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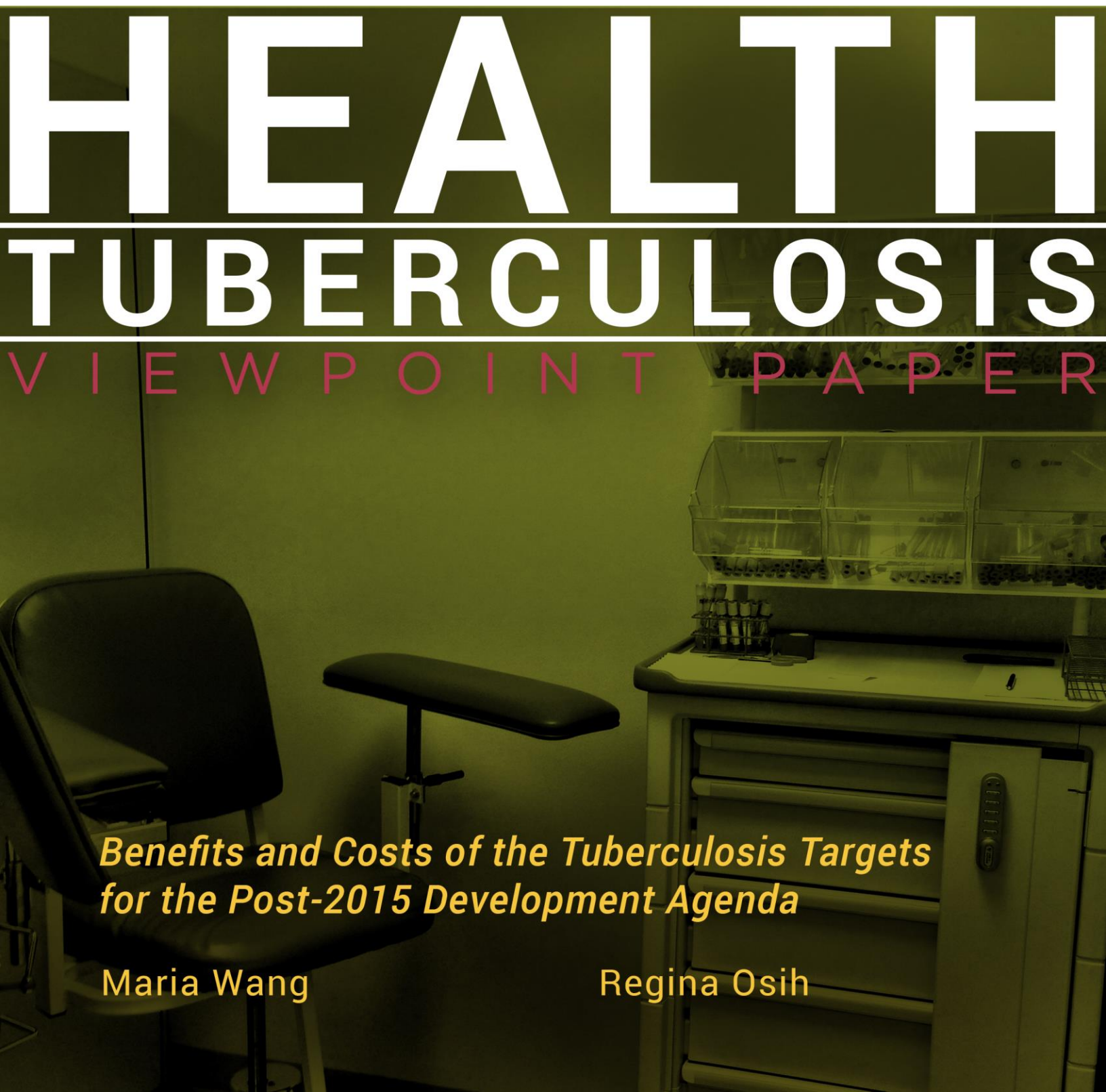
VIEWPOINT PAPER



Benefits and Costs of the Tuberculosis Targets for the Post-2015 Development Agenda

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POST-2015 CONSENSUS

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'[T]he concept of essential drugs enshrined in the national drug policy conforms to the WHO's definition of appropriate technology for health – that is, it is scientifically, socially and economically sound.'

'The Rational Use of Drugs', Report of the Conference of Experts, Nairobi, 25-29 November, 1985

Introduction

In 2015, the world is pausing to take stock of progress made on the MDGs and reconvening at UN Headquarters to set targets for health coverage in the post-2015 era. It is ushering in a new era of bolder aspirations, of renewed hope, of recommitted funds, and of hopefully wiser efforts. To this last point, a key question will likely be: what have we learnt from the last 15 years so that we do not make the same mistakes in the next 15? Interestingly, technology, in the form of mHealth and in the name of innovation and efficiency, will receive even more hype and investment of time and energy than ever before, but what of the most fundamental technology for health: drugs?

How much attention will be paid to whether:

- and how well the drugs we have work (and that what we are using are the ones that work best)
- the drugs we have are acceptable to those who need to take them and to those tasked with administering them
- the drugs we have are affordable (but also priced sustainably so that the market for these drugs remains healthy and full of competition)?

This viewpoint focuses on tuberculosis (TB) and argues that it is imperative to consider these questions if we are to make the kinds of gains that the post-2015 TB strategy strives for. It will focus on drugs to treat multi-drug resistant tuberculosis (MDR-TB) because this is the area in TB treatment that is lagging furthest behind.

Millennium Development Goal (MDG) 6 set a target of halting and reversing TB incidence and halving the 1990 TB prevalence and death rates by 2015. While incidence is falling globally and in most of the high-burden countries, the world is not on track to meet the target of 50 percent reduction in mortality by 2015, and incidence, prevalence and mortality in Africa, Eastern Mediterranean and European Regions are not falling fast enough to meet the 2015 targets.[1] Without being able to say for certain, due to significant data limitations, MDR-TB incidence is likely trending in the opposite direction. The 2015

[1] WHO (2014). *Global Tuberculosis Report 2014*. Retrieved from: http://www.who.int/tb/publications/global_report/en/.

MDG recognized that to reverse TB incidence and halve TB prevalence and deaths by 2015, there was a need to detect 70 percent of sputum smear positive cases and treating 85 percent of cases successfully by end of 2005.[2] By comparison, in 2013, 45 percent of MDR-TB cases were detected and 48 percent were successfully treated.

Scientifically sound: proved efficacy

The world has been waging a war against TB for thousands of years. The infectious, airborne disease is believed to have caused more deaths than wars and famines combined. Then in the mid-20th century, an antibiotic called streptomycin was discovered; it was the first medicine that could cure TB and heralded a new era that would be TB-free.[3] The bacteria, however, evolved, and drug resistance began to emerge. Giving the patient streptomycin with a second drug (para-aminosalicylic acid or PAS) and later a third (isoniazid) worked to safeguard against resistance but its effects wore off over time; thiacetazone then replaced PAS, reducing the 18-month treatment course to 12 months. Fast forward to modern day, past many more such iterations on treatment, and the most effective regimen against drug-sensitive TB is currently a four-drug regimen combining isoniazid, rifampicin, ethambutol and pyrazinamide administered over 6 months.

As the scientific knowledge base grows, the arsenal of drugs at our deployment should continue to evolve like it did when the first drug discoveries occurred. But those discoveries, coupled with a strategy of direct observation of patients to ensure they were taking their drugs daily until they are cured, worked so well that TB incidence in the developed world fell dramatically. The world was led to believe that TB was a disease of the past. In other words, the world became complacent.

Meanwhile, TB, a resilient organism highly capable of evolution, fought back, and so today, old medicines like PAS are being resurrected to combat MDR-TB, a strand of TB that is resistant to both isoniazid and rifampicin. The efficacy of these drugs, however, is often unclear because the standards of drug development have changed over the last five decades and they have not been tested against these new, updated standards. In the fifty or so years that have lapsed since the first suite of TB drugs were launched, there has been waning enthusiasm for making changes to treatment that would make a difference in the outcomes of patients with MDR-TB. For example, ofloxacin, another antibiotic in the MDR-TB regimen, has not been recommended for the treatment of MDR-TB since the revised WHO guidelines of 2011 and yet continues to appear on the WHO Model List of Essential

[2] Dye, C. and Floyd, K. *Disease Control Priorities in Developing Countries* (2nd ed). Chapter 16: Tuberculosis. Retrieved December 9, 2014 from: http://www.ncbi.nlm.nih.gov/books/NBK11724/.
[3] WHO (2011). *Bugs, drugs and smoke: stories from public health*. Chapter 6: Tuberculosis: complacency kills. Retrieved December 9, 2014 from: http://www.who.int/about/bugs_drugs_smoke_chapter_6_tuberculosis.pdf

Medicines[4] and continues be used in practice.[5] The system, instead of being attuned to signals of efficacy, is attuned to signals of safety. While we should hold new drug development to higher standards than before – because safety is paramount – it is harder to justify a preference for older drugs that were not rigorously tested and that are known to cause very severe side effects to newer compounds that have undergone much more stringent testing simply because of a perceived lack of experience using them. There is now an inertia that comes with using more or less the same treatment for decades, and a risk-aversion with trying something new and not yet 'proven' through the entire gamut of clinical trials – in stark contrast to the decision to administer ZMapp to Ebola patients before it had even been tested in humans. MDR-TB (with treatment) has similar mortality rates as Ebola (without treatment) – at around 50 percent –and affects exponentially more people than Ebola, and yet MDR-TB is seen as much less of a global health emergency. It is almost as if the world has taken a collective sigh and wondered: we've lived with it for so long, what's another year or decade?

The time has come for TB, and MDR-TB in particular, to be recognized for the public health emergency that it is, and a two-prong approach to be taken:

i) where evidence does exist to point to the superiority of certain drugs above others: this evidence should be disseminated urgently and deliberately, so that essential medicines lists and procurement practices are up-to-date and consistent with the latest scientific knowledge. This must be coupled with the transparent and evidence-based national processes for the selection of essential medicines, as was called for in the Resolution on Access to Essential Medicines, adopted at the 67th World Health Assembly in May 2014.[6]

ii) where the efficacy of anti-TB drugs remains unclear but shows promise enough to warrant testing against modern standards, according to a globally representative body of experts given the mandate to make this judgment call: a solid evidence base should be gathered, and this should be done as much as possible in settings and using protocols that will maximize its acceptance by all countries, to avoid repetition of clinical trials where the originally studied population is perceived to be different from the population targeted.

[4] WHO, Model List of Essential Medicines (18th List, April 2013). Retrieved December 9, 2014 from: http://www.who.int/medicines/publications/essentialmedicines/18th_EML_Final_web_8Jul13.pdf
[5] Ahuja, S. D. et al (2012, *Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients*. PLOS Medicine 9(8): e1001300.
[6] WHO, Resolution on "Access to essential medicines", A67/B/CONF./6, 67th World Health Assembly, May 24, 2014. Retrieved December, 9 2014 from: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_BCONF6-en.pdf.

Socially sound: acceptable to those on whom it is used and those who use it

Drugs that are clinically efficacious are of little use if the side effects associated with them are so severe that patients won't take them for long enough to be cured. The side effects that MDR-TB drugs can produce in patients are so horrendous that they do often beg the question: to treat or not to treat? One such side effect is the onset of irreversible deafness, which happens in one out of three patients who take an injectable called kanamycin – the only way to manage for this is to monitor and consider discontinuation of kanamycin taking into account patient preference and the (few) alternatives that may be available. The absence of viable options to manage for these severe adverse events is commonly referred to as the "hearing or death?" paradigm, a case of "which is the lesser of two evils?" Another such severe side-effect is depression and suicidal ideation when using cycloserine or terizidone, two drugs that are the cornerstone of MDR-TB treatment.

For other side effects, like intractable vomiting and nausea, adjunctive medicines are needed. This sounds straight-forward enough, but in practice it is less so. Ensuring the availability and accessibility of the best ancillary medicines is complicated in part because most resource limited settings lack the pharmacovigilance systems needed to know how frequently severe adverse events will occur and therefore what quantity of ancillary medicines will be needed. In addition, ancillary medicines often risk being overlooked when countries formulate national drug policy and decide their list of essential drugs, or when they apply for grants to cover their treatment programs. A stark example of this is ondansetron, a powerful anti-emetic for the management of severe vomiting and nausea. This drug has been on the WHO Model List of Essential Medicines List for several years, and a generic is available and therefore reasonably affordable, and yet it is omitted from the essential medicines list of many countries, mostly due to the perception that it is costly and unaffordable as it was reserved for use in patients who undergo chemotherapy

Nutritional supplementation is another essential element in supportive care in MDR-TB patients. Patients often have very low body weights, and given that the disease is associated with poverty, are often unable to provide for themselves while ill. Nutritional support is often available while hospitalized but not continued when patients are discharged, leading to poor adherence during the long course of treatment. Despite evidence that nutritional support is important for MDR-TB treatment success, consensus around a standardized approach has not been developed globally and few programs include outpatient nutritional packs.[7]

[7] Podewils, L. J., et al. "Impact of malnutrition on clinical presentation, clinical course, and mortality in MDR-TB patients." Epidemiology and infection 139.01 (2011): 113-120.; Seung, Kwonjune J., et al. "Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa." PloS one 4.9 (2009): e7186.

Therapy should be patient-centered and should strive to provide the best outcomes for the patient. Issues of patents, costs, and other barriers should be weighed against the irreversible damage that occurs due to side-effects. There is an urgency to get better supportive care and to re-focus the debate on the patient, rather than the system.

Economically sound: affordable and sustainable

Finally, drugs will only be used to the extent that they are affordable to the patient, to the national treatment program, and to society as a whole.

TB is a poor person's disease, and the complicated nature and long duration of treatment (6 months for drug-susceptible TB, and an average of 24 months for MDR-TB) bring with it substantial opportunity costs. Most patients are not able to be gainfully employed during their treatment course, the result of the debilitating effects of the disease and treatment side effects, and the time-consuming nature of adhering to treatment. Often, there is an additional direct cost of transportation to a health clinic for injections (daily) in the first 6 to 9 months. TB and MDR-TB in particular also place a substantial burden on the health system. To name just a few aspects of this: the current model of care emphasizes the daily observation of the patient taking their drugs by a health care worker (or alternatively, a counselled and trained community or family member); MDR-TB in many countries is treated by hospitalizing the patient for the first several months, and every country hospitalizes patients presenting with complicated cases; and the severe adverse events require dedicated resources for appropriate monitoring and care. Finally, the costs to society, though harder to quantify, are significant too, in terms of life years lost, lost productivity, missed schooling for children, and broken families.

Being economically sound is about more than just affordability for patients and for national treatment programs. The price of medicines must also be set at a level to sustain a health pharmaceutical industry – both for research and development, and to meet country demand. Funding in TB research and development is at an all-time low – with only 33 percent of the 2 billion estimated R&D funding need being met[8] – and is another symptom of the world's complacency around TB. The innovators in the pharmaceutical industry too see a smaller, less profitable market in TB, now a disease that afflicts almost exclusively low- and middle-income countries, and even generic manufacturers are hard pressed to enter or stay in this market because of the low reward to effort ratio. It is worthy to note that the market shortcomings have in part to do with the fuzziness around the relative efficacy of drugs within one class, such that the WHO guidelines on treatment are vague, permitting countries to construct highly varying regimens and therefore purchase a large number of products. This results in fragmentation of an already small market, where

[8] Frick, M., *Treatment Action Group (2014). 2014 Report on Tuberculosis Research Funding Trends 2005-2013*. Retrieved December, 11 2014 from: http://www.treatmentactiongroup.org/tbrd2014.

suppliers get even smaller volumes because countries have their own individual preferences. The rationalized use of drugs will serve a market-shaping end: consolidating volumes purchased around clinically superior or more cost-effective clinically equivalent products, to drive up volumes and therefore economies of scale and competition. The end goal is a healthier, more vibrant and stable market, innovating and offering drugs at a lower price to national treatment programs.

Conclusion

Sustainable development is development, economic, social and scientific, that is resilient and difficult to reverse. Continuing to wage a war against an age-old organism and periodically letting it outsmart our commitment and capacity to deploy new medicinal innovations against it is not sustainable. Let us acknowledge TB in all its forms to be the public health emergency that it is, and simultaneously invest in finding new and better drugs and deploying more rationally the drugs we do have. When it comes to TB and MDR-TB, we still have a long ways to go.

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Founded in 2002 by President William J. Clinton, the Clinton Health Access Initiative (CHAI) works to broaden access to life-saving treatment for HIV/AIDS, tuberculosis and malaria patients in the poorest parts of the world. As part of this mission, CHAI's "Access Programs" approach global public health challenges with market-based strategies, using simultaneous engagement on both the supply and demand sides of the market.

This paper was written by Maria Wang and Regina Osih, Clinton Health Access Initiative, for the Post-2015 Consensus Project. The Project brings together 60 teams of economists with NGOs, international agencies and businesses to identify the goals with the greatest benefit-to-cost ratio for the next set of UN development goals.

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