Postprint

This is a pre-copyedited, author-produced PDF of an article accepted for publication in the [*Journal of Bioethical Inquiry*] following peer review. The definitive publisher-authenticated version [Degeling C, Mayes C, Kerridge I, Lipworth W, Upshur R. The political and ethical challenge of multi-drug resistant tuberculosis, Journal of Bioethical Inquiry. Published online 29 Jan 2015] is available online at http://link.springer.com/article/10.1007/s11673-014-9595-3.

Please cite as:

Degeling C, Mayes C, Kerridge I, Lipworth W, Upshur R. The political and ethical challenge of multi-drug resistant tuberculosis, Journal of Bioethical Inquiry. Published online on 29 Jan 2015; available online http://link.springer.com/article/10.1007/s11673-014-9595-3

The political and ethical challenge of multi-drug resistant tuberculosis

Chris Degeling, Chris Mayes, Wendy Lipworth, Ian Kerridge, Ross Upshur (2015)

ABSTRACT

This article critically examines current responses to multi-drug resistant tuberculosis and argues that bioethics needs to be willing to engage in a more radical critique of the problem than is currently offered. In particular, we need to focus not simply on market-driven models of innovation and anti-microbial solutions to emergent and re-emergent infections such as TB. The global community also needs to address poverty and the structural factors that entrench inequalities—thus moving beyond the orthodox medical/public health frame of reference.

The problem of drug-resistant tuberculosis

Twenty years after tuberculosis (TB) was declared a global public health emergency, it remains a leading infectious cause of death worldwide. TB also remains primarily a disease of poverty; higher rates of incidence follow in lock step with social and economic disadvantage. Two billion people are known to be infected with *Mycobacterium tuberculosis*. In its most recent report, The World Health Organization (2012) estimated that 8.6 million people develop TB each year and 1.3 million people die from active infection – the vast majority amongst the poor and marginalized in low- and middle-income countries.

Data from surveillance programs and drug resistance surveys suggests that almost 4 percent of newly diagnosed cases and 20 percent of re-activated infections are caused by multi-drug resistant strains [MDR-TB] of the bacterium. About 630,000 (roughly 10 percent) of these MDR-TB cases exhibit extensive drug resistance [XDR-TB], which means that at least one of the two most potent first-line TB medications

and at least one of the three injectable second-line medications are no longer effective (Center for Disease Control 2013). Currently, less than half of identified MDR-TB patients are successfully treated – reflecting high mortality rates and discontinuation of treatment (World Health Organization 2012).

It has been recognized since the 1950s that TB requires a combination of therapeutic agents because of the bacterium's capacity to develop resistance. Drug resistant cases often require more than twenty months of access to second-line drugs (that can have serious side effects - especially when given to people who are also HIV positive). It is also known that the successful administration of these agents requires relative social, economic and political stability. The effects of inadequate socio-political infrastructure and irrational prescribing, particularly the use of single agents, combine to present significant barriers to patients receiving and adhering to effective treatment, which can further foster resistance to therapeutic agents. MDR-TB also has deleterious impacts on existing programs and structural resources. For example in South Africa the incidence of resistant strains is less than 3% of all TB cases. Yet efforts to treat these people consume about 35% of the budget allocated for TB control threatening the viability of established national programs (Pooran et al. 2013). Moreover the global emergence of socially dis-advantaged populations with XDR-TB who receive no institutional support and are consequently at large in their communities, indicates that XDR-TB is not only a significant risk to global health but an increasingly acute ethical and medico-legal challenge (Denholm et al. 2014; Selgelid 2008; Hughes, Cox, and Ford 2012).

The innovation gap and the logic of market incentives

Medications currently used in first-line treatment regimens for TB are more than fifty years old. While drug resistance has always been a concern (Daniels and Hill 1952; Fleming 1945), TB has become increasingly drug resistant during this time, and it is now broadly accepted that the effective treatment of TB requires the development of new pharmaceutical agents that allow for shorter, simpler and more tolerable treatment regimens that can be used across a range of different contexts and settings (Stop TB Partnership 2006). Since the 1990s global efforts to overcome social and structural barriers to effective TB control have focused on the directly observed treatment short-course or DOTS strategy (World Health Organization 2006). However, it is now becoming clear that the reification of this simple standardised approach to TB diagnosis and treatment has harmed the development of locally appropriate programs. Indeed in some ways, DOTS has been in tension with, and, thereby, a hindrance to, on-the-ground efforts to deal with MDR-TB emergence (Keshavjee and Farmer 2012; Harper 2010). Experiences with implementing DOTS and our extensive knowledge of the biosocial and structural drivers of incidence and resistance tell us that a multilayered approach is necessary. Even as TB remains a disease of social disadvantage and deprivation, developing an effective armamentarium remains a pre-condition of sustainable progress in the fight against MDR-TB, especially in resource-poor and endemic settings (Zumla et al.

2014; Dheda et al. 2014).

Yet despite the desperate need for new TB medicines and new ways of avoiding resistance, the TB drug pipeline is still considered to be fragile and thin (Ma et al. 2010; Grosset, Singer, and Bishai 2012). While spending on pharmaceuticals has been the fastest growing segment of healthcare budgets in most countries for decades (Danzon and Nicholson 2012), most large pharmaceutical companies have now left the antibiotic discovery field altogether in favour of developing drugs for more lucrative chronic diseases. In this regard, it is sobering to realize that only sixteen drugs were developed between 1975 and 1999 for infectious diseases endemic in the world's poorest countries, including TB, malaria, Chagas Disease and others (Trouiller et al. 2002).

Even where they do exist, drug development and regulatory processes for TB are slow. For example, one new agent, *Bedaquiline* was first reported in *Nature* in 2005 but only approved by the FDA in December 2012. Many new drugs are repurposed raising questions about their increased susceptibility to resistance, and completely novel agents have limited safety data. There is also a translation gap between clinical trial efficacy and program effectiveness and evidence of "real world" safety. Indeed, it is arguable that rolling out medicines that may have significant adverse effects such as *bedaquiline* in the absence of adequate pharmacovigilance is a form of global malpractice. Compounding this, patent issues make the necessary combination studies difficult, further delaying whatever "real world" impact a new drug may have by years (Wallis 2013). And because research efforts are inevitably tied to pharmaceutical markets, the resulting culture of competition between industries, researchers, and institutions results in duplication of effort and data hoarding (So et al. 2012).

There are two possible reasons to explain the limited development of new pharmacotherapies to treat tuberculosis: the science is too hard and/or there is a lack of commercial incentive for innovation—i.e. there is a clear failure of the market to address a public good (Breitstein and Spigelman 2013; Iseman 2007; Pogge 2007, 2005; Theuretzbacher 2012). There is evidence to support both of these possibilities. With respect to the science, the widespread adoption of genomic-based methods of target discovery for new antimicrobial agents has had limited success (Boucher et al. 2009; Livermore et al. 2011). And with respect to the way in which markets fail to attend to clear public needs, the potential market for new TB drugs is not attractive enough commercially to stimulate a corporate appetite for the risks of funding research and development. Given the enormous global burden of disease, market size is clearly not the issue. Rather, the limiting factor is the relatively low price that the market can sustain. In this regard it is noteworthy that WHO recommends that TB drugs should be provided free of charge (World Health Organization 2006 9). The root cause of the inattention of markets to TB-related pharmacological research has been attributed both to poverty (insufficiently developed economies and mostly poor patients), and to intellectual property restrictions (patents), international trade agreements (e.g. TRIPS), and to systems of

research and research governance (Trouiller et al. 2002; Piddock 2012; Gathii 2005; Sonderholm 2010). Whatever the respective merits of these opposing arguments, the effect is the same.

Attempts to boost innovation

Proposed solutions to the lack of market incentive to address global unmet needs have come from within and outside the pharmaceutical industry and include both 'push' and 'pull' mechanisms that either seek to decouple the cost of research from the need for shareholder profit, or reinforce existing intellectual property protections. Push mechanisms generally support research by reducing the costs and risks of research and development through global funds, government grants, public / private partnerships and philanthropy. Other mechanisms include tax breaks for companies that undertake research on TB, or selectively fast-tracking regulatory approval by abridging or even scrapping regulatory requirements for demonstrating safety and efficacy (Piddock 2012).

Pull mechanisms support research by guaranteeing the viability of a market for a new drug through pre-purchase agreements (which effectively subsidise access for disadvantaged populations), patent extensions or 'wild-card' patent trades whereby the company is rewarded for developing a new treatment by getting to keep a patent on another product [i.e. a blockbuster drug] of their choosing for longer than would otherwise be permitted (Ravvin 2008). Other pull measures suggested include Pogge's (2012)model of graded compensation from a Health Impact Fund, with the amount of money awarded being based on analysis of the reduction of the global burden of the disease attributable to the new products. This model has three components: (i) any effective drugs developed to treat neglected diseases are to be free of IP restrictions, diminishing price exclusion and access problems; (ii) the developers are then rewarded from a health fund, in proportion to the impact of the new agent on the global burden of disease – thereby generating and incentive for innovation and effective administration; and, (iii) the fund is supported by developed nations – based on prudential concerns such as lower prices on all essential medications in all markets, the economic value of biomedical research, and increasing global capacity to respond to health emergencies.

Consistent with the history of pharmaceutical development push mechanisms have been the most subscribed, although pharmaceutical companies reportedly remain open to – or, less generously, are holding out for – highly commercially favourable pull mechanisms such as patent trade arrangements (Outterson, Samora, and Keller-Cuda 2007). Public-private partnerships such as the *Global TB Alliance,* the *Critical Path to TB Drug Regimens Initiative* and The Gates Foundation-funded *TB Drug Accelerator* have had some success in bringing new drugs/agents to market (Zumla et al. 2014). The *TB Alliance* funded the development of *Bedaquiline,* which was approved by the FDA in December 2012 (the first novel drug since Rifampacin 1967). *Delamanid* was approved by the European Medicines Agency in November 2013 – notably, both of these drugs were approved after only Phase 2b trials. The *Global TB*

Alliance is currently testing a 4-drug regimen for sensitive TB to reduce treatment periods from 6 to 4 months and testing bedaquiline in multi-agent combinations (Wraight 2012). Ten other drugs are in late stage clinical trials (although 6 of these are repurposed). There are also 10 candidate vaccines and 2 immunotherapeutic agents in late clinical trials (Abubakar et al. 2013).

However, while there clearly has been some success, both industry insiders and external analysts agree that current approaches to incentivising drug development are not sufficiently enticing to the pharmaceutical industry (Hamad 2010; Osborne 2013). The numbers support the view that industry commitment is patchy at best. Total research funding for TB has fallen between 2010 and 2013 from US$660 to US $620 million (Burki 2014), and pharmaceutical companies have reduced their input by 22 percent, such that the private sector now contributes less than 20 percent of total R +D funding. Much of the cost of development is already borne by the public – through funding basic science in universities and charitable research foundations (Garattini and Chalmers 2009). In addition, both push and pull mechanisms have met with prudential concerns, equity questions and competing consequentialist and libertarian objections, based on the erosion of established safety mechanisms and their potential to distort existing drug development pathways and pharmaceutical markets to produce perverse outcomes (Sonderholm 2010; Peterson, Hollis, and Pogge 2010). It seems, therefore, that existing approaches to overcoming market disinterest have had limited success and that we need new ways of conceptualising the problem of drug resistant TB.

Reformulating the problem

Leading experts point to recent progress in developing new agents, but agree that further effort is needed (Dheda et al. 2014; Zumla et al. 2014; Abubakar et al. 2013). We believe that this is where bioethics comes in, because it can offer important perspectives that are not tied to a particular solution and help us to keep what is ethically important in focus—promoting global equity by reducing poverty, optimising public health and preventing the spread of disease. Bioethics, as we understand it, is a field of critical inquiry characterised by methodological pluralism and capacity to identify and apply normative theories appropriate to the content and context of morally complex techno-social and socio-political issues (Dawson 2010; Bishop and Jotterand 2006). In Catherine Mills's (2010 145) terms, a bioethics grounded in the "lived-realities and ethical practice everyday life" can remind us that MDR and XDR-TB are primarily products of human agency – 'we have taken the curable and made it nearly incurable' – and that we are collectively responsible for finding a solution (Pogge 2005; Farmer and Gastneau Campos 2004; Upshur, Singh, and Ford 2009). More specifically, a critical bioethics can alert us to the possibility of more radical solutions to market disinterest, while at the same time helping us to balance the innovation imperative against the need to:

- address structural issues, such as lack of universal health coverage, employment and education—measures that are arguably more effective than any new drug;

- ensure that innovative drugs are regulated, reimbursed and administered in such a way that safety and efficacy are assured, and resistance to new agents does not develop (thereby further entrenching health inequities); and
- ensure that the needs of those currently infected with TB are not overlooked in the pursuit of longer term market and structural reforms.

Rebooting innovation

Existing approaches to enhancing innovation all start from assumptions that innovation must be market- rather than needs-driven (Williams 2012) and therefore all centre on either uncoupling the development of new pharmaceuticals and income from selling them (push mechanisms), or instituting measure that entrench profitable monopolies for private interests (pull mechanisms).

In this paper, we argue that what is needed is not simply pushes and pulls, but rather a radical 'rebooting' of drug development pathways (Shlaes et al. 2013). One alternative is to weaken the pharmaceutical industry's privileged position as a gatekeeper to innovation (which remains the case even in the context of the public-private partnerships described above) and instead find ways to attain broad institutional support for Open Science projects. These are large-scale enterprises that enable scientists and citizens to work through a free repository for biological and molecular data – such as that created by Collaborative Drug Discovery funded by NIH/BMGF, which has data on three hundred thousand compounds (Ekins and Williams 2014). Citizen led research strategies have so far proved effective in physics, astronomy, environmental sciences, and geology. This research could be supported by cheap/free-ware Apps for data mining and predictive modelling and publications devoted to TB could be free (Médecins Sans Frontières Access Campaign 2012).

This is not a new idea, but its realisation has been impeded by existing TRIPS system. As recently as 2012 *Médecins Sans Frontières* demanded, amongst other measures, the pooling of intellectual property to promote TB research (2012). The World Health Organization rejected the application in December 2013, even though it is widely recognized that without access to a large library of compounds, then the majority of both industry-led and Open Science-based innovation will inevitably remain restricted to target-based research strategies (Osborne 2013; So et al. 2012).

Another way to reboot innovation would be to institute new forms of taxation. In 2011 *Médecins Sans Frontières* called for a financial transaction tax (FTT) to support global health initiatives, such as funding TB diagnosis, treatment and drug development. MSF's call coincided with the proposal at the European Union for a FTT to create a fund to bailout the banking sector in case of another global financial crisis. The idea of the FTT, also known as the 'Robin Hood Tax', is to impose a small tax (between 0.01% and 0.1%) on financial transactions between financial institutions. MSF argued that the accumulated funds should be used to "bailout"

global health. Although widely popular among EU citizens, only 11 member states agreed to participant and the proposal is currently stalled.

The popularity of FTTs as measure to address global inequality is further reflected in the unexpected celebration of Thomas Piketty's *Capital in the 21st Century*. Piketty argues that wealth inequality in the 21st century might reach or surpass the oligarchic levels of the 19th century. Following earlier proposals from economists such as James Tobin and Joseph Stiglitz, Piketty seeks to democratise wealth via 'progressive global tax on capital', he claims '[s]uch a tax would provide a way to avoid an endless inegalitarian spiral and to control the worrisome dynamics of global capital concentration' (Piketty 2014 360). The implementation of this tax would require unprecedented international cooperation, which Piketty is not optimistic about. However, in acknowledging the utopian features of his proposal, Piketty suggests it can be used as an aspirational ideal and reference point to measure alternate proposals.

Bioethicists could draw on the current popularity of Piketty among publics and politicians to call for a global tax that targets the pharmaceutical industry. The tax would be hypothecated to attend to therapeutic and structural needs of MDR and XDR-TB. A global tax on Pharma, whether the target is revenue or non-TB R&D, would produce a sizeable fund that could be put towards development of MDR and XDR-TB therapies as well as providing assistance and incentives to developing countries for structural reform in education, infrastructure and healthcare. Additional levies could be placed on tissue and biological specimen exportation and a reputational tithe on researchers in high income nations who get tenure on data derived from low income nations.

While the pharmaceutical industry might not embrace such a proposal, a number of factors could see it gain some traction where the FTT did not. First, unlike the FTT, the tax would be global and therefore would not affect competition. Pharmaceutical companies could not remove themselves from one tax jurisdiction and move to a more favourable one. Second, a global tax might limit the opportunities for pharmaceutical companies to seek tax havens—something that has been enormously frustrating to countries like the United States. Third, a global pharma tax would be consistent with moves to reduce global wealth inequality and increase social justice. In this regard it is noteworthy that citizens within the EU gave significant support to the FTT, suggesting that a wider global population may also be supportive of a tax scheme to address TB and global health inequalities.

Beyond innovation

In addition to prompting radical thinking about global markets in pharmaceuticals, when bioethics is grounded in peoples' lived realities it also reminds us that biomedical innovation is only a partial solution to the problem of drug-resistant TB. Upshur has argued that the emergence of XDR-TB is a rupture in the narrative of biomedical progress that dominates medicine and bioethics (Upshur, Singh, and Ford

2009). It is thus necessary to keep in mind the limits of positivistic scientific solutions to social, political and economic problems and step beyond the bounded reasoning of market mechanisms and individually oriented interventions. Therefore, whether funds for TB are derived from a Piketty-like tax, the MSF's FTT or crowd sourced, it is important that they be used to develop new therapeutic agents, locally appropriate mechanisms of implementation *and* address poverty and structural factors such as lack of universal access to health care, education and housing. To do this, we may consider incentivising innovation in other domains such as environmental engineering, housing design and urban planning, with a focus on mitigating poverty and preventing the spread of infection.

It is also important to bear in mind that market disinterest extends to the ways in which medicines are paid for, and the ways in which they are prescribed. Everyone accepts, in principle, that new agents and regimens for TB must be accessible and affordable to those who need them, and administered appropriately to avoid resistance. But support for programs that aim to achieve this are not priorities for companies who simply want to get their products to market, and are also highly dependent upon political and social climates.

At the same time, a balance must be found between the need to improve treatment of patients who are currently infected with TB, and the need to research and develop new agents, and control access to the most effective regimens so that resistance does not develop (Kesselheim and Outterson 2010). This is a delicate situation. For if we do not move beyond DOTS and fail to adequately attend to the economic and structural conditions that enable effective administration of therapeutic agents, it is likely that XDR-TB will develop a resistance to new therapies and result in a situation in which pathogens have established resistance to all available anti-microbials (Raviglione 2006). However, if new therapies are developed, but we refuse to administer them until adequate infrastructure is established, then we abandon those currently infected to suffering and death (Farmer 2003 199).

Conclusion

If we are to address the problem of drug resistant TB, then we need to be willing to engage in a more radical critique of the problem than is currently offered. In particular, we need to focus not simply on market-driven models of innovation and anti-microbial solutions to emergent and re-emergent infections such as TB. We also need to address poverty and the structural factors that entrench inequalities—thus moving beyond the orthodox medical/public health frame of reference. At the same time, we need to ensure new medicines are safe, available to those who need them, and administered in such a way that resistance does not develop, all while considering the needs of existing patients. Bioethics can help in this complex situation, but only if it radically rejects the notion that MDR-TB is 'business as usual'.

Disclosure of Competing Interests and Funding
No competing interests to declare. This research was in part funded by the NHMRC CRE for TB Control [CRE1043225]. Funding agencies had no role in study design, data collection, analysis and interpretation, or in the writing of the article.

References

Abubakar, I., M. Zignol, D. Falzon, M. Raviglione, L. Ditiu, S. Masham, I. Adetifa, N. Ford, H. Cox, and S. D. Lawn. 2013. "Drug-resistant tuberculosis: time for visionary political leadership." *The Lancet infectious diseases* no. 13 (6):529-539.

Bishop, J. P., and F. Jotterand. 2006. "Bioethics as biopolitics." *Journal of Medicine and Philosophy* no. 31 (3):205-212.

Boucher, H. W., G. H. Talbot, J. S. Bradley, J. E. Edwards, D. Gilbert, L. B. Rice, M. Scheld, B. Spellberg, and J. Bartlett. 2009. "Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America." *Clinical Infectious Diseases* no. 48 (1):1-12.

Breitstein, J., and M. Spigelman. 2013. "The Role of Product Development Partnerships in Advancing the Development of Drugs for Unmet Needs." *Clin Pharmacol Ther* no. 93 (6):468-470. doi: 10.1038/clpt.2013.53.

Burki, T. 2014. "Improving the health of the tuberculosis drug pipeline." *The Lancet Infectious Diseases* no. 14 (2):102-103.

Center for Disease Control. 2013. TB Elimination: Extensively Drug-Resistant Tuberculosis (XDR TB). In *CDC Fact sheet*. http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm: Center for Disease Control.

Daniels, M., and A. B. Hill. 1952. "Chemotherapy of pulmonary tuberculosis in young adults." *British medical journal* no. 1 (4769):1162.

Danzon, P. M., and S. Nicholson. 2012. "Introduction." In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, edited by P.M. Danzon and S. Nicholson, 1-19. Oxford University Press, USA.

Dawson, A. 2010. "The future of bioethics: three dogmas and a cup of hemlock." *Bioethics* no. 24 (5):218-225.

Denholm, J., J. Amon, R. O'Brien, A. Narain, S. Kim, A. El Sony, and M. Edginton. 2014. "Attitudes towards involuntary incarceration for tuberculosis: a survey of Union members." *The International Journal of Tuberculosis and Lung Disease* no. 18 (2):155-159.

Dheda, K., T. Gumbo, N. R. Gandhi, M. Murray, G. Theron, Z. Udwadia, G. B. Migliori, and R. Warren. 2014. "Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis." *The Lancet Respiratory Medicine* no. 2 (4):321-338.

Ekins, S., and A. J. Williams. 2014. "Curing TB with open science." *Tuberculosis* no. 94 (2):183-185.

Farmer, P. 2003. *Pathologies of power: Health, human rights, and the new war on the poor*. Vol. 444. Berkeley: University of California Press.
Farmer, P., and N. Gastneau Campos. 2004. "New Malaise: Bioethics and Human Rights in the Global Era." *The Journal of Law, Medicine & Ethics* no. 32 (2):243-251.
Fleming, A. 1945. *Penicillin - Nobel Lecture*. Nobel Media [cited 12 June 2014. Available from http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.html.
Garattini, S., and I. Chalmers. 2009. "Patients and the public deserve big changes in evaluation of drugs." *BMJ* no. 338. doi: 10.1136/bmj.b1025.
Gathii, J. T. 2005. "Third world perspectives on global pharmaceutical access." In *Ethics and the Pharmaceutical Industry in the 21st Century*, 336-351. Cambridge University Press.
Grosset, J. H., T. G. Singer, and W. R. Bishai. 2012. "New drugs for the treatment of tuberculosis: hope and reality " *The International Journal of Tuberculosis and Lung Disease* no. 16 (8):1005-1014. doi: 10.5588/ijtld.12.0277.
Hamad, B. 2010. "The antibiotics market." *Nature Reviews Drug Discovery* no. 9 (9):675-676.
Harper, I. 2010. "Extreme condition, extreme measures? Compliance, drug resistance, and the control of tuberculosis." *Anthropology & Medicine* no. 17 (2):201-214. doi: 10.1080/13648470.2010.493606.
Hughes, J., H. Cox, and N. Ford. 2012. "Sanatoria for drug-resistant tuberculosis: an outdated response." *The Lancet* no. 379 (9832):2148.
Iseman, M. 2007. "Extensively drug-resistant Mycobacterium tuberculosis: Charles Darwin would understand." *Clinical Infectious Diseases* no. 45 (11):1415–6.
Keshavjee, S., and P. E. Farmer. 2012. "Tuberculosis, Drug Resistance, and the History of Modern Medicine." *New England Journal of Medicine* no. 367 (10):931-936. doi: doi:10.1056/NEJMra1205429.
Kesselheim, A. S., and K. Outterson. 2010. "Fighting Antibiotic Resistance: Marrying New Financial Incentives To Meeting Public Health Goals." *Health Affairs* no. 29 (9):1689-1696. doi: 10.1377/hlthaff.2009.0439.
Livermore, D. M., M. Blaser, O. Carrs, G. Cassell, N. Fishman, R. Guidos, S. Levy, J. Powers, R. Norrby, and G. Tillotson. 2011. "Discovery research: the scientific challenge of finding new antibiotics." *Journal of antimicrobial chemotherapy* no. 66 (9):1941-1944.
Ma, Z., C. Lienhardt, H. McIlleron, A. J. Nunn, and X. Wang. 2010. "Global tuberculosis drug development pipeline: the need and the reality." *The Lancet* no. 375 (9731):2100-2109.
Médecins Sans Frontières Access Campaign. 2012. *Test Me, Treat Me: A Drug-Resistant TB Manifesto*. Médecins Sans Frontières [cited 12 June 2014]. Available from https://www.msfaccess.org/TBmanifesto/.
Mills, C. 2010. "Continental Philosophy and Bioethics." *Journal of Bioethical Inquiry* no. 7 (2):145-148.
Osborne, R. 2013. "First novel anti-tuberculosis drug in 40 years." *Nature Biotechnology* no. 31 (2):89-91.

Outterson, K., J. B. Samora, and K. Keller-Cuda. 2007. "Will longer antimicrobial patents improve global public health?" *The Lancet infectious diseases* no. 7 (8):559-566.
Peterson, M., A. Hollis, and T. Pogge. 2010. "A Critique in Need of Critique." *Public Health Ethics* no. 3 (2):178-185. doi: 10.1093/phe/php037.
Piddock, L. J. V. 2012. "The crisis of no new antibiotics—what is the way forward?" *Lancet Infectious Disease* no. 12:249-53.
Piketty, T. 2014. *Capital in the Twenty-first Century*. Translated by Arthur Goldhammer: Harvard University Press.
Pogge, T. 2005. "Human Rights and Global Health: A Research Program." *Metaphilosophy* no. 36 (1-2):182-209.
Pogge, T. 2007. "Montreal Statement on the human right to essential medicines." *Cambridge Quarterly on Healthcare Ethics* no. 16 (1):97-108.
Pogge, T. 2012. "The Health Impact Fund: Enhancing Justice and Efficiency in Global Health." *Journal of Human Development and Capabilities* no. 13 (4):537-559. doi: 10.1080/19452829.2012.703172.
Pooran, A., E. Pieterson, M. Davids, G. Theron, and K. Dheda. 2013. "What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa?" *PloS one* no. 8 (1):e54587.
Raviglione, M. 2006. "XDR-TB: entering the post-antibiotic era? [Editorial]." *The International Journal of Tuberculosis and Lung Disease* no. 10 (11):1185-1187.
Ravvin, M. 2008. "Incentivizing Access and Innovation for Essential Medicines: A Survey of the Problem and Proposed Solutions." *Public Health Ethics* no. 1 (2):110-123. doi: 10.1093/phe/phn017.
Selgelid, M. J. 2008. "Ethics, Tuberculosis and Globalization." *Public Health Ethics* no. 1 (1):10-20. doi: 10.1093/phe/phn001.
Shlaes, D. M., D. Sahm, C. Opiela, and B. Spellberg. 2013. "The FDA Reboot of Antibiotic Development." *Antimicrobial Agents and Chemotherapy* no. 57 (10):4605-4607.
So, A. D., Q. Ruiz-Esparza, N. Gupta, and O. Cars. 2012. "3Rs for innovating novel antibiotics: sharing resources, risks, and rewards." *BMJ-British Medical Journal* no. 344 (3):e1782.
Sonderholm, J. 2010. "Ethical Issues Surrounding Intellectual Property Rights." *Philosophy Compass* no. 5 (12):1107-1115. doi: 10.1111/j.1747-9991.2010.00358.x.
Stop TB Partnership. 2006. The Global Plan to Stop TB. Geneva, Switzerland World Health Organization.
Theuretzbacher, U. 2012. "Accelerating resistance, inadequate antibacterial drug pipelines and international responses." *International Journal of Antimicrobial Agents* no. 39:295-299.
Trouiller, P., P. Olliaro, E. Torreele, J. Orbinski, R. Laing, and N. Ford. 2002. "Drug development for neglected diseases: a deficient market and a public-health policy failure." *The Lancet* no. 359 (9324):2188-2194.
Upshur, R., J. Singh, and N. Ford. 2009. "Apocalypse or redemption: responding to extensively drug-resistant tuberculosis." *Bulletin of the World Health Organization* no. 87 (6):481-483.

Wallis, R. S. 2013. "Sustainable Tuberculosis Drug Development." *Clinical Infectious Disease* no. 56 (1):106-13.

Williams, O. D. 2012. "Access to medicines, market failure and market intervention: A tale of two regimes." *Global Public Health* no. 7 (sup2):S127-S143. doi: 10.1080/17441692.2012.725753.

World Health Organization. 2006. *The Stop TB Strategy: Building on and Enhancing DOTS to Meet the TB-related Millennium Development Goals*. Geneva: World Health Organization.

World Health Organization. 2012. Global tuberculosis report 2012. Geneva: World Health Organization.

Wraight, S. 2012. "The future of TB treatment: trial shows potential for a new TB drug." *Future Microbiol* no. 7 (9):1033.

Zumla, A. I., S. H. Gillespie, M. Hoelscher, P. P. J. Philips, S. T. Cole, I. Abubakar, T. D. McHugh, M. Schito, M. Maeurer, and A. J. Nunn. 2014. "New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects." *The Lancet Infectious Diseases* no. 14 (4):327-340.