New prescriptions for neglected diseases

James Maskalyk

James Maskalyk is Assistant Professor in the Division of Emergency Medicine, Faculty of Medicine, University of Toronto. He has recently finished a posting in Abyei, Sudan, with Médecins San Frontières. You can read his blog at http://www.msf.ca/blogs/JamesM.php

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The manufacture of pharmaceuticals is big business. From 1995 to 1999, for example, the value of medicine production grew four times faster than the world's income.[1] Most of the world's medicines are purchased by affluent countries such as the United States and Japan, where most pharmaceutical consumption involves daily medication for relatively healthy older people with chronic disease. The purchasing power of these countries sets global therapeutic priorities, and the impact is dramatic. With the exception of antibiotics, the top 10 therapeutic classes — i.e., those with the highest global production value — are targeted toward chronic illness.[1]

Elsewhere are populations that bear a disproportionate burden of acute illness. They are poor and suffer from diseases particular to their low- or middle-income nations. The few resources that their health systems have are often consumed by the more evident problems of HIV, tuberculosis and malaria. If any attention is given to geo-specific diseases, it is often in the more affordable form of prevention rather than treatment. Left behind are those infected with tropical diseases such as onchocerciasis or trypanosomiasis, for which treatment is limited and prevention comes too late. They have neither the economic authority nor the political capacity to encourage research into and development of effective therapies for neglected diseases. Yet, if one includes malaria along with this group, these patients suffer from the most burdensome illnesses in the world.[2]

Consider that, between 1975 and 1999, only nine medicines of the 1393 that were developed targeted the most neglected diseases. (This figure rises to 16 if one considers tuberculosis and malaria.[3]) Of the remaining 1377 medicines developed, only two made the World Health Organization's Model List of Essential Medicines. All 16 new medicines for neglected diseases did. In the ensuing five years, an additional 163 drugs were brought to market, of which four were for the treatment of malaria and one targeted a neglected disease — the drug miltefosine for treatment of leishmaniasis.[4]

The case of Chagas disease, a characteristic neglected disease, clearly illustrates the disparity between the demand for and supply of drugs for such illnesses. It is a "silent" parasitic disease that affects the poorest in Latin America; its vector — a biting insect — lives in thatched roofs and can readily be avoided with the purchase of a clay or tin roof. Many people become infected with the parasite, Trypanosoma cruzi, as children. Then, after a brief acute illness, most live without symptoms until middle age, when approximately one third die from gastrointestinal or cardiac complications of the disease.

In Latin America, an estimated 16 million to 18 million people are infected with the parasite, and Chagas disease is a leading cause of congestive heart failure.[5] Diagnosis of Chagas is cumbersome and unreliable. The cure rate is low, therapeutic regimens are complex, and side effects in adults are so prevalent that, until recently, therapy was limited to children. Yet there is no approved pediatric formulation, and the effectiveness of established treatments for chronic cases is largely unknown.[6] Several countries in the region have been able to slow transmission rates by eradicating the insect vector, but in the poorest countries, such as Bolivia, infection rates remain high.[7]

Prevention has proved to be an important strategy in the control of Chagas disease. Between 1975 and 1995, the Brazilian government invested $420 million in vector-control efforts and realized an estimated $3 billion in return (equivalent to US$7.16 per dollar spent).[8] However, there are millions of people for whom prevention is too late, and millions more who will become infected in spite of prevention efforts. For these people, there is no effective therapy and no relevant clinical trials are in progress. Even if their countries make treatment for Chagas disease a national priority, none will be forthcoming until it becomes a global priority.

The two drugs currently used as therapies for Chagas, benznidazole and nifurtimox, were developed decades ago and are neither particularly effective nor readily available. Benznidazole, the first-line therapy, was initially developed by Roche in 1974 for veterinary use. Since then, its production has been intermittent — driven largely by demand from non-governmental organizations (NGOs) advocating on behalf of those infected. These NGOs have managed to organize donations or to arrange for a subsidized wholesale purchase of the drug. Roche is in the midst of transferring its technology to a small public laboratory in Brazil, after which it will discontinue manufacture of

the drug. This transfer has been under discussion since at least 2002, and progress has been slow. Once the transfer is complete, this facility will be the only supplier of the drug to the 21 Latin American countries with endemic Chagas disease.[9] In addition, the facility to which the transfer is directed is producing and registering drugs for exportation for the first time, and has had difficulty finding a reasonably priced and reliable supply of the active pharmaceutical ingredient. Nifurtimox, the second-line drug, is produced by Bayer. The WHO has organized a donation of 250,000 tablets of nifurtimox; if there proves to be enough need, more will be purchased at a "discounted price." Meanwhile, the estimated need for benznidazole stands at 1.5 to 3.0 million tablets a year.

Physicians in high-income countries would not tolerate such scarcity of an essential drug, or such a poor side-effect profile, without a call for further research. In the case of Chagas disease, as will so many similarly neglected illnesses, that call has come from NGOs such as the Pan American Health Organization and the Drugs for Neglected Diseases initiative (DNDi).

Nearly 20 years ago, in 1988, the WHO targeted Chagas disease for elimination.[10] Although progress toward this goal has been slow, there have several promising developments. These fall outside of the realm of advocacy and may prove to be more sustainable. In 2004, for example, the British government made a commitment to purchase large quantities of a malaria vaccine and an AIDS vaccine once they are developed.[11] This move drives medical research in a new way: it provides an economic incentive for pharmaceutical companies to research and produce a reliable product, and it lessens the uncertainty and expense of post-development marketing. Although this initiative has yet to bear fruit in the case of malaria or AIDS, and has been criticized as simplistic,[12] a similar deal could be struck to encourage the development of new treatments for Chagas disease. Such an agreement need not be made with multinational pharmaceutical companies, given the developing world's growing capacity for research and production (particularly in Brazil, India and China). Also, it need not only be high-income countries that sign on to advance purchases. As Brazil has demonstrated through its prevention efforts, tackling Chagas disease is not just an ethical decision but also a highly economical one. However, unlike prevention, which takes at least 30 years,[13] treatment saves lives today. Success will come only when treatment and prevention are used in concert.

Another new idea is that of the nonprofit pharmaceutical company. The Institute for OneWorld Health, one of the first, was established in 2000. Using an innovative model that relies on basic research, donated intellectual property, industry expertise in drug development and the productive capacity of the developing world, OneWorld Health has identified several candidate compounds to treat neglected diseases (including two for Chagas). OneWorld Health has taken an off-patent medicine, paromomycin, through a phase III clinical trial and awaits regulatory approval for its use in the treatment of leishmaniasis.[14] Its work in low- and middle-income countries, which ranges from clinical trials to pill manufacturing, has also helped to build local expertise.

Most recently, two scientists in the United Kingdom developed a model they have termed "ethical pharmaceuticals" because it allows new drugs to be brought to market for a fraction of the cost charged by multinational pharmaceutical companies. By altering the chemistry of an existing drug for hepatitis C, they have created what is technically a new medicine, for which they hold the patent. Collaboration with the Indian government will take this "new" medicine through clinical trials; if successful, the drug will be made and sold cheaply around the world.[15] Time will tell whether a similar mechanism will result in the development of new medicines for neglected diseases.

As the case of Chagas disease makes clear, the traditional method of bringing drugs to market has left people with poor options for treatment. The same is true for other neglected diseases, such as leishmaniasis. Fortunately, the past few years have seen the emergence of new solutions that may finally help to solve this long-standing problem. Although they have yet to put pills in the hands of those who need them, the future looks promising.

Meanwhile, as the capacity for drug development and production expands in the low-income countries most burdened by neglected diseases, wealthy countries such as Canada can support initiatives similar to Britain's. New treatments for Chagas disease would be a good starting place for Canadian involvement, given that the Canadian International Development Agency has important development partners in Latin America, including Bolivia. Canada can also contribute by supporting university-based research into important neglected fields, as they are most likely to provide innovations free from market pressures and that can be used by such organizations as OneWorld Health and DNDi. New chemical entities should be made freely available by industry and universities for testing on neglected diseases. Canadian researchers and physicians should provide expertise through academic partnerships as well as through established mechanisms such as the United Nations-supported Special Programme for Research and Training in Tropical Diseases; and, medical journals, including this one, should strive to reserve space to publish new research and discussion about these diseases.

Recently, the medical community has recognized the large burden of chronic illnesses in low-income

countries.[16] Many leading scientists in affluent countries are already hard at work finding solutions to chronic illness, whether by optimizing diabetes treatments or developing safer drugs to ameliorate the pain of osteoarthritis. These are worthwhile goals. But if more attention were paid to developing affordable medicines to treat the infectious diseases that kill so many poor, young people, more of the world's population would live long enough to enjoy their benefit.

References

1. World Health OrganizationGeneva: World Health Organization: 2004. The World Medicines Situation.
2. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich SS, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. *PLoS Med*. 2006;3(5):e102.
3. Troullier P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet*. 2002;359:2188–94.
4. Chirac P, Torreele E. Global framework on essential health R&D. *Lancet*. 2006;367(9522):1560–1561.
5. Cubillos-Garzón LA, Casas JP, Morillo CA, Bautista LE. Congestive heart failure in Latin America: the next epidemic. *Am Heart J*. 2004;147(3):412–417.
6. Reyes PA, Vallejo M. Trypanocidal drugs for late stage, symptomatic Chagas disease (Trypanosoma cruzi infection); *Cochr Database Sys Rev*. 2005. p. CD004102.
7. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz*. 2003;98(5):577–591.
8. Akhavan D. *Análise de custo-efetividade do Programa de Controle da Doença de Chagas no Brasil*. 2000.
9. Médecins Sans FrontièresCampaign for Access to Essential Medicines. Chagas disease [factsheet]. Geneva: MSF: 2005.
10. World Health Organization51st World Health Assembly, Resolution WHA51.14. 1998.
11. Kremer M, Glennerster R. A magnet for vaccines. *Fortune*. 2004;150(13):52.
12. Farlow A. Over the rainbow: the pot of gold for neglected diseases. *Lancet*. 2004;364:2011–2.
13. Wilson LS, Strosberg AM, Barrio K. Cost-effectiveness of Chagas disease interventions in latin america and the Caribbean: Markov models. *Am J Trop Med Hyg*. 2005;73(5):901–910.
14. Institute for One World HealthVisceral leishmaniasis clinical program. 2007.
15. Bosely S. Scientists find way to slash cost of drugs.. *Guardian Unlimited*. 2007 [accessed 2007 June 17].
16. Anderson GF, Chu E. Expanding priorities—confronting chronic disease in countries with low income. *N Engl J Med*. 2006;356(3):209–11.

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