Innovation Tackling Antibiotic Resistance
Open Source Drug Discovery Initiative in India

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Innovation Tackling Antibiotic Resistance

The challenge of growing antibiotic resistance has placed the effectiveness of antibiotics in treating infections in jeopardy. In so doing, the benefits of modern day medicine, from surgical prophylaxis to chemotherapy, have been compromised. There exists, however, a paradox between patients receiving unnecessary antibiotic treatment and those who go without such access. Across the pharmaceutical value chain, the challenge of ensuring access to needed antibiotics might be characterized by therapeutic, financial and structural barriers. Overcoming each of these barriers, this paper describes innovative approaches to tackling antibiotic resistance.

Therapeutic access most directly relates to the R&D of new antibiotics. The dearth of novel antibiotics over the past few decades is symptomatic of a stalled pharmaceutical pipeline, which could be improved by the sharing of resources, risks, and rewards. India’s Open Source Drug Discovery Initiative (OSDD) is one example of these three “Rs” in action, and this initiative has built a network of online and wet-lab collaborators to innovate treatment by crowdsourcing contributions that advance pre-clinical research, publicly funding clinical trials for diseases such as tuberculosis and malaria, and eventually licensing scale-up at close-to-marginal cost pricing.

Financial access requires not only ensuring the affordability of needed antibiotics, but also a price point that enables the sustainability of that treatment’s supply. A solution that delinks the return on investment from volume-based sales is crucial to addressing both the supply- and demand-side barriers to financial access. Finally, structural access is linked to the delivery system of antibiotics and involves the relationships among prescriber, dispenser and consumer. Innovations seeking to improve structural access can improve the rational use of antibiotics by targeting the consumer, but must not neglect the need to examine the patterns, incentives, and guidelines that influence the behavior of health providers. The Antibiotic Smart Use (ASU) Project in Thailand is an example of such a multi-pronged approach. Working through a staged implementation process, ASU has seen impressive declines in inappropriate antibiotics use by substituting culturally appropriate herbal remedies for viral or self-limited infections when antibiotic use is unnecessary, improving diagnostic capabilities by providing illuminators, and introducing a more robust discussion of the rational use of medications among local health providers. The case studies throughout this paper examine the issues of therapeutic, financial, and structural access along the pharmaceutical value chain and illustrate innovative approaches that work towards tackling antibiotic resistance.
Open Source Drug Discovery Initiative

Generic production of medicines has played an important role in ensuring affordable access to those in need. Much concern has arisen in India’s transition in 2005 to implementing the World Trade Organization’s Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement under which the country recognized patents on pharmaceutical products.

Prior to this transition, India’s Council on Scientific and Industrial Research (CSIR) had developed alternative and less costly processes for manufacturing triple-drug therapy for AIDS and transferred this technology to Cipla, an Indian generic drug firm (1). In 2001, Cipla’s offer of triple-drug therapy for AIDS at $350 per patient per year ushered in generic competition with multinational companies that had failed to provide affordable pricing on these drugs (2). By 2008, Indian generic firms accounted for nearly 90% of the purchase volumes of antiretroviral drugs globally (3). The world’s reliance on sourcing life-saving medicines from Indian generic companies has prompted much attention not only to how TRIPS flexibilities might apply to India’s treatment of intellectual property rights, but also to what alternative pathways for bringing needed medicines into health markets might work.

Starting in 2008, CSIR piloted the Open Source Drug Discovery Initiative (OSDD) to innovate for neglected diseases, first targeting tuberculosis and later broadening its scope to projects on malaria, filariasis and leishmaniasis. OSDD ambitiously seeks to change the way knowledge is produced, owned and harnessed in order to reduce global health inequities and provide affordable healthcare for all. Through a model of open source innovation and collaboration, OSDD is reengineering the means of bringing a new drug to market by sharing resources, risks and rewards (4).

OSDD shares resources through an online collaboration platform—a semantic, web-based, wiki portal built with donated support from InfoSys—to which participants agree through a click-wrap license not to remove for proprietary gain knowledge generated from the online commons. Crowdsourcing their collective talents, this platform brings together a network of scientists, students and universities across different countries and disciplines. To date, this includes over 7600 registered participants from 130 countries; 10 engaged CSIR labs, 39 academic institutions and 14 industry partners; and signed partnerships with product development partnerships, from the Drugs for Neglected Diseases Initiative to the TB Alliance and Medicines for Malaria Venture. Presently OSDD hosts over 240 projects, led by over 180 principal investigators.
The network infrastructure bridges work both on-line in virtual collaboration and offline in wet labs. On-line, well-defined and coordinated “work packages” reframe large complex problems into more discretely manageable tasks. These collaborations range from projects on the experimental gene expression of targets and the optimization of successful hits to pre-clinical toxicity catalogs and profiles of an experimental drug. OSDD also maintains publicly accessible databases, including an integrative genomics map of *Mycobacterium tuberculosis*.5 Engaging its on-line community, OSDD recently conducted a YouTube Video competition on “The Need for New Drugs for TB.” One product from the OSDD network has already involved network volunteers, who re-annotated the entire *M. tuberculosis* genome, telescoping 300 person-years of effort into four months (6).

Off-line OSDD has sought to line up the infrastructure to translate early stage discoveries into first-in-human trials, facilitating the transfer from basic research scientists to those who might translate this work into a druggable compound. Biological resources are available through such collections as a plant-derived, anti-infective library of compounds for screening and an open access repository of *Mycobacterium tuberculosis* clones. The Open Source Drug Discovery Initiative has also assembled a diverse small molecule repository, synthesized by a community of synthetic chemists, numbering about 80 from 35 institutions.

Risk is shared through OSDD with US $12 million in Indian government funding and private sector donations from in-kind IT support from Infosys to grants from foundations like the Sir Dorabji Tata Trust. Funding is, in turn, released to projects, both as awards to principal investigators or as projects commissioned and coordinated by OSDD itself. OSDD uses the online portal to accept and process applications through an open peer review format. The Tata Trust grant has supported students and early career researchers to participate in crowdsourcing their efforts in the open source discovery of drugs for neglected diseases.

The OSDD initiative also shares rewards, both at the individual and collective levels. Individual rewards have ranged from activities encouraging women scientists to small prizes in the form of credit for phone usage and Internet access. Largely supported by the Indian government, scientists and students alike contribute voluntarily to the network’s activities. The collaboration platform tracks the contributions of individuals through a micro-attribution system that is peer reviewed and awarded through defined credit points. Those contributing more than 1% to the online community project receive authorship and acknowledgement in subsequent publications. Moreover, the best performers in the OSDD community
have leveraged their participation into competitive applications for fellowship training in programs abroad.

By publicly financing the R&D of novel antibiotics, OSDD seeks fair returns from this investment by keeping drug costs affordable through generic licensing. Along these lines, OSDD has secured a non-exclusive right to PA-824 from the TB Alliance for testing this drug in a new combination regimen (pyrazinamide + moxifloxacin + PA-824) in Phase IIB clinical trials. This has the potential of shortening TB treatment from six to two months. To advance its virtual R&D pipeline, OSDD engages partners in such undertakings in two ways: 1) it contracts service providers on a “work for hire” basis, and 2) it collaborates with partners that donate their services, with the resulting intellectual property belonging to the OSDD community.

OSDD’s non-hierarchical structure carries over to its governance. A Science Support Group, comprised of seven core members and people drawn from the OSDD community, guides the direction of the OSDD initiative and makes decisions on policies governing its open access repositories.

Though the vision and mission of OSDD is to improve innovation for neglected diseases and provide affordable healthcare to all, its efforts have also inspired a generation of young minds. By sharing resources, risks and rewards, not only is OSDD developing a publicly owned R&D pipeline for bringing new health technologies to market, but it is also building a pipeline for training its future scientists.

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Chapter 5 – Annex 3

Thailand’s Antibiotic Smart Use Initiative

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Incentives in the healthcare delivery system—both financial and non-financial—often are misaligned. This can result in underuse, overuse and misuse of drugs. For antibiotics, overuse can drive greater drug resistance. Thailand’s Antibiotics Smart Use (ASU) project has sought to improve the rational use of these medicines through a step-wise approach beginning by improving education over antibiotic use and overuse locally and lowering barriers to behavioral change by offering alternative treatments for non-bacterial infections.

ASU has unfolded in three phases. It began as a partnership with pharmacists and doctors from Srinakharinwirot University and Chulalongkorn University. They piloted educational and training reforms to improve rational prescribing in 10 hospitals and 87 primary health centers in the Saraburi province. During this first phase, the provincial health office monitored four areas: antibiotic prescription rates; provider attitudes of effectiveness and knowledge of antibiotics; non-prescription rates in cases of non-bacterial infections; and patient health and satisfaction. Applying these same indicators, the second phase scaled up this intervention to 44 hospitals and 621 primary health centers in 3 provinces and two hospital networks. The National Health Security Office (NHSO) piloted a pay-for-performance system to realign financial incentives to prescribers and providers. Under the guidance of the Thai FDA, local health authorities managed this initiative with additional assistance from the NHSO and the Health Systems Research Institute. The third phase has strengthened and grown this network to 22 public hospital systems in 15 provinces, with the focus on longer-term sustainability (1).

Without hierarchical leadership, Antibiotics Smart Use built decentralized networks that engaged local partners to adapt these guidelines in their own healthcare settings and communities. These local partners were comprised of networks of multidisciplinary groups across the healthcare, government and academic sectors. They included hospital directors, provincial health administrators, university researchers, medical and pharmacy students as well as local physicians, nurses and pharmacists.

Thailand’s Drug Act classifies antibiotics as drugs with potentially serious side effects or ya-an-talai which literally means dangerous drugs. Colloquially, however, antibiotics are sometimes called ya-gae-ug-sep, which means “drugs that counter inflammation.” This reinforces the layperson’s belief that all inflammatory symptoms can be cured with antibiotics, whether or not the cause is bacterial. Through local partners, Antibiotics Smart Use has worked to address these local misperceptions about the purpose of these important medicines.
The program targeted three conditions not requiring antibiotic treatment--upper respiratory infections, acute diarrhea and simple wounds. Antibiotics Smart Use focused its efforts on healthy ambulatory patients older than 2 years old, but took care in excepting those who were hospitalized, diagnosed with diabetes or a compromised immune system, or suffering from serious co-morbidities.

In the first phase of the ASU intervention, educational programming consisted of a half-day training focused on clinical guidelines targeting physicians, nurses and pharmacists. These efforts bolstered provider self-confidence that antibiotics were neither appropriate nor needed for treating patients with a viral infection. The program equipped healthcare providers with posters and pamphlets to communicate better with patients and white light illuminators in lieu of flashlights to improve the diagnosis of sore throat. Sharing the names of healthcare providers committing to the pilot along with the treatment guidelines helped to encourage greater local participation by others.

During the pilot phase, hospitals received seed money from WHO and the Thai FDA to fund the implementation and evaluation process. ASU officials found that local networks took initiative in approaching these problems. The ASU project has encouraged ownership among local partners by enabling them to brand and design locally effective methods to improve the use of antibiotics in their communities, bolstered by regional and national support networks and educational and some financial guidance (1). The project seeks to integrate these changes into local healthcare systems by influencing individual behavior rather than enforcing guidelines through a heavy-handed, top-down approach.

In Cha-laе District in Songkha Province, ASU advocates added the principles of rational use of antibiotics into their own local “health constitution,” and they signed memoranda of understanding with grocery store owners not to sell antibiotics over the counter. In the Muaklek District in Saraburi, the ASU network enlisted not only local hospitals, but also the community bank in efforts to promote rational use of antibiotics. The community bank rewarded patients who successfully completed a self-assessment quiz on how to care for oneself without antibiotics in the face of an upper respiratory infection, acute diarrhea or a simple wound. An educational booklet provided a checklist of steps for self-care, from drinking enough fluids to getting enough sleep, in responding to an upper respiratory infection. The reward took the form of reimbursement for grocery items such as sugar or vegetable oil. This initiative engaged stakeholders across the community (2).
The network harnesses and shares success stories from local partners within the provider, hospital and pharmacist networks. In propagating this intervention, social media, the ASU website and a newsletter distributed to health facilities helped to spread the word to all 77 provinces. A sequence of meetings brought together local stakeholders to evaluate the effectiveness of their current approach and to strengthen cooperative efforts. Extending this outreach, seed monies supported data collection and monitoring by hospitals, and training on treatment guidelines increased physician confidence. DVD players offered a way to educate patients; however, this did not always compete effectively for the attention of patients waiting to be called in crowded waiting rooms (1).

The first stage of the ASU project resulted in impressive declines in antibiotic prescription rates in hospitals (decreases ranging between 18% and 23%) and in primary health centers (decreases between 39% and 46%) (3). Scaling up the ASU project, the second phase has involved 44 hospitals and 621 health centers in three provinces as well as two hospital networks. A third phase began in 2010 to ensure sustainability of these policy initiatives.

Persuaded by the success of ASU’s phase 2 results, the National Health Security Office (NHSO)--responsible for universal health coverage for 47 million Thais--changed the capitated, pay-for-performance system to ensure greater compliance with antibiotic prescribing guidelines. It did so by moving from a process evaluation to an output evaluation. The process evaluation had relied on a checklist of key activities while the output evaluation measured the actual level of antibiotic prescriptions for upper respiratory infections and acute diarrheal cases.

In addition to these measures, ASU developed packages of herbal medicines for non-bacterial infections to offer providers another option for treatment. These traditional Thai medicines were approved on the national formulary for relieving symptoms of viral infections and were packaged in capsules similar to antibiotics. This afforded an alternative for prescribers who might otherwise have overprescribed antibiotics to placate patients insistent on drug treatment. However, herbal medicines are not without side effects, and providers are being taught that the best treatment at times may be watchful waiting.

The ASU project also recognized that pharmacists were rewarded for dispensing more antibiotics under a fee-for-service system. This fee-for-service system still applies to Thai civil servants and those willing to pay privately out-of-pocket. To curb potential overuse of antibiotics in these setting, the ASU project conducted a pilot study that focused on lowering consumer demands for these drugs.
Participating pharmacies enabled consumers to self-diagnose whether they likely had a bacterial throat infection based on four clinical criteria. Using a stand with a mirror, the patient could examine his own tonsils with a tongue depressor and white light illuminator and contrast this against side-by-side pictures of typical bacterial and viral throat infections. When consumers asked for antibiotics, pharmacists would ask them for their self-evaluation. By providing alternatives that relieved the patients’ symptoms, the pharmacists both reduced inappropriate antibiotic use and also realized income from offering these substitute remedies. While not preventing the over-the-counter purchase of antibiotics, the pilot study found that over 90% of the 998 patients fully recovered and greater than 80% were satisfied with treatment outcomes (2).

ASU believes these types of interventions may be the next step to addressing challenges in the fee-for-service model. The ASU project has also looked into the incentives under the Diagnosis-Related Group-based payment system and into establishing an audit system that would provide hospital-level comparisons. Where positive financial incentives may not suffice, these may, in the future, need to be complemented by negative financial incentives, or penalties.

The Antibiotics Smart Use project in Thailand shows the interplay between providers and patients, national guidelines and locally inspired efforts to implement them, and incentive systems and culturally mediated interventions. The project reveals the importance of local stakeholder ownership as well as the challenges of sharing and scaling these practices and sustaining such efforts.

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