix 2: Malaria

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Malaria infection in a human originates from the bite of a female Anopheles mosquito carrying the sporozoite form of *Plasmodium* parasites in her salivary gland.[1] The sporozoites, deposited under the skin of the host, enter the blood stream and then cross the sinusoidal cellular layer separating the blood and liver parenchyma to infect hepatocytes in the liver.[2] Temporarily safe from the host's immune response, the sporozoites multiply rapidly to form schizonts, each containing merozoites (a second form of the parasite).[3] The schizonts then rupture, spilling thousands of merozoites into the bloodstream where they invade red blood cells and multiply until the host cells burst.[4] This cycle continues until "the person dies of anemia, kidney failure, or brain damage, or until the disease is brought under control by the person's immune system or by drugs."[5]

Because transmission of the disease occurs only through bites from specific species of mosquitos, malaria is common only in countries where those mosquitos flourish. Thousands of years ago, when the disease first emerged, the mosquitos were widely distributed in Eurasia and Africa and thus the disease acquired a large geographic footprint – in temperate areas as well as tropical areas. However, unlike the tuberculosis bacterium, the malaria parasite did not accompany humans across the temporary land bridge between Siberia and the Aleutian peninsula and thus was unknown in the western hemisphere prior to the sixteenth century. Its importation by the European colonists contributed at least modestly to the decimation of the Native American population between the sixteenth and the eighteenth centuries.[6]

As late as 1900, malaria was prevalent in roughly half of the world's land area. Thereafter, the constriction of the zone occupied by Anopheles mosquitos (primarily through the widespread use of insecticides and the conversion of swampland to agricultural land) combined with public health-initiatives gradually reduced its footprint. The stages in its retreat are shown in Figure 1.

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[1] *See* Gina Kolata, *The Search for a Malaria Vaccine*. 226 SCIENCE 679, 680 (November 9, 1984). There are roughly 70 species of Anopheles mosquitos, of which roughly 40 play a significant role in transmitting malaria. The differences among them partly account for the variations in the way in which malaria takes form in different parts of the world. For thorough discussion of these variations, see James L.A. Webb, Jr., *Humanity's Burden: A Global History of Malaria* (New York: Cambridge University Press, 2009).

[2] *See* Maria M. Mota and Ana Rodriguez, *Migration through host cells: the first steps of Plasmodium sporozoites in the mammalian host*, CELLULAR BIOLOGY Vol. 6, No. 12 at 1113 (2004). The exact mechanism by which sporozoites reach the blood vessel and then cross the blood/liver barrier is unknown, although it is believe that the sporozoites migrate through host cells. *See id.* at 1114.

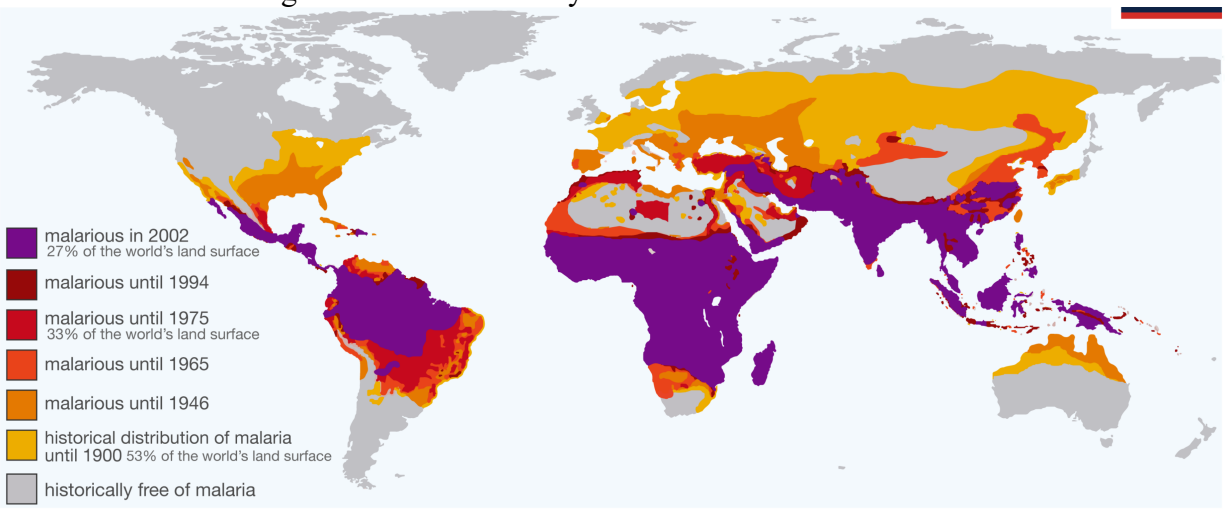
[3] *See supra* Kolata at 680.

[4] See id.

[5] *Id.* In developing countries, the majority of malaria deaths occur in infants, young children and pregnant women; most adolescents and adults have developed natural immunity that limits the most severe forms of infection. *See* Stephen Hoffman, *Save the Children*, NATURE Vol. 430 at 940 (Aug. 19, 2004).

[6] See Webb, *Humanity's Burden*, 66ff.

Figure 1: Modern History of the Prevalence of Malaria[7]



Source: Hay et al. (2004) – The global distribution and population at risk of malaria: past, present, and future. In The Lancet Infectious Diseases. Redrawn by Our World in Data.
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Currently, five species of the Plasmodium parasite are capable of causing the disease: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*.[8] *P. falciparum*, by far the most lethal, is the dominant species in Africa.[9] *P. vivax* accounts for roughly half of the cases in Latin American and Southeast Asia,[10] but is rare in Africa, apparently because most of the people there carry a genetic mutation that renders them immune to *vivax* infections.[11]

As yet, there is only one approved vaccine for malaria, and its effectiveness is modest. In clinical trials, RTS,S/AS01 (developed by GlaxoSmithKline with support from the Malaria Vaccine Initiative) revealed an efficacy of roughly 36% in children and 26% in infants.[12] That effect was beneficial enough to support approval of RTS,S/AS01 by the EMA and to prompt the WHO in 2019 to initiate pilot projects in Malawi, Ghana, and Kenya to ascertain its potential for

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[7] Source: https://ourworldindata.org/malaria.

[8] See Melanie Figtree et al., "Plasmodium Knowlesi in Human, Indonesian Borneo," *Emerging Infectious Diseases* 16, no. 4 (2010).

[9] See David Bell and Peter Winstanley, "Current Issues in the Treatment of Uncomplicated Malaria in Africa," *British Medical Bulletin* 71 (2004): 30.

[10] See Vincent Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," *Trends in Parasitology* 29, no. 12 (2013).

[11] "Although *P. vivax* can occur throughout Africa, the risk of infection with this species is quite low, because of the absence in many African populations of the Duffy gene, which produces a protein necessary for *P. vivax* to invade red blood cells." WHO, "World Malaria Report," (2014): 3. See also Webb, *Humanity's Burden*, 21ff.

[12] See Navneet Arora, Lokhesh C Anbalagan, and Ashok K Pannu, "Towards Eradication of Malaria: Is the Who's Rts,S/As01 Vaccination Effective Enough?," *Risk Management and Healthcare Policy* 14 (2021); P.A. Zimmerman, "Efficacy and Safety of the Rts,S/As01 Malaria Vaccine during 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites," *PLoS Med* 11, no. 7 (2014). Early test results had been more promising. See Pedro L. Alonso et al., Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomized controlled trial, THE LANCET Vol. 364 at 1411 (Oct. 16, 2004).

reducing childhood mortality.[13] However, the facts that its efficacy diminishes over time and that it shows reduced power when deployed in populations afflicted with multiple variants of the *P. falciparum* parasite limit sharply the public-health benefit to which it will give rise.[14] Several other research projects are underway, but none is close to developing an effective vaccine.[15]

In the absence of a robust vaccine, inhibition of the spread of the disease is achieved primarily through vector control: protecting people in malaria-endemic countries against mosquito bites. Two strategies are employed for this purpose: supplying residents with bed nets treated with insecticide to shield them from bites while sleeping; and reducing the number of mosquitos in homes by spraying the walls with insecticide. The first of these initiatives has been the most extensive and successful. In the past decade, bed nets treated with insecticides (ITNs) have been widely distributed (usually for free) in malaria-endemic countries. Roughly 50% of the population in those countries now sleeps under nets.[16] They are inexpensive to produce, and their effect is dramatic. Studies suggest that they reduce malaria incidence by half.[17] The second approach – known as "indoor residual spraying" (IRS) – is equally effective but less widely used; indeed, usage appears to be diminishing, rather than increasing.[18]

Unfortunately, both of these approaches are threatened by increases in the resistance of the pertinent species of mosquitos to the most commonly used insecticides.[19] To slow the development of this resistance, the WHO recommends that distributors of the chemicals used in IRS and the manufacturers of insecticide treated bed nets rotate the insecticides they employ. Some countries abide by this guideline, but most as yet do not.[20]

Persons who, despite these efforts at vector control, acquire malaria can and should be treated with drugs. Starting in the early nineteenth century, the drug used most often was chloroquine, derived from the bark of a tree native to the Andes and later farmed in parts of Southeast Asia.[21] In the 1950s, *P. falciparum* parasites began to exhibit resistance to chloroquine, so many health-care systems in regions dominated by that species switched to sulphadoxine-

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[13] See Arora, Anbalagan, and Pannu, "Is the Rts,S/As01 Vaccination Effective ?," 1037.

[14] See ibid., 1036; Malaria Vaccine Initiative, "Path and Gsk Welcome Progress toward Rts,S Malaria Vaccine Pilot Implementation with Selection of Countries," (2017), https://www.malariavaccine.org/news-events/news/path-and-gsk-welcome-progress-toward-rtss-malaria-vaccine-pilot-implementation.

[15] See "Mvi Portfolio," (2019), https://www.malariavaccine.org/projects/mvi-portfolio.

[16] See WHO, "World Malaria Report," (2019), xvi, 28-29, 46-48.

[17] See Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews, 2004 (2):CD000363 [*recheck]. For slightly less favorable assessments of the efficacy of ITNs, see Mark Musumba, Aklesso Egbendewe-Mondzozo, and Bruce A. McCarl, "Analysis of the Cost of Malaria in Children and Use of Insecticide-Treated Bednets in Africa," African Development Review 26, no. 1 (2014).

[18] See WHO, "2019 Malaria Report," xvi, 48-49.

[19] *See* Stephen Hoffman. *Save the Children*, NATURE Vol. 430 at 940 (Aug. 19, 2004); Michelle L Gatton et al., "The Importance of Mosquito Behavioral Adaptations to Malaria Control in Africa," *Evolution* 67, no. 4 (2013).

[20] See WHO, "Malaria Report 2014," 16-17.

[21] See Webb, *Humanity's Burden*, 92-126.

pyrimethamine (SP).[22] Resistance to SP emerged soon thereafter.[23] Today, most health services outside of Latin America use artemisinin-based combination therapy (ACT) as the primary means of treatment.[24] Artemisinins are remarkably effective. For example, they have been shown to reduce infant mortality caused by malaria by 99%.[25]

The use of artemisinins has been increasing fast, especially in Africa. The percentage of persons who seek treatment at African public health facilities for malaria-like symptoms who are given ACT has risen sharply since 2005.[26] Unfortunately, administration of these drugs to people who are not infected by the malaria parasite but instead suffer from other ailments has also grown rapidly.[27] This has had two bad effects. First, the drugs do those people no good, which causes some of them to lose faith in western medicine and makes them less likely to rely on the health-

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[22] In Central America, where most malaria cases are caused by *P. vivax*, chloroquine remains the drug of choice. Recently, however, some resistance to that drug has been observed, prompting health-care services to shift increasingly toward ACT – described below.

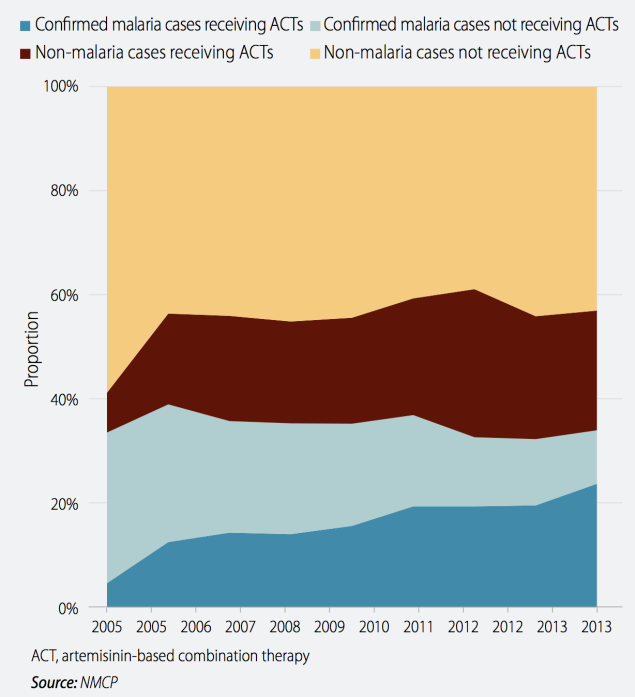
[23] See Bell and Winstanley, "Treatment of Malaria in Africa," 31.

[24] *See* Robert Ridley, *Winning the Drugs War*, NATURE Vol. 430 at 942 (Aug. 19, 2004). Forty-two malaria endemic countries have switched to ACT. *See* WHO: *First Global Report on Efforts to Roll Back Malaria*, available at: www.who.int/mediacentre/news/releases/2005/pr17/en/index.html (May 3, 2005). For the WHO's current recommendations concerning their use, see WHO, "Malaria Report 2014," 24.

[25] See ibid., 4. The effects on mortality and morbidity of the cycles of drugs and resistance thereto – and the large gains achieved through the swtich to ACT – are well illustrated by the recent history of malaria in South Africa. See R Maharaj et al., "Epidemiology of Malaria in South Africa: From Control to Elimination," *South African Medical Journal* 103 (2013).

[26] See WHO, "2019 Malaria Report," 59.

[27] The following chart tracks estimated ACT treatment received among malaria and non-malaria cases at public-health facilities in the WHO Africa region. The growth of the dark blue zone is encouraging; the equally dramatic growth of the maroon zone is alarming.

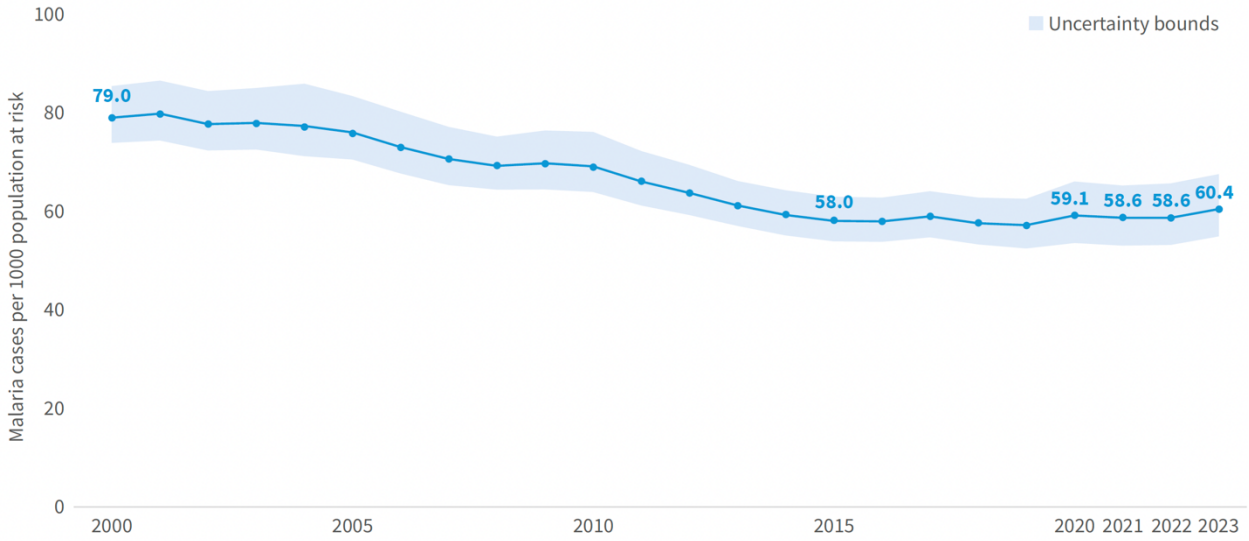


See "Malaria Report 2014," 27.

care system in the future. Second, it accelerates the emergence of strains of the malaria parasites that are resistant to the drugs. Fortunately, artemisinins are less likely than their predecessors to provoke resistance, apparently because they kill off the parasites more rapidly and thus shorten the window for mutation.[28] But, despite this advantage, resistance to them is now showing up increasingly often. (The problem is exacerbated by continued sales of oral artemisinin monotherapies [which lead to resistance more quickly than the combination therapies] by some Indian generic companies, despite opposition to the practice by the WHO.[29])

Pregnant women and infants can be shielded against the active form of malaria through prophylactic administration of the same drugs. A regimen known as "intermittent preventive treatment in pregnancy" (IPTp), which entails periodic administration of SP during the second and third trimesters, has been shown to reduce maternal anaemia, low birth rate, and perinatal mortality.[30] A similar regimen given to infants (IPTi) substantially reduces anaemia and other manifestations of the disease during the first year of life. A slightly different combination, when given to healthy children between 3 and 59 months old living in areas of highly seasonal malaria transmission, has also proven effective.[31]

In the twentieth century, the vector-control programs and the increasingly widespread distribution of ACT drugs, in combination, substantially reduced both the incidence and the mortality of malaria. Since the turn of the century, however, progress has slowed. The charts below, derived from the most recent report by the WHO, show the trends in incidence rate and mortality rate in the 103 countries considered at risk:

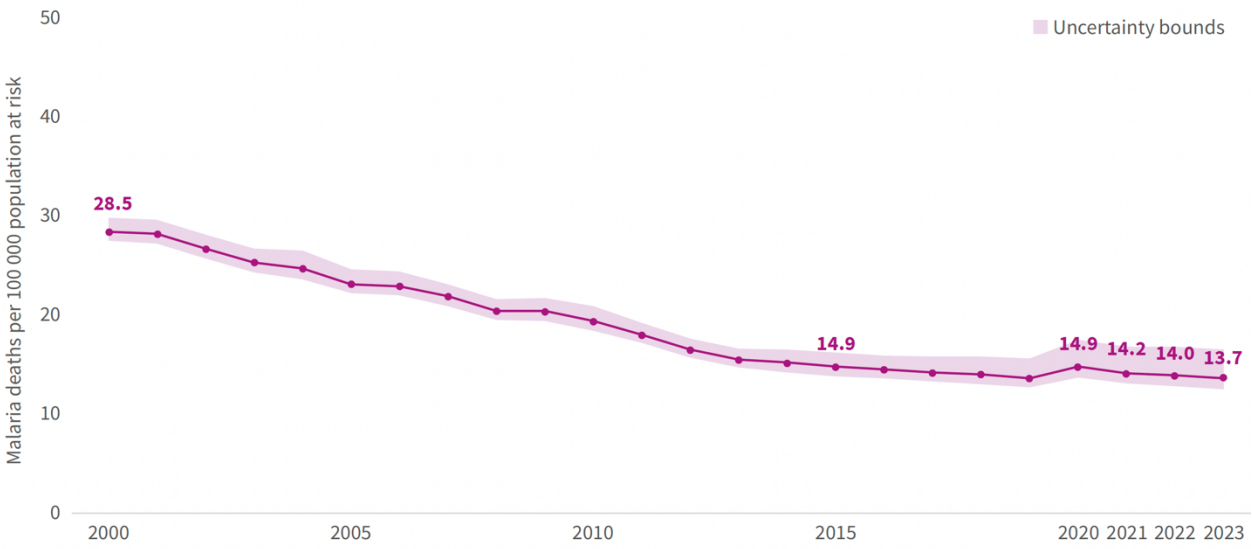


[28] See Bell and Winstanley, "Treatment of Malaria in Africa," 32.

[29] See WHO, "Malaria Report 2014," 28.

[30] See ibid., 4; WHO, "Intermittent Preventive Treatment in Pregnancy (Iptp)," (2019), https://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/.

[31] See "2019 Malaria Report," 14, 21-22.



The gains, such as they are, have been uneven. At least three countries – Sri Lanka, Uzbekistan and Kyrgyzstan – have been able in recent years to eliminate malaria entirely.[32] However, three others – Ethiopia, Madagascar, and Pakistan – saw huge surges.[33] Overall, the campaign to rid the world of malaria seems to have stalled.

If we are obliged to rely exclusively on our current disease-control strategies, the chances that we will soon eradicate malaria are not good. Especially worrisome is the recent emergence near the Mekong River of variants of *P. falciparum* that are at least partially resistant to all currently available drugs, including the ACTs.[34] If the offspring of those parasites reach Africa, millions of people could die. That prospect has prompted some observers to plead for redoubled suppression efforts in Southeast Asia, in hopes of eliminating the deadly variant before it can spread. But purging the disease from the highly mobile populations along the national borders in the region and from the residents of the remote forest villages is a daunting task.[35]

Once again, therefore, we confront the importance of developing new, more efficacious drugs and, better yet, an effective vaccine. Unfortunately, the obstacles to the discovery, testing, and deployment of a new malaria vaccine are formidable. At least in theory, three strategies are possible. The first approach would attack the sporozoites as they enter the body and reproduce in the liver. Ideally, this kind of vaccine would induce both an antibody and a T-cell response, similar to that observed in the development of natural protective immunity. If successful, this type of vaccine would result in complete protective immunity. (This is the strategy employed by RTS,S/AS01, discussed above.) The second approach would limit the invasion of erythrocytes and the subsequent multiplication and pathological effects. This approach would still permit

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[32] "World Malaria Report," (2024): 4.

[33] Between 2022 and 2023, the incidence rate in Ethiopia increased by 82%; in Madagascar by 71%; and in Pakistan by 59%. See ibid., 10.

[34] See WHO, "2019 Malaria Report," 68-71.; Mallika Imwong et al., "The Spread of Artemisinin-Resistant Plasmodium Falciparum in the Greater Mekong Subregion: A Molecular Epidemiology Observational Study," *Lancet Infectious Diseases* 17, no. 5 (2017).

[35] See Corbel et al., "Challenges and Prospects for Dengue and Malaria Control in Thailand, Southeast Asia," 631.

infection, but would prevent at least the more severe outbreaks of the disease. The third approach would prevent the spread of viable parasites to other people, thus limiting the potential for an outbreak within a given population. All three approaches are hampered by a common technical problem: Parasites have much larger genomes than viruses. They also undergo multi-stage life cycles and produce enormous variability in proteins, making the development of an effective single vaccine difficult. The recent completion of the *P. falciparum* genome sequence as well as the genome sequences of model rodent parasites may help scientists to surmount this hurdle, but have not done so yet.[36]

The impediments created by this technical barrier are compounded by some more prosaic difficulties. Clinical trials of vaccine candidates must be performed on infants in communities where malaria is endemic. Persuading mothers, many of whom are illiterate, that they should allow their children to be treated with drugs that have not yet been shown to be safe and effective is no easy task.[37] But unless we can meet these challenges, we are unlikely to eradicate the disease.

[36] See Patrick E. Duffy et al., Malaria vaccines: using models of immunity and functional genomics tools to accelerate the development of vaccines against Plasmodium falciparum, VACCINE Vol. 23 at 2235 (2005); Daniel Carucci, *Know thine enemy*, NATURE Vol. 430 at 945 (Aug. 19, 2004). The ability to develop vaccines through newly refined techniques for infecting healthy volunteers may also accelerate research, see Michael F. Good, "The Ability to Inoculate Purified Malaria Sporozoites Will Accelerate Vaccine and Drug Discovery," *American Journal of Tropical Medical Hygiene* 91, no. 3 (2014). – although it is difficult to imagine large numbers of people volunteering for such projects.

[37] See Muhammed O. Afolabi et al., "Early Phase Clinical Trials with Human Immunodeficiency Virus-1 and Malaria Vectored Vaccines in the Gambia: Frontline Challenges in Study Design and Implementation," ibid.90, no. 5; David I Ojakaa et al., "Acceptance of a Malaria Vaccine by Caregivers of Sick Children in Kenya," *Malaria Journal* 13 (2014).

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