Brief for GSDR – 2016 Update

Sustainable drug development for Neglected Tropical Diseases

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Introduction

The pace of drug discovery paralleled the pace of science in general for most of the 1900s. As more was learned about the basic principles of biology and the molecular basis of disease, it became easier to develop rational medicines to treat diseases (Fricker, 2013). The advent of penicillin after World War II heralded a new phase in the history of the pharmaceutical industry, as it fast-tracked mass production methods (Quinn, 2013). However, penicillin was not protected by patents. As a result, many companies entered the market, ultimately making its production unprofitable (Moors et al., 2014).

For almost 100 years, physicians and pharmacists had successfully opposed the idea that drugs are industrial commodities like any other. The incident with penicillin though caused a shift towards patenting drugs that spurred a wave of legal measures establishing procedures for patenting drugs in Europe (Gaudilliere, 2008) and the USA. Thereafter, pharmaceuticals began investing heavily in the discovery of new products, and taking out patents. The expansion of publicly funded biomedical research also provided a boost to the research and development of the industry (Moors et al., 2014). The golden age of the pharmaceutical industry had begun and the world – or at least part of it -was going to benefit from a wealth of drugs that would go on to cure or contain diseases that had plagued humankind for centuries.

The problem

There are 17 neglected tropical diseases (NTDs) widespread across the tropical areas of Africa, Asia and Latin America. These parasitic and bacterial diseases are among some of the most common infections in the estimated 2.7 billion people living on less than $2 per day (Hotez et al., 2007). NTDs impose a heavy burden on poor people, their families, communities, and countries. People in the bottom billion are the poorest in the world, and suffer from at least one of these diseases, which can last for decades and cause severe disability and disfigurement with profound economic, social and political consequences (Hotez et al., 2009).

As the term alludes, these diseases are "forgotten" by the pharmaceutical industry, because they are dominant among the most impoverished communities, rarely affecting

tourists or spreading to the developed world. To illustrate the extent of the problem, out of 1,223 drugs commercialized worldwide between 1975 and 1996, less than 1% was destined for tropical diseases, of which only a minority were genuine products of their research for this intent (Trouiller and Olliaro, 1999). On the contrary, diseases that originated in the developing world, but spread in West have received significant attention, as in the case of AIDS/HIV, and the recent outbreaks of Ebola and Zika.

There are structural reasons explaining the industry's reluctance to invest on drugs for NTDs. These are:

1. The significant attrition rate from original chemical targets to actual products has resulted in a structure of high R&D costs, which then must be recouped through massive sales of the few drugs that are finally used in clinical practice (Gaudilliere and Thoms, 2013). For example, it is estimated that pharmaceutical companies the USA spent $50 billion in aggregate on research and development in 2008 alone (Siddiqui and Rajkumar, 2012). Consequently, drug producing companies prefer to develop drugs that target chronic diseases – since this guarantees long-term sales - preferably manifested in high-income countries, where patients and their health insurers are willing and able to absorb the cost, largely insensitive to price. Conversely, average spending for health services in low income countries was just $23 per capita in 2001 (Ridley et al., 2006). More to the point, in a growing economy like India, more than 80% of healthcare expenditure is still born by patients, and medications tend to be overpriced and unaffordable (Ahmad et al., 2015). Unsurprisingly, drug development centered in the developed world has therefore focused its R&D efforts on "rich" world diseases, such as heart diseases, and diabetes. The situation is further aggravated by considerable R&D efforts concentrating on non-life threatening but potentially highly profitable conditions, such as male pattern baldness.
2. The patent system creates a monopoly resulting in high prices and artificial profits, even if intellectual property rights have a limited duration and provide access to the formal description of the protected invention (Gaudilliere, 2008). In this context, there is limited interest in investing in high-risk, low-profitability drugs for NTDs.
3. Companies producing generic versions of branded drugs have entered the arena waiting for patents to expire – normally 20 years after submission – to produce them at a lower cost. In southern Africa, where there is a high burden of HIV and a lack of access to resources for health care and medicines, the industry is particularly important (Penfold, 2015). However, while generics have been a boon for persons with HIV/AIDS in developing countries and patients everywhere, an

unintended consequence has arguably been on investment in a vital class of drugs, namely antibiotics. For instance, half of all pharmaceutical firms in the USA and Japan ceased their antibiotic activities in the late 1980s due to a market saturated by antibiotics and their generics with similar indications (Quinn, 2013). This is particularly alarming considering some bacteria have developed resistance towards existing antibiotics.

4. Under WTO agreements, countries can impose compulsory licenses to allow generic production so that in the event that a really successful therapy is developed, the patentee may never be able to make any meaningful sales in the developing countries (Hollis, 2005).
5. The regulatory system of medicines in the developed world is often criticized as bureaucratic, hampering innovation, not science-driven, and keeping competition and new entrants out, and delaying availability of new drugs (Moors et al., 2014). Moreover, abiding by the complex and ever expanding guidelines further cause an increase in costs that prevent especially small companies from entering the market and big ones from investing in new and possibly "unprofitable" drugs.

Efforts to address NTDs

Multi-sector engagement through public-private partnerships and product development partnerships are increasingly being recognized as a strategy to address NTDs (Mackey and Liang, 2012).

Drug development partnerships for tropical infectious diseases have already been successfully established by the WHO Special Programme for Research and Training in Tropical Diseases (Stirner, 2008). Another prominent example is the Drugs for Neglected Diseases initiative (DNDi), which is a collaborative, non-profit drug research and development organisation developing new treatments for, among others, five NTDs.[1] Other successful partnerships include Merck & Co.'s partnership for onchocerciasis; Pfizer's partnership with the International Trachoma Initiative; and the Global Alliance to Eliminate Lymphatic Filariasis comprised by GlaxoSmithKline, WHO, Merck & Co., and Eisai Co. that provides medicines for lymphatic filariasis (Hotez et al., 2007). Also, the Carter Center has a dedicated program for the elimination of five NTDs, and since 1986 has led the international campaign to eradicate the Guinea worm disease resulting in the reduction of instances by more than 99.99% in 2015.[2] Lastly, 13 pharmaceutical companies, the U.S., U.K. and U.A.E governments, the Bill & Melinda Gates Foundation, the World Bank and other global health organisations announced in 2012 a new coordinated push to accelerate

[1] Drugs for Neglected Diseases Initiative: http://www.dndi.org/about-dndi/founding-partners/

[2] The Carter Center: http://www.cartercenter.org/health/index.html

progress toward eliminating or controlling 10 NTDs by the end of the decade.[3]

Issues for policy recommendation

First and foremost, it is vital for policy-makers across the board to recognize the importance and long-term implications of NTDs for the achievement of sustainable development by developing countries. Considering that the spread of some emerging and reemerging NTDs is accelerated by ever-increasing globalization, travel, and trade, climate change, population growth, migration, urbanization etc. (Mackey et al., 2014), urgent action to tackle NTDs should be prioritized. After all, fighting global threats to health is an important element of the 2030 Agenda.

As far as public-health interventions are concerned, the World Health Organization recommends the following five to accelerate the prevention, control, elimination and eradication of NTDs: preventive chemotherapy; innovative and intensified disease management; vector control and pesticide management; safe drinking-water, basic sanitation and hygiene services, and education; and zoonotic disease management.[4]

The following are policy suggestions to stimulate drug development for NTDs:

1. The US (1983), European Union (2000), Japan (1993), Australia (1998) and Singapore (1997) have introduced orphan drug legislation that provide different types of incentives to drug manufacturers to develop drugs for rare (orphan) diseases, which have been neglected by the industry but are prevalent in these countries. It could be suggested to expand the scope of the law to include NTDs.
2. To overcome the problem of drug affordability (for developing countries) and profitability (for the pharmaceutical industry), governments and pharmaceuticals should engage in a dialogue to identify mutually beneficial solutions. For instance, governments could offer economic and tax incentives to generate interest and companies could establish different price levels for each country based on elasticity.
3. A steady increase in R&D investing for rare diseases has been witnessed in the last decade, which however, does not correspond to an equal increase in product development and marketing. The promotion of public-private partnerships could lead to more actual drug development for NTDs.
4. Lastly, more developing countries should take advantage of compulsory licensing, permitted by the 2001 Doha Declaration, to boost national drug manufacturing of generic versions of patented drugs for NTDs. This policy though should be utilized in moderation, as it can deter companies

[3] Bill & Melinda Gates Foundation: http://www.gatesfoundation.org/media-center/press-releases/2012/01/private-and-public-partners-unite-to-combat-10-neglected-tropical-diseases-by-2020

[4] World Health Organization: http://www.who.int/neglected_diseases/5_strategies/en/

from engaging in partnerships due to the potential loss of profit.

References:

Ahmad, Akram, Muhammad Umair Khan and Isha Patel (2015). Drug pricing policies in one of the largest drug manufacturing nations in the world: Are affordability and access a cause for concern? *Journal of Research in Pharmacy Practice* 4 (1): 1-3. DOI: 10.4103/2279-042X.150043

Fricker, Lloyd D (2013). Drug Discovery over the Past Thirty Years: Why Aren't There More New Drugs? *Einstein Journal of Biology & Medicine* 29 (1/2): 61-65. https://www.einstein.yu.edu/uploadedFiles/Pulications/EJBM/EJBM%2029.1%20Fricker.pdf

Gaudillière, Jean-Paul (2008). How pharmaceuticals became patentable: the production and appropriation of drugs in the twentieth century. *History & Technology* 24 (2): 99-106. DOI: 10.1080/07341510701810906.

Gaudillière, Jean-Paul, and Ulrike Thoms (2013). Pharmaceutical firms and the construction of drug markets: from branding to scientific marketing. *History & Technology* 29(2): 105-115. DOI: 10.1080/07341512.2013.828867.

Hotez, Peter, Alan Fenwick, Lorenzo Savioli, and David H. Molyneux (2009). Rescuing the Bottom Billion Through Control of Neglected Tropical Diseases. *Lancet* 373: 1570-1575. http://www.who.int/neglected_diseases/Bottom_billion_ntd_control.pdf

Hotez, Peter, David H. Molyneux, Alan Fenwick, Jacob Kumaresan, Sonia Ehrlich Sachs, Jeffrey D. Sachs, and Lorenzo Savioli (2007). Control of Neglected Tropical Diseases. *The New England Journal of Medicine* 357(10): 1018-1027. http://www.nejm.org/doi/pdf/10.1056/NEJMra064142

Mackey, Tim K., and Bryan A. Liang (2012). Threats from emerging and re-emerging neglected tropical diseases (NTDs). *Infection Ecology & Epidemiology* 2: 1-7. DOI: 10.3402/iee.v2i0.18667.

Mackey, Tim K., Bryan A. Liang, Raphael Cuomo, Ryan Hafen Kimberly C. Brouwer, and Daniel E. Lee (2014). Emerging and Reemerging Neglected Tropical Diseases: a Review of Key Characteristics, Risk Factors, and the Policy and Innovation Environment. *Clinical Methodology Reviews* 27(4): 949-979. DOI:10.1128/CMR.00045-14.

Moors, Ellen H.M., Adam F. Cohen, and Huub Schellekens (2014). Towards a sustainable system of drug development. *Drug Discovery Today* 19(11):1711-1720. DOI:10.1016/j.drudis.2014.03.004

Penfold, Erica (2015). Explainer: The Problem Drug Patents Pose for Developing Countries. *World Affairs Journal*. http://worldaffairsjournal.org/content/problem-drug-patents-pose-developing-countries

Ridley, David B., Henry G. Grabowski, and Jeffrey L. Moe (2006). Developing drugs for developing countries. *Health Affairs* 25(2): 313-324. DOI: 10.1377/hlthaff.25.2.313

Siddiqui, Mustaqeem and S. Vincent Rajkumar (2012). The High Cost of Cancer Drugs and What We Can Do About It. *Mayo Clinic Proceedings* 87(10): 935-943. DOI: 10.1016/j.mayocp.2012.07.007

Stirner, Beatrice (2008). Stimulating Research and Development of Pharmaceutical Products for Neglected Diseases. *European Journal of Health Law* 15(4): 391-409. DOI: 10. 1163/157180908X338278.

Trouiller, Patrice, and Piero L, Olliaro (1999). Drug Development Output from 1975 to 1996: What Proportion for Tropical Diseases? *International Journal of Infectious Diseases* 3(2): 61-63. http://www.ijidonline.com/article/S1201-9712(99)90010-3/pdf

Quinn, Roswell (2013). Rethinking Antibiotic Research and Development. *American Journal of Public Health* 103(3): 426-434. DOI: 10.2105/AJPH.2012.300693.