Precarious connections: Making therapeutic production happen for malaria and tuberculosis

Susan Craddock

University of Minnesota, Department of Gender, Women, and Sexuality Studies, The Institute for Global Studies, Minneapolis, MN 55455, USA

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ABSTRACT

The One Health Movement has been a primary advocate for collaboration across disciplinary and organizational sectors in the study of infectious diseases. There is potentially much to be gained by incorporating the interrelations of animal and human ecosystems, as well as the expertise of veterinary, medical, and public health practitioners. Too often, however, the idea rather than the realities of collaboration become valorized within One Health approaches. Paying little or no attention to the motivations, ontologies, and politics of collaborative arrangements, however, is a critical mistake, one that diminishes considerably One Health framework explanatory powers. Using Anna Tsing’s framework of friction, in this paper I take the examples of malaria and tuberculosis pharmaceuticals collaborations, often called Product Development Partnerships, to argue for the need to attend to the conditions under which collaborations across divergent disciplines, geographies, organizations, and institutions might work productively and when they do not.

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1. Introduction

Concepts of connectivity have held traction in global health approaches for a while now. The One Health Movement is a recent example of this, with its call to recognize the interrelations among animal, ecosystem, and human health; and for its claim that greater collaboration among veterinary, medical, public health, and — to a lesser extent — social science arenas are essential to “ensure well-being within human, animal, and ecosystem interfaces” (Papadopoulos and Wilmer, 2011, 1). Undergirding this interface of the animal, human, and environment is the broader notion also maintained within the global health field writ large that disease impact in one part of the world ultimately impacts the rest of the world. In this paper, I want to take malaria and tuberculosis as infectious diseases that illustrate on the one hand the promise One Health holds for more effective interventions into any number of diseases by highlighting the need for collaborative approaches, and for mitigating the balkanization of scientific practice within disciplines and institutions. On the other hand, malaria and tuberculosis illustrate as well the limits to One Health’s approach given how connectivity plays out across divergent nonprofit, philanthropic, and industry actors, and within larger contexts of inequitable global health politics and finance.

The kind of connectivity that One Health espouses, and its insistence on bringing to bear upon a particular disease or health problem the expertise of multiple partners, suggests the kinds of possibilities that Anna Lowenhaupt Tsing discusses in her book Friction: An Ethnography of Global Connection (2005). Focusing on her case study of logging in Indonesia, Tsing discusses the conditions under which actors who typically maintain competing if not conflicting agendas might come together to work tentatively but collaboratively towards a common goal. These conditions are unpredictable and not necessarily lasting, yet one of her points is that for the duration of the collaborative moment, the ‘friction’ of having very different actors trying to work together can be highly productive if not transformative because it can be “the stuff of emergent politics” making “new objects and agents possible” as it creates the political, scientific, or financial conditions to move beyond entrenched ways of seeing and responding (2005, 247).

Yet Tsing also recognizes that these collaborations hold within their very infrastructure the threat of cooptation as funders or international organizations wield their inequitable degrees of power, and when the ideas of community — or diseases — get ‘imagined and imposed’ by outside actors with particular, and particularly entrenched, visions (ibid, 264). In the case studies I present below, I argue that friction is indeed productive for the most part, yet the end goals of the actors in collaborations focused on malaria and tuberculosis therapeutic development can create a friction that stalls rather than accelerates any movement towards emergent...
politics. Positive achievements still occur, yet the end result is unpredictable because the political, financial, and ontological relations bringing actors together are shifting as well as potentially incompatible. Tsing’s ability to see both the productive potential of ‘global connection’ but also the fundamental precariousness of having actors of divergent scale, power, and vision is key. The One Health movement only sees the productive side minus the precariousness of connection and collaboration, and this is a critical mistake.

In particular, One Health’s call to collaborate across fields and populations sounds a peculiarly flattened note despite the compelling reasons for initiating it. Absent is any recognition of the stakes creating parameters of institutional or individual action, and dictating their often competing rather than coordinating agendas. In One Health’s focus on infectious diseases, for example, discussions of connections between humans, animals, and vectors (where relevant) unfold with little to no reference to the social or political forces shaping specific coordinates of interaction, or the highly uneven geopolitical fields within which understandings of, and responses to, infectious disease outbreaks occur. Indeed, it is precisely in times of alarming disease outbreak that this unevenness can become much more accentuated given that the stakes of who gets what resources, who appears responsible for initial transmission, and which borders are the most threatened become immeasurably higher. These stakes and their consequences were evident during the recent SARS and H1N1 epidemics, for example, despite the outbreaks providing further momentum for the One Health movement (cf Zinnstak et al. 2012).

For these kinds of ‘crossover diseases’ – that is, outbreaks threatening both the global North and South – coordination of agencies and surveillance systems was accomplished in part because it was in the direct interests of Canada, the US, and the EU to galvanize action in efforts to mitigate impact of these diseases within their respective borders. Though it is beyond the scope of this paper to elaborate the problems inhering in these efforts, it is important to note that institutional, surveillance, professional, and governmental ‘coordination’ at times supported, and at other times did nothing to alleviate, misguided public policies, racialized scapegoating, and highly uneven allocations of resources (cf Ali and Keil, 2008; Giles Vernick and Craddock, 2010). It cannot be presumed, in other words, that partnering always generates mutual understandings, or more equitable and effective responses.

The efforts of One Health to expand from large-scale infectious diseases to food security, zoonotic diseases, and neglected diseases including malaria and tuberculosis are commendable given the movement’s encompassing approach (Zinnstak et al., 2011), but in addition to the concerns raised above is the additional concern that collaboration and coordination for many of these issues become more difficult in the absence of adequate financing. Those diseases and threats to wellbeing that do not pose risks to the majority of the world – that in fact belie the One Health label in impacting only particular and predominantly low-income regions – are precisely those that struggle consistently to garner a level of resources that would enable cross-professional or institutional attention, much less effective responses. Zinnstak et al. (ibid, 155) in discussing ongoing challenges for the One Health movement, question why for example there still is no effective new vaccine for tuberculosis.

The discussion below will go towards answering that and other questions regarding some current responses to tuberculosis and malaria. I focus specifically on Product Development Partnerships in Global Health, dynamic collaborations among nonprofit organizations, academic researchers, funders such as the Bill and Melinda Gates Foundation, and pharmaceutical companies to develop new therapies for infectious diseases such as tuberculosis and malaria that have seen few or no new drugs or vaccines in decades. For this paper and the larger book project of which it is a part, I utilize dozens of interviews I conducted with nonprofit officers, representatives of the Gates Foundation, pharmaceutical industry researchers, scientists, and WHO officials, among others. I also draw from news releases generated by the nonprofits and pharmaceutical companies, and from conversations, formal interviews, and notes taken at international conferences on tuberculosis, vaccines, and malaria. Finally, I draw from a clinical trial site visit outside of Cape Town, South Africa. Using Tsing’s framework of global friction, I discuss these partnerships and how they exemplify why collaboration is necessary in responding to many infectious diseases, but why it remains nevertheless precarious in accomplishing what it sets out to do. In what follows, I first highlight a few of the tuberculosis and malaria PDP initiatives before elaborating on the variable nature of collaborative frictions inhering in endeavors to develop new therapeutics for these diseases.

2. Tuberculosis

The statistics on tuberculosis are compelling. An estimated nine million new or relapsed cases occur every year, and in 2012 around 1.4 million people died of the disease (WHO, 2012). High rates of AIDS in turn fuel higher rates of tuberculosis: of the 13.7 million estimated total number of tuberculosis cases worldwide in 2007, an estimated 687,000 were co-infected with HIV (Jassal and Bishai, 2010). Though effective drug therapy exists and is inexpensive, it takes six to nine months to complete – a factor that in part explains lower rates of adherence and the growth of multidrug resistant tuberculosis. A vaccine has existed for decades, but is ineffective outside of pulmonary tuberculosis in infants. For these reasons, product development partnerships, or PDPs, emerged in the early 2000s to develop new tuberculosis vaccines and drug regimens for the first time in over four decades. The Global Alliance for Tuberculosis Drug Development (TB Alliance) and Aeras are the principle nonprofit organizations spearheading efforts to generate new drug and vaccine candidates, respectively; and they in turn form various collaborations with academic and industry partners with funding primarily from the Bill and Melinda Gates Foundation, but also USAID, the Wellcome Trust, government donors, and others.

On the positive side, these collaborations have succeeded in getting numerous compounds and vaccines in the research and development pipeline where ten or twelve years ago there were none at all. Most of these are in the preclinical phase – that is, just coming out of the laboratory or in the animal testing phase; some however have reached Phase II clinical trials – mid-level trials that test the efficacy and safety of new therapies in individuals at high risk of tuberculosis (in the case of vaccine testing) or who have been diagnosed with the disease (in the case of drugs). The exact way the partnerships work varies. Aeras and TB Alliance both proactively seek partners from universities, pharmaceutical companies, biotech firms, governments, or foundations who display either promising research discoveries or relevant funding priorities; but individuals from these sectors also approach Aeras and TB Alliance when they need particular kinds of expertise or financial subsidization for moving discoveries down the development pipeline. The Gates Foundation in particulargalvanized both TB Alliance and Aeras into being, shaping their mandates for drug and vaccine development and generously funding their efforts. Despite their Gates-driven parameters, the relative novelty of what PDPs are trying to accomplish and their departure from the highly privatized norms of therapeutic production create latitude for greater malleability in the structural and qualitative architecture of collaborations. Every partnership that Aeras or TB Alliance forges differs to fit the particularities of each partner, the products
themselves, the nature of the pathogen, and variant patenting regimes.

A point that many interviewees mentioned as a positive feature of both Aeras and TB Alliance is that these organizations bring scientists of varying disciplinary and institutional affiliations together in the same room — or the same laboratory, perhaps more accurately. Where scientists working for industry and even in academia tend to work in silos, Aeras and TB Alliance facilitate cross-disciplinary communications that together become larger than the sum of their parts in their capacity to generate new technical and logistical scientific understandings. This facet of the current tuberculosis drug and vaccine production landscape perhaps best illustrates what one Health proponents hope to achieve — a deeper understanding of any particular arena of scientific intervention gained through cross-scientific communication. As noted by Stephen Gillespie of the University of St Andrews and head of the REMox trials, PDPs like Aeras and TB Alliance “change the complexity of science” by transforming the landscape of scientific practice to ‘make the good science possible’ by focusing and funding research. At the meeting outside of Cape Town, South Africa where TB Alliance emerged, funders and researchers coalesced around the formation of the Alliance and more critically, according to Gillespie, gained a sense of purpose: for the first time in decades, with scientists as well as funders coming together to focus on the same problem, the tuberculosis research community’s efforts had the potential to result in a product rather than simply another academic paper. They had the possibility of impacting millions of lives (Gillespie, 2013).

This second point of not just bringing scientists together, but bringing funding together with scientists, is thus key. Some of what TB Alliance or Aeras does is initiated internally. But part of what both organizations also do is to provide funding for academic or industry projects that stalled somewhere in the pipeline because there was no further funding to develop them. For academia, there simply is inadequate funding to take promising candidates through enormously expensive late-stage clinical trials and beyond. In industry, compounds or vaccine candidates for diseases like tuberculosis or malaria may end up in pharmaceutical company portfolios as a result of mergers with smaller biotech or pharmaceutical companies that specialized in niche markets. Once acquired, however, these compounds and vaccine candidates are usually left dormant given their lack of potential to earn the minimum level returns on investments demanded by industry shareholders. Funding from TB Alliance or Aeras thus becomes the redress to dormancy and stagnation.

The results of scientific and financial convergence, as suggested above, have been tentatively positive. Though Aeras’s most advanced vaccine ultimately failed in Phase IIb trials, it nonetheless signaled success in terms of the ability of scientists, donors, biotech, and Aeras to advance a vaccine candidate in collaboration. The vaccine was developed by Dr. Helen McShane of Oxford University, who partnered with a small biotech firm, Emergent Biosolutions, to use one of their vaccine ‘platforms,’ or solutions anchoring the basic components of the vaccine. In 2001 Dr. McShane received funding from the Wellcome Institute to move the vaccine into early clinical trials, and by 2005, she partnered with the South African Tuberculosis Vaccine Initiative (SATVI), part of the University of Cape Town, to move clinical trials to individuals more commensurate with the targeted population of the vaccine (2012).

Beyond this stage, however, the difficulty finding funders for larger, more expensive Phase II and especially Phase III clinical trials has resulted in the designation of this point in research and development the ‘valley of death.’ But as Steve Lockhart of Emergent suggested, it is not just scaled-up funding that is logistically difficult to find; it is that funders will not support further trials unless they see the potential to scale up production of the vaccine for eventual rollout in the event of successful results. In the case of tuberculosis, this means the capacity to manufacture upwards of one hundred million doses of vaccine a year to capture the global annual rate of babies born in higher burden countries (2012). Oxford and Emergent Biosolutions then joined with a French pharmaceutical company, Vivalis, to use their patented duck embryo cell line which would better enable scaling up of vaccine manufacturing, and subsequently Aeras and Wellcome agreed to fund Phase IIb trials.

Since that vaccine’s failure, Aeras has focused on other candidates in its pipeline and the partners involved with these particular candidates. One of them involves a co-produced vaccine between Aeras and Crucell, now part of Johnson and Johnson, called Crucell Ad35/Aeras-402, currently in Phase Ila and IIb trials in both infants and adults. Another is a collaboration with GlaxoSmithKline and its vaccine candidate, M72, due to start testing two different doses in Phase IIb trials in healthy adults living in endemic countries (clinicaltrials.gov; aeras.org). A third, just announced in a November 8, 2013 press release, involves a collaboration with the Danish Statens Serum Institute, an “international research, production, and service enterprise” dedicated to vaccine and other biologics research and production (ssi.dk; aeras.org).

Like its vaccine counterpart, TB Alliance has compound candidates at all stages of research and development, but its recent emphasis has moved from testing individual new drugs to testing drug combinations. This makes sense for the disease given that, like HIV, tuberculosis requires a drug regimen to clear the body of bacteria. The most advanced of its combination trials substitutes the drug Moxifloxacin, owned by Bayer and already approved for other indications, for two first-line tuberculosis drugs in two separate arms, against a control arm taking the standard first-line drug regimen. The two moxifloxacin-containing arms take the regimen for four months against the control arm’s six month regimen, in hopes that one or both of these arms will result in a shorter and even more effective course of treatment.

This is a Phase III trial being carried out in forty-eight sites across nine countries in drug-susceptible (i.e., not drug-resistant or multi-drug resistant) tuberculosis, with TB Alliance and Bayer also in collaboration with University College London, the Gates Foundation, the European and Developing Countries Trials Partnership, NIH, and the Medical Research Council (tballiance.org). As indicated by Jan Gheuens, the Deputy Director for Tuberculosis Drugs for the Gates Foundation, funding for late-stage clinical trials has to be thought of flexibly — that is, Gates writes the lions’ share of the check for supporting the trials, but NIH support comes from having already developed several of the trial sites through their Aids Clinical Trials Group, while Bayer makes in-kind contributions worth several millions of dollars through safety reporting, making blisters, producing placebos, and providing moxifloxacin free of charge for the trials (personal communication 2013).

TB Alliance is also testing several other regimens in earlier-stage clinical trials, recognizing that the REMox trials are not meant for those with MDR-TB nor will they work for HIV positive individuals because of negative drug interactions. New Combination-002 is a Phase II trial testing Pa824, a drug developed by TB Alliance, with Moxifloxacin and Pyrazinamide, an already-established tuberculosis drug. Because Pa824 uses a new mechanism of action against tuberculosis, these trials are enrolling individuals with both drug-sensitive and multi-drug resistant tuberculosis. In fact, as explained by Ann Gardner, TB Alliance’s Vice President for Market Access, drugs with new mechanisms of action — that is, new methods of killing or preventing replication of the tuberculosis bacteria — de facto have the capacity to make irrelevant the whole concept of drug-resistant tuberculosis (2011). NC-002 thus hopes to
show not only success in treating those with both multi-drug resistant and drug susceptible tuberculosis, but to be able to harmonize treatment for both in a four-month, three-drug regimen (tballiance.org). Currently, those with multi-drug resistant tuberculosis take up to twenty-seven pills a day as well as an injectable drug for eighteen to twenty-four months, and often endure severe and irreversible side effects.

3. Malaria

Malaria's history of public health response is often divided into epochs describing particular approaches and whether they aimed for mitigating or eradicating the disease. Like tuberculosis, though, a period of retrenchment in the latter part of the 20th century resulted in resurgence and its designation as neglected (Packard, 2007; Webb, 2009; Reusch et al., 2010). According to the WHO, in 2010 there were an estimated 219 million cases of malaria and an estimated 660,000 deaths (www.who.int/mediacentre/factsheets).

Galvanized attention to infectious disease scourges in recent years has also meant that malaria — like tuberculosis — has seen the multiplication of partnerships addressing the development of new therapies and vaccines, partnerships that include the PATH Malaria Vaccine Initiative (MVI), and the Doctors Without Borders offshoot organization, Drugs for Neglected Diseases initiative (DNDi).

As a self-described 'virtual,' 'patients' needs-driven' research and development organization (Wells et al., 2013, 1), DNDi “does not conduct research but instead capitalizes on existing fragmented R&D [research and development] capacity, complementing it with additional expertise as needed” (Pécoul et al., 2008, 82). Consequently, one of DNDi’s projects was the possibility of creating a fixed dose combination of two existing malaria drugs, artesunate (AS) and amodiaquine (AQ). One of the persistent problems in intervention efforts for malaria is that of drug resistance. In 2001, the WHO responded to increasing evidence of chloroquine resistance by recommending the worldwide abandonment of chloroquine in favor of artemisinin-based combination therapies for falciparum malaria. By 2006 WHO had developed guidelines for the use of artemisinin-based combination therapies in all countries with malaria burdens, and in fixed dose combinations where possible (Pécoul et al., 2008). Artesunate is one of several quasin-synthetic analogs of artesemia, a longstanding and highly potent Chinese herbal cure for malaria. Artemisinin derivatives like artesunate quickly clear symptoms and parasites from the body, but also clear out of the body quickly; thus they are typically used in combination with a slower-acting drug to continue clearing malaria parasites over three days of treatment (Wells et al., 2013, 2).

With the new guidelines, DNDi’s mission in the field of malaria was to develop two fixed-dose artemisinin-based combination therapies for international registration. DNDi thought ASAQ optimal for countries in Africa and Asia where resistance to amodiaquine was low but malaria burdens high (Pécoul et al., 2008, 77); evidence had also been compiled since 1998 that this combination was effective against falciparum malaria among several African countries (Pécoul et al., 2008). Indeed, DNDi had at their advantage multiple studies which had already been conducted for AS and AQ both in loose and fixed dose combinations: all studies, encompassing over 10,000 patients, showed efficacy of both forms of ASAQ (ibid). The agenda, then, was to make the fixed-dose combination that could cover all age ranges, simplify the drug regimen with a once-a-day pill, lessen the risk of resistance, strengthen compliance, be affordable and accessible, easy for clinicians to implement, and high quality (Kiechel, 2013; Pécoul et al., 2008).

To do that DNDi partnered with academic institutions in Burkina Faso, Thailand, France, England, and Malaysia for technology assistance and 'relevant assets' (Pécoul et al., 2008), while getting sanofi-aventis on board by 2004. Sanofi-aventis in turn carried out further pre-clinical and clinical studies using the existing data on the drug combination (ibid) and using its own as well as European and UK government funds. In what DNDi touts as unprecedented, sanofi-aventis and DNDi signed an agreement that no patent protection would be sought over the ASAQ combination pill, and a non-exclusivity agreement was also signed so that third-parties could submit 'simplified applications' to produce generic versions of the drug (ibid). By 2007, ASAQ was registered in seventeen African countries, and marketed in both public and private sectors. Sanofi-aventis is paying DNDi 3% of the private sector earnings over seven years, and DNDi uses this money to further lower the cost of ASAQ in the public sector (ibid).

The second fixed-dose combination, artesunate and mefloquine, came about with a different set of partners. Originally discovered by the Walter Reed Army Institute of Research, mefloquine was effective against malaria but expensive to produce until the WHO's Special Program on Research and Training in Tropical Diseases worked with Hoffman La-Roche to develop and test a cheaper synthetic version, registered in 1984. Thailand in turn effectively used mefloquine in combination with artesunate, and further testing of this combination showed good results for Latin America and Southeast Asia. The WHO subsequently suggested producing a fixed dosage formulation of ASMQ to be used over three days (Wells et al., 2013), so DNDi joined with several universities and research institutes, the WHO, and the Brazilian-owned pharmaceutical company Farmanguinhos/Fiocruz to create the Fixed-dose Artesunate-based Combination Therapy (FACT) consortium. Analytical and quality control methods, toxicology, and testing were all conducted among the partners, while Farmanguinhos undertook finding the formulation to scale up manufacturing. The combination was registered in Brazil in 2008 as an alternative to first-line treatment of uncomplicated falciparum malaria; but to make it more accessible in Southeast Asia a technology transfer agreement was negotiated in 2009 between Farmanguinhos, and the Indian pharmaceutical company, Cipla. So far ASMQ is registered in Malaysia and is going through registration processes in other Southeast Asian countries and the Western Pacific (ibid).

4. Social politics of friction

If following a One Health model, the assessment of PDPs would stop at seeing their promise, well enough evidenced in the number of vaccine and drug candidates populating an research and development pipeline that was empty a mere twelve years ago; and in the widespread acknowledgment from those involved in PDPs that better science happens with collaboration across scientific disciplines, with environments less constrained by the micromanagement and timelines typical of industry (Firestone, 2011), and with sufficient funding to make research goals potentially turn into products helping millions of lives. PDPs also produce agglomerative effects in the capacity building that happens around clinical trial sites, laboratories, vaccine and drug manufacturing facilities, contract research organizations, universities, and research institutes. Even regulatory innovations are happening because PDPs do things differently: the FDA has now agreed to approve drug regimens rather than only single drugs given TB Alliance's combination drug clinical trials. The Alliance has understandably touted this regulatory departure as an innovation, one that not only addresses the realities of a complicated disease, but which seeks to save ten to twelve years off of the typical time-to-approval of new regimens when they are tested one drug at a time (tballiance.org). DNDi's unprecedented South—South technology transfer agreement underscores the desirability of bolstering pharmaceutical capability
and nurturing relations among pharmaceutical companies embedded within high-burden regions. This promising picture, then, is not an inaccurate one. On the contrary it exemplifies Tsing’s insistence on the productivity of friction — that extremely different actors can converge upon an issue and find ways to work towards a common goal because in that moment and in that particular formation, there is a convergence of motives, desires, and expediencies which make things happen. Or as Joao Biehl puts it in describing the ascendency of product development partnerships in the field of global health, “Whatever differences there are across corporate, activist, and public health agendas the new rubric of ‘value’ appears to reconcile these differences and folds them into an ethos of collective responsibility” (2011, 106). PDPs like TB Alliance, the Drugs for Neglected Diseases initiative, and Aeras are forging institutional-political-techno-scientific connections that strain against twenty-first century capitalism’s market-driven parameters and demand the instantiation of public health need and the more malignant embodiments of acute global economic inequalities into pharmaceutical research and development. Despite critiques of PDPs’ focus on technological fixes versus broader social interventions, attempts to “devise instruments to ensure the provision of life’s basic needs to populations on the margin of survival” are, as Peter Redfield concludes, hard to denounce (2012, 178).

Yet stopping with this more optimistic picture, as a flattened One Health perspective would indicate, in fact misses what kinds of relations make PDPs productive — that is, what kinds of friction turn a divergent set of actors into formations that gain traction in the way they work together. It would also, however, miss the political and social relations sometimes creating nonproductive friction for PDPs and potentially threatening their futures. For one thing, the ‘value’ of which Biehl speaks appears from the outside to cohere among the various PDP partners, yet the moment of cohesion can be fleeting. The value for most nonprofits involved in therapeutic production is humanitarian, tied to addressing those infectious diseases made intractable by national incapacity and transnational indifference. The point is not to rearrange pathogenic social and economic orders but to ease burdens of human suffering through the delivery of appropriate, affordable pharmaceauticals. Though it is not nonprofits’ objective to underscore the creation of ‘neglected diseases’ by pharmaceutical practices focused on markets rather than disease burdens, the very efforts to address these diseases is an implicit challenge to the integrity of this particular facet of neoliberal capitalism. The value for industry is something quite different — working towards vaccines and drugs for diseases like malaria and tuberculosis is in part a way past plateaus in innovation and profit, saturated markets, negative publicity, drug recalls, and litigations. It is a way to repair images of rapacity and fraud by way of ‘doing good,’ while at the same time getting a foot in the door of emerging markets. Once a presence is established, the pharmaceutical company can, and most likely will, go on to market drugs for chronic diseases (Evans, personal interview, 2012).

The productive friction of these divergent values occurs when developing pharmaceuticals for tuberculosis and malaria align with both interests. In this present moment, these interests line up and gain traction through mutually beneficial intellectual property arrangements; data sharing; nonprofits’ relations with the WHO, national governments, and local communities; industry’s resources; and philanthropic largess. The “awkward, unequal, unstable, and creative qualities of interconnection across difference” (Tsing, 2004, 4) works because producing pharmaceutical products at the end of the day gains value — however differentiated — for each party. The parties’ sometimes awkward negotiation and unequal status works as long as each actor continues to need what the other one has to offer, and the end result addresses all underlying ontological and financial motives. Yet as Tsing points out, these unstable connections are transient (ibid, xi). Eventually, industry is likely to lose interest in nonprofit collaborations once more lucrative endeavors coalesce. And even now, productive friction does not always result from these ‘interconnections across difference.’

Industry involvement, for example, remains in many ways a source of tension in PDP interactions. Though negotiated arrangements between nonprofits and industry obviously happen, nonprofits ultimately have little sway over pharmaceutical companies’ decisions about funding or product management when or if they own the patents on new pharmaceuticals. One of the issues is the precarious balance industry itself has about the degree of funding it is willing to put into infectious disease projects, a balance driven in part by the variable motivations pharmaceutical companies have for pursuing unprofitable infectious disease initiatives. For some, it is a stepping stone to breaking into emerging economy markets; for others, it is more about repairing damaged images of an industry perceived as intent on profits to the detriment of peoples’ lives. Pharmaceutical companies do not expect to earn profits on tuberculosis or malaria initiatives, so this is not a motivating factor; but nor can they risk losing on their investments. Comments by a GlaxoSmithKline Biologicals scientist at a recent tuberculosis vaccines conference were fairly representative: despite Glaxo’s heavier involvement in developing a malaria vaccine, and despite acknowledging the ‘huge medical need’ for a tuberculosis vaccine, the representative reminded the audience that at the end of the day, GlaxoSmithKline could not lose money on developing such a vaccine. It was, he lamented, a question of return on investment (Lapiere, 2013). What he meant was not the act but rather the degree of collaboration and the precarious contours of engagement. One shift in the vaccine’s scientific or financial vigor could turn productive frictions into collapsed collaborations.

Another example of tensions with industry became apparent at a recent international lung health conference where researchers and members from the activist organization Treatment Action Group demanded to know from a Johnson & Johnson speaker why the company was ‘dragging its feet’ on further testing of the company’s new tuberculosis drug, bedaquiline, and why after ‘doing the right thing’ by championing the drug, the price of bedaquiline was so high that no one could afford it. Bedaquiline carries huge symbolic as well as therapeutic value as the first tuberculosis drug with a new mechanism of action approved by the FDA in almost fifty years. But the FDA approved bedaquiline for use in patients with multi-drug resistant tuberculosis through fast-track channels after only Phase IIb testing, with the stipulation that Johnson & Johnson begin Phase III testing immediately. Data from Phase III testing typically is required for drugs progressing through normal channels of regulatory approval. In the case of bedaquiline, however, further testing was even more urgent because clinical trial data showed elevated mortality rates in the bedaquiline arm of the study — rates that only further testing could prove were or were not actually associated with the drug.

Almost a year after the FDA approval, however, Johnson & Johnson has still not begun further testing, with the reasoning that it is negotiating with both the FDA and its European counterpart, the European Medical Association, on the protocol for these trials (Kambili, 2013). This response did not satisfy audience members, however, who claimed that Johnson & Johnson was betraying the tuberculosis community because it was clear to them that Johnson & Johnson, not the FDA, was responsible for such critical delays — a charge the speaker did not deny. And because Johnson & Johnson owns the patent for bedaquiline, TB Alliance has no control over its price despite engaging early on in negotiations making clear that
working with the Alliance meant ensuring any successful product would be made affordable and available to those in need.

What is happening with Johnson & Johnson will most likely not be unique. The problem with PDPs negotiating relations of capital, technology, and global health by developing pharmaceuticals destined for the world’s impoverished is that this undertaking is enormously expensive. Funding has to come from somewhere if not from profits, and as indicated by the GlaxoSmithKline representative and echoed by numerous other pharmaceutical company representatives, industry cannot ‘go it alone’ given the parameters set by their companies and shareholders. The Gates Foundation thus far has been the primary financial underwriter of TB Alliance and Aeras efforts towards drug and vaccine production, but this has its own parameters. For one thing, Gates is emblematic of the new ‘philanthropic capitalism’ in not just handing the money to PDPs, but rather playing an integral role in defining the problem and the path to its resolution. As one Gates representative put it, “Gates people are not sitting passively awaiting people to ask them [for money]; they develop strategies for addressing problems, then they seek those who can help with that.” (Gheuens, personal interview, 2013).

What this means, in the case of TB Alliance for example, is requiring annual progress reports indicating what has been accomplished; Gates representatives attending scientific committees and sitting on the Board; and helping define the annual work plan (ibid).

It is of course typical rather than surprising to find that one member of a collaboration — the one with the money — has more power than other members. This does not suggest that TB Alliance and Aeras have no say in how they go about developing new pharmaceuticals, it is simply to acknowledge that decisions within partnerships get made through mechanisms and channels particular to the specific collaboration, and with varying levels of tension or latitude accompanying them. Funding not surprisingly can play a role in creating positive friction, as when the CEO of Aeras suggested that tight resources produced better decisions over which vaccine candidates to move forward, and in not wasting money on duplicate vaccines (Evans, personal communication 2012). It can also produce negative friction, however, when too little funding exists to expand scientific discovery and development of vaccine and drug candidates, too few resources are available for late-stage trials, or pharmaceutical companies co-opt nonprofit agendas through pricing and marketing strategies. Ominous, too, is the recognition — more implicit rather than stated — that philanthropic funding is temporary and will need to be replaced with other means of financing — a challenging prospect given the low-profit, high expense nature of these endeavors.

5. Uneven geopolitical fields of interaction

The Drugs for Neglected Diseases initiative has managed to escape some of these dynamics by seeking most of their funding from European and British governments, and from their parent organization Doctors Without Borders. Yet even limited funding has also informed DNDi’s tactic of avoiding new drug development in favor of less expensive drug-combination projects. Unlike the other three PDPs highlighted here, they also work primarily with partners from the Global South. Yet even here, challenges can emerge from forging new collaborative terrains of pharmaceutical production.

On the one hand, as described by Jean-René Kiechel of the Drugs for Neglected Diseases initiative, DNDi consciously sought partners with knowledge of ‘the world of the diseases’ in which DNDi wanted to intervene, and who could consequently offer advice on designing region-specific programs capable of ‘transforming ideas into products.’ On the other hand, finding partners capable of performing all the scientific and logistical steps necessary in drug research and development, while at the same time navigating funder-imposed or scientific/logistical timelines, was difficult. Furthermore, being a PDP and working with smaller pharmaceutical companies like Brazil’s Farmanguinhos also meant difficulties getting suppliers of needed active pharmaceutical ingredients to deal with them. Buying a few hundred kilograms of these active ingredients, as Kiechel put it, did not make them ‘customers worthy of being groomed,’ and this subsequently meant a delay of one or one and a half years in getting the ASMQ fixed-dose combination developed. India’s Cipla, as a larger generic pharmaceutical company, was more experienced in working with multiple suppliers and therefore more adroit in maintaining steady drug production (personal interview, 2013).

Forging South—South relationships speaks as well to a critique of many PDPs for global health, that they replicate rather than renegotiate inequalities between North and South. To a certain extent, this is true: Aeras and TB Alliance are not exceptional in being overwhelmingly composed of western scientists, board members, and chief executives (cf Craddock, 2012). As indicated in the beginning of this article, these PDPs did not emerge from grassroots movements agitating for more attention to diseases like tuberculosis in high burden countries; they emerged in DNDi’s case from the European-based Doctor’s Without Borders, or in the cases of Aeras and TB Alliance from Gates Foundation, and all with directives and activist scientists wanting to do more to intervene in highly preventable diseases through biotechnological means. The funding behind these initiatives is thus almost entirely from western sources, and consequently the contours of engagement have emerged primarily from Gates representatives, western scientists, CEOs, and financial advisors.

Yet this is a partial picture of what the geopolitical terrains of TB Alliance and Aeras and their partners in particular look like as they have nurtured products down the pipeline. Clinical trial sites are one arena for example that both depend upon the results of chronic ‘unevenness’ in global politics and economies, while simultaneously intervening in them. Worcester, the tuberculosis vaccine trial site outside of Cape Town used by Aeras and the South African Tuberculosis Vaccine Initiative to test vaccine candidates, is a good example of this. It works well as a trial site because it juxtaposes state-of-the-art hospitals, clinical facilities, physicians, and researchers against extreme poverty and its outcome, one of the world’s highest tuberculosis rates. Participants in the trials are drawn from these communities devastated by apartheid and post-apartheid economic and political policies, while highly trained researchers monitor the results of the trial or care for those who come down with tuberculosis during or after the course of the trial.

One thing that often gets overlooked in the inequities that by default characterize most clinical trial sites is the fact that participants do have the option of not enrolling. And while this political leverage in the context of commercial pharmaceutical trials does not typically result in the power to influence trial practices, it does, in the case of Aeras or TB Alliance, result in numerous community engagement endeavors and in forming community advisory boards that act in the interests of potential trial participants by communicating fears, doubts, and dislikes to researchers. These cross-communications have resulted, inter alia, in further educational outreach to communities, better designed informed consent documents, and better trained recruitment personnel. As suggested by Marijke Geldenhuys, the Professional Development and Quality Control Manager of the South African Tuberculosis Vaccines Initiative, huge strides have been made in recent years in getting
clinical trials as ethical, fair, and compassionate as possible (personal communication, 2011).

They have not, however, resulted in more input on the part of participants into clinical trial protocols, a step indicated by several tuberculosis researchers at a recent international lung health conference as critical if trial designs are going to be more attuned to local practices and understandings of disease, and if they are going to be more equitable (Workshop on Community Engagement, 2013). Such incorporation would characterize what Cori Hayden argues (2007) is a shift from being research participants — i.e., research subjects — to becoming participants in the research process. But moving towards greater inclusion of participants and community members into the basic design of clinical trials, while a step in the right direction, to some degree highlights rather than mitigates the intractability of inequalities characterizing clinical trials. As Wenzel Geissler discusses, there is a practice of ‘not knowing’ that goes on with clinical trials, a way of understanding while not explicitly acknowledging the unevenness of location across participants, researchers, community members, and levels of expertise in producing new medical knowledge.

As he suggests, “while producing scientific facts, people invest effort in ‘unknowing’ difference. In doing so, they neither deny, hide, nor ignore it, yet they do not establish it as explicit truth.... Unknowing serves to make scientific collaboration feasible” (2013, 17). In other words, gaining the knowledge that will result in potentially effective interventions into a disease of poverty ironically requires an exacting participation of the poor and vulnerable. Incorporating these individuals into the trial design process would help meet particular desires and needs within specified trial parameters, then, but would not change the fact that their poverty and vulnerability to infectious disease are requisites for the production of new drugs or vaccines for those same diseases. For Tseng and her notion of friction, however, inequalities do not necessarily undermine collaborations. Rather, under particular conditions differences can even ‘invigorate social mobilizations’ and the productive frictions produced from these. In tuberculosis clinical trials, inequality becomes its own generative friction in the critical role it plays in pharmaceutical knowledge production.

6. Conclusion

The One Health framework is certainly not awry in its insistence on working across institutional and disciplinary differences, especially since doing so tacitly recognizes that diseases are complex no matter where they occur. Yet recognizing this complexity has not translated into recognizing the complexity of collaborative undertakings, and in this One Health undermines its own value. There is nothing magical about collaboration across the sciences, or across divergent academic, nonprofit, governmental, and private-sector actors. These collaborations become productive only when particular interests converge and when larger financial and political conditions fall in line with collaborative ambitions. Returning to Zinnstag and colleague’s question of why there is no new tuberculosis vaccine, the answer is not that collaborations have failed to coalesce around this problem, or that these collaborations are not composed of all the various actors required to undertake vaccine research and development. It is that these collaborations face their own internal frictions over divergent interests, missions, and end goals; and that they navigate within larger global economic parameters resistant to endeavors forging new terrains of high-cost pharmaceutical development destined for low-cost markets.

Collaborations reflecting the interconnections characterizing disease, in other words, collide among themselves and with the larger forces in which they function. As Tsing indicates so compellingly, these collisions can cause frictions that are enormously productive — as in the case of PDPs, in galvanizing innovative scientific practices, new paradigms of pharmaceutical production, and heightened attention to global health issues and their attendant burdens of suffering. And Tsing’s concept of friction does not stop at normative concepts of productivity, but rather recognizes that even with unstable and fleeting convergences new political actors, social practices, and relations are forged. “The knowledge that makes a difference in changing the world is knowledge that travels and mobilizes, shifting and creating new forces and agents of history in its path” (2005, 8). So the PDPs described above might be precarious, but their impact will be felt both in their current moment of productivity and in their innovative aftermath. The point is that answering whether a tuberculosis or malaria vaccine, or drugs, will be developed or why requires the ability to scrutinize the dynamic, fractured, precarious, and contentious nature of ‘interconnections across difference’ and the larger milieu in which they operate. Failing to do so will keep One Health approaches marginal at best.

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