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Manufacturing neglect: What happens to drugs once the epidemic has passed?

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By Jeremy Greene

We like to think that drugs help put an end to disease, although in the aggregate this is seldom the case. However many individual infections and infestations might have been cured by timely doses of antibiotics, antifungals, antiparasitics, or antivirals, very few diseases have been eradicated because of biomedical therapeutics. Yaws, a chronic treponemal disease now limited to 14 countries in West Africa and Southeast Asia, is a rare exception of a malady whose displacement has been driven by antibiotics. More often, diseases are controlled by surveillance, prophylaxis, and other preventive measures than by specific treatments. The limited successes of malaria eradication came more from vector control than antimalarials, polio and diphtheria are no longer scourges of childhood in North America and Europe because of widespread vaccination. If early 21st century debates over the management of the HIV/AIDS and MDRTB pandemics have rightly challenged any facile dichotomy between treatment and prevention as public health strategies, the relationship between the two remains an uneasy site of intersection between medicine and public health. More recently, a subtler antagonism between prevention and treatment has become apparent: the paradoxical influence of successful prevention on the availability of efficacious treatments.

Take, for example, the displacement of hookworm from the southern United States, widely remembered as a successful local eradication effort that owed more to the development of sanitation systems and social uplift than the deployment of antiparasitic drugs. While hookworm remains one of the most common nematode infestations of humans worldwide, the website of the US Centers for Disease Control (CDC) discusses the American subtype, *Necator americanus*, exclusively in the past tense: a parasite which "was widespread in the Southeastern United States until the early 20th century." Although hookworm was once widespread, the CDC continues, "improvements in living have greatly reduced hookworm infections."

These "improvements in living" were part of a coordinated regional campaign by the Rockefeller Foundation that would ultimately launch the

foundation to the forefront of international public health interventions. When the Rockefeller Sanitary Commission for the Eradication of Hookworm was launched in 1910, roughly 40% of the population of the southern United States was believed to be infested with hookworm. Rockefeller's "American method" for hookworm eradication involved surveillance, treatment, and prophylaxis: all individuals in an area would be screened, all affected would be treated with cheap and highly effective (if noxious) antihelminthic cocktail, and these demonstrations would be leveraged to build privies and other sanitation systems to prevent recurrence. As historian John Ettling noted, the Foundation leveraged the visible efficacy of antihelminthic drugs to accomplish broader preventive sanitary projects—and as an "entering wedge" to an escalating involvement in disease eradication projects around the world, from hookworm to yellow fever to malaria.

But what happened to the availability of these drugs once the disease had been displaced? Paradoxically, for those who contracted hookworm in the United States in the year 2016, it has become more difficult to find treatment. The vermifuges used by the Rockefeller Foundation in the early 20th century (such as thymol and chennipodium oil, which could have severe side effects) are no longer marketed, having been largely replaced by more specific products of the postwar pharmaceutical industry (such as albendazole and mebendazole). Even though these newer medicines are themselves quite old at this point, and have been off-patent and open to generic competition for decades, they are now quite difficult to find at affordable prices in the United States.

Albendazole was originally introduced in 1971, and by the 1980s its cost was so low and its efficacy so well-established that it was added to the Essential Drugs List of the World Health Organization. Yet when I tried to prescribe the drug to a patient in my Baltimore clinic last year suffering from pinworm (another nematode infestation), I learned that the price tag for 2 pills of albendazole had risen to $330. Partly because the market for the drug was seen to be limited, the U.S. market for albendazole had been cornered by a small pharmaceutical company called Amedra and retrofitted into a newly exclusive brand, Albenza, at more than $150 a pill. The rights to sell the only other drug in its therapeutic class—mebendazole—had also been purchased by Amedra as Teva (the world's largest generic drug manufacturer) had ceased distributing the drug to American markets. To date, mebendazole remains unavailable to American consumers. In turn, Medicaid spending on albendazole increased from less than $100,000 per year in 2008 to more than $7.5 million in 2013. For people without insurance, however, the medication simply became unavailable.

Albendazole and mebendazole have not attracted any robust generic

competition in the United States largely because the antihelminthic market in the US is not perceived to be significant. The same holds true for other antiparasitic drugs. This became widely visible last summer after another small pharmaceutical company, Turing Pharmaceuticals, acquired the sole U.S. distribution rights to pyrimethamine, another antiparasitic drug on the WHO Essential Drugs List, and boosted its price by 5,000 percent. Like albendazole, pyrimethamine was an old, off-patent, and effective antiparasitic agent whose market was considered marginal in an American population now perceived to suffer infrequently from parasitic infestations. And so even though the drug was available for a few cents in parts of the world with greater endemicity, in the US the drug prices were allowed to climb as an effective monopoly on the drug traded hands from Glaxo to Amedra, from Amedra to Turing.

The reduced availability of pyrimethamine has had real consequences in the lives of people with cerebral toxoplasmosis, for decades a condition understood to be manageable with an old drug nobody stopped to think could become inaccessibly expensive. Last fall, a team of my colleagues at Johns Hopkins admitted a patient who had been stable on pyrimethamine for years but who lost the ability to speak after the dormant parasite in her brain reawoke: Turing's price hike and restricted distribution system left her without access to the medicine. Even once hospitalized, she suffered further adverse effects after Turing and their sole distributor took four and a half days to supply pyrimethamine despite several urgent requests.

Since that time, former CEO of Turing Pharmaceuticals has become a new sort of villain in the passion play of the pharmaceutical industry, part of a new cohort of pharmaceutical executives who employ retro-monopolistic strategies to corner the market on old cheap drugs that no longer attract competition and remake them as old expensive drugs. Their actions bring into question longstanding assumptions that old drugs remain accessible and cheap in the decades after the importance of their innovation wanes from public memory. The increasing unaffordability of off-patent drugs that constitute noncompetitive markets has since taken on increasing urgency among policymakers in the executive and legislative branches of the U.S. government.

There is an unusual paradox at work here: if generic competition is understood as the principal means of making drugs affordable in the early 21st century, then any successful bid to reduce the prevalence of a disease runs the risk of decreasing the competitiveness of that market and therefore the accessibility of treatments for those who remain afflicted. As recent rolling waves of generic drug shortages and recent escalations in generic drug prices should remind us, the market's invisible hand works until it doesn't, and then we are left with conditions of market failure when

supply doesn't meet demand. As a given disease—like nematode infestation—is no longer perceived to present a viable market, generic competition dwindles from a robust field to oligopoly to duopoly to monopoly. In some cases, such as mebendazole, the drug simply becomes unavailable.

The historical orientation of biomedicine is overwhelmingly directed towards the future: when we do look back we tend to tell progressive narratives of diseases already vanquished as tokens for future eradication efforts. We focus on the innovations that permitted past public health successes and assume they will stay with us in the future. One of the more eagerly anticipated pieces of health policy in the United States today, 21st Century Cures Act, is entirely focused on fostering the development of new therapeutics—even though events of the past year would suggest that the problem of access to older drugs is just as pressing.

For all of the successes of hookworm control in the early 20th century, the US of the 21st century still contains many people with parasitic infestations who need regular access to affordable antiparasitic drugs. For these individuals, access to potentially life-saving medicines would paradoxically be easier if they were living elsewhere, in a place where preventive efforts had not been as successful, perhaps, but which continued to maintain the affordability and accessibility of 20th century cures. As our health systems continue to imagine promissory cures of the future to address the ills of today, we neglect the disappearance of cures that addressed those diseases we would like to relegate to the past, and we continue to fail those for whom that past has not yet come to an end.

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