# Effects of the Global Pharmaceutical Drug Trade on Multi-Drug Resistance Tuberculosis (MDR-TB) in India

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## Abstract

Antimicrobial resistance (AMR) occurs when infectious agents—such as bacteria, viruses, fungi, and parasites—change in ways that make curative medicines and treatments ineffective. AMR threatens the effective prevention and treatment of an increasing range of infections—especially, HIV, malaria, and tuberculosis, leading to prolonged illness, deaths, and disabilities with important economic consequences to

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low- and middle-income countries. In recent years, counterfeit drugs, particularly in South Asia, hinder progress in dealing with AMR. This case study offers a description of the Multi-Drug Resistant Tuberculosis (MDR-TB), which is a type of microbial infection that did not respond to isoniazid and rifampicin—two most powerful anti-TB drugs. In mitigating this health-threatening issue, numerous countries and international agencies—such as World Trade Organization (WTO) and World Health Organization (WHO)—join their efforts in regulating the global pharmaceutical trade. The WTO in particular adopted the Trade-Related Aspects of Intellectual Property Rights (TRIPS), which established the ground rules for patent protection on pharmaceutical drugs.

The purpose of this case study is to enhance an understanding of how India deals with the AMR situation within the international regulatory framework governing the global pharmaceutical trade. India is one of the countries in which MDR-TB has frequently been encountered in recent years. In 2013, one quarter of all TB patients in the world (2.2 million people) were reported in India. The WHO estimates that about one million TB patients in India are not aware of their status. And, despite a high treatment success rate of 88%, the current number of patients with MDR-TB in India was 63,000 in 2013. Importantly, the majority of MDR-TB patients in India are socio-economically disadvantaged populations. As such, the MDR-TB situation in India does not only involve the biomedical issues, but also the social, economic, and political issues for the Indian government.

**Keywords:** Anti-microbial Resistance, Global Pharmaceutical Trade, Trade Agreement, Multi-drug Resistant Tuberculosis

# ผลกระทบจากการค้ายาระหว่างประเทศต่อภาวการณ์ดื้อยาหลายขนานของเชื้อวัณโรคในประเทศอินเดีย

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## บทคัดย่อ

ภาวะการดื้อยาปฏิชีวนะ (Antimicrobial Resistance: AMR) เกิดขึ้นเมื่อสิ่งที่ทำให้เกิดโรคติดต่อ ได้แก่ แบคทีเรีย ไวรัส เชื้อรา และเชื้อปรสิต เกิดการเปลี่ยนแปลงที่ลดประสิทธิภาพของยาและวิธีการรักษาโรค AMR ถือเป็นอุปสรรคสำคัญในการแก้ไขปัญหาโรคติดต่อร้ายแรง เช่น โรคเอดส์ โรคมาลาเรีย และวัณโรค ซึ่งก่อให้เกิดการเจ็บป่วยระยะยาว การเสียชีวิต และทุพพลภาพ ตลอดจนผลกระทบเชิงเศรษฐกิจที่เป็นลบต่อประเทศกำลังพัฒนา ทั้งนี้ ในหลายปีที่ผ่านมา ปัญหายาปลอมในแถบเอเชียใต้ทำให้ปัญหา AMR ทวีความรุนแรงมากขึ้น

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กรณีศึกษานี้เกี่ยวกับสถานการณ์เชื้อวัณโรคที่ดื้อยาหลายขนาน (Multi-Drug Resistant Tuberculosis: MDR-TB) ซึ่งเป็นอาการติดเชื้อที่ไม่ตอบสนองต่อยา Isoniazid และ Rifampicin ซึ่งเป็นยาต้านเชื้อ TB ที่มีประสิทธิภาพมากที่สุดในปัจจุบัน ทั้งนี้ เพื่อเป็นการแก้ไขปัญหา MDR-TB องค์กรระหว่างประเทศหลายองค์กร อาทิเช่น องค์การการค้าระหว่างประเทศ (WTO) และองค์การอนามัยโลก (WHO) เป็นต้น ได้ร่วมกันกำหนดมาตรการเพื่อควบคุมการค้ายาระหว่างประเทศ โดยเฉพาะข้อตกลง TRIPS เพื่อคุ้มครองทรัพย์สินทางปัญญาของสินค้าและการออกแบบทางอุตสาหกรรม รวมทั้งยาและเวชภัณฑ์ด้วย

วัตถุประสงค์ของกรณีศึกษานี้จึงเป็นการเพิ่มพูนความรู้ความเข้าใจในความสลับซับซ้อนของสถานการณ์ AMR ในประเทศอินเดีย และกระบวนการทางด้านกฎหมายระหว่างประเทศที่เกี่ยวข้องกับการค้าขายยาระหว่างประเทศ ทั้งนี้ ประเทศอินเดียเป็นหนึ่งในประเทศที่ประชาชนประสบวิกฤติการเจ็บป่วยจากเชื้อวัณโรค โดยในปี พ.ศ. 2556 ผู้ป่วยวัณโรคจำนวน 1 ใน 4 คนทั่วโลก หรือ 2.2 ล้านคน เป็นผู้ป่วยชาวอินเดีย นอกจากนี้ องค์การอนามัยโลกยังได้ประมาณการไว้ว่า ผู้ป่วยวัณโรคจำนวน 1 ล้านคน ในประเทศอินเดียไม่ทราบสถานะการติดเชื้อของตนเอง และแม้ว่าการรักษาอาการติดเชื้อวัณโรคในประเทศอินเดียจะประสบความสำเร็จถึงร้อยละ 88 กลับพบว่า ประเทศอินเดียมีจำนวนผู้ป่วยโรค MDR-TB 63,000 คน ในปี พ.ศ. 2556 ประการสำคัญ คือ ผู้ป่วยโรค MDR-TB ในประเทศอินเดียโดยส่วนใหญ่เป็นประชากรกลุ่มด้อยโอกาสทางเศรษฐกิจและสังคม ทำให้ปัญหา MDR-TB เป็นทั้งปัญหาในเชิงวิทยาศาสตร์การแพทย์และปัญหาทางด้านเศรษฐกิจ สังคม และการเมืองที่ท้าทายรัฐบาลของประเทศอินเดีย

**คำสำคัญ:** ภาวะการดื้อยาปฏิชีวนะ การค้ายาระหว่างประเทศ ข้อตกลงระหว่างประเทศ ภาวะเชื้อวัณโรคดื้อยาหลายขนาน

## Overview

*What started out as a perfect day where everything was in order, ended in a catastrophe, with a sudden turn of events. The roaring and deafening noise like an angry lion was heard. Then, it clicked: the trembling noise heard earlier was an earthquake. Suddenly, you were aware something was not right. A course of action was needed. "Run!" was all we could hear at the moment when we saw a high wall of water came crashing over the reef towards us at a speed of 40-50 kilometers per hour. This was how Multi-drug resistance Tuberculosis (MDR-TB) was going to affect infectious disease management if no comprehensive policies and regulations were implemented. MDR-TB was like a silence Tsunami; it had taken people by surprise.*

Antimicrobial resistance (AMR) occurred when microorganisms—such as bacteria, viruses, fungi, and parasites—changed in ways that rendered the medications used to cure the infections they cause ineffective (Cockburn et al., 2005; WHO, 2016). These microorganisms were usually referred as "superbugs" when they became resistant to more than one antimicrobial. Threatening the effective prevention and treatment of an ever-increasing range of infections—especially, HIV, malaria, and tuberculosis—AMR led to prolonged illness, deaths, and disabilities with important economic consequences to low- and middle-income countries (Eliopoulos et al., 2003). In recent years, there was a rise of counterfeit drugs in the market, and South Asia accounted for the biggest share of counterfeit pharmaceutical drug trade (Howard et al., 2003; Cockburn et al., 2005). Counterfeit drugs were hindering progress in tackling AMR unless comprehensive trade policies were implemented (Laxminarayan et al., 2013)

One example of AMR was multidrug-resistant tuberculosis (MDR-TB). MDR-TB referred to a type of tuberculosis infection that did not respond to isoniazid and rifampicin—two most powerful anti-tuberculosis drugs. In 2015, approximately 10.4 million people were infected with MDR-TB. Of this number, about 1.8 million died (WHO, 2016). In India, China, and Russia alone, the estimated number of patient

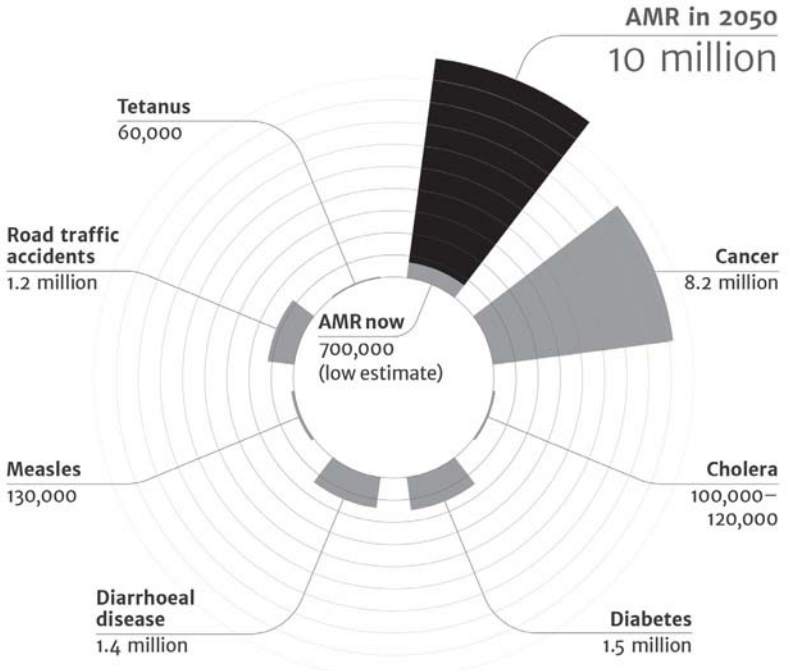
infected with MDR-TB was 580,000—accounting for 45% of all reported MDR-TB cases around the world (WHO, 2016).

MDR-TB and other types of drug resistance were caused by the prevalent use of counterfeit medicines (Laxminarayan et al., 2013). In addressing this health-threatening issue, countries and international agencies—such as the World Trade Organization (WTO) and World Health Organization (WHO)—joined their efforts in regulating the global pharmaceutical drug trade. The WTO adopted the Trade-Related Aspects of Intellectual Property Rights (TRIPS), which established the ground rules for patent protection on pharmaceutical drugs, despite concerns that such regulatory framework might affect the vulnerable populations' access to affordable drugs.

## Antimicrobial Resistance Situations at a Glance

### Global AMR Situation

The magnitude of AMR accounted approximately for 700,000 cases/ year (Figure 1). Only 5% were diagnosed and treated, with only 3% of all cases treated with good quality drugs (O'Neil, 2016). Since AMR became an important global public health issue, it required an action across all government health sectors to collaborate. Patients with infections caused by drug-resistant bacteria were at an increasing risk of adverse clinical outcomes and death, and consumed more healthcare resources than patients infected with non-resistant strains of the same bacteria (Cars, 2005).




*Source*: O'Neil (2016)

**Figure 1:** Major Causes of Death at the Global Level

## AMR Situation in India

India is a country in South Asia sharing borders with Myanmar and Bangladesh to the east, Pakistan to the west, and China, Nepal and Bhutan to the northeast. India is bounded by the Indian Ocean on the south, the Arabian Sea on the southwest, and the Bay of Bengal on the southeast. The country is the world's seventh largest country by area of 2.97 million $km^2$ and the second most populous country with over 1.31 billion people. The majority of people (67.25%) reside in the rural areas with an average life expectancy of 68 years. In 2015, the country's adult literacy rate is 72.23%. In the same year, per capita income stood at $1,581.59, which was ranked 169th out of 197 countries worldwide. On average, the Indian government invests around 5% of its GDP on health, while most of health investments were the private sector's contributions. In 2013, around 80% of private health contributions came from out-of-pocket expenditures mostly for medications (WHO, 2013).This trend strains India's economy, as AMR and other health-related issues are becoming too complicated for the country's existing health service system.

## The Political Economy of Tuberculosis Drug Trade

### Counterfeit Drug Trade and International Actions

In recent years, there was a rise in counterfeit drugs in the market. In 2009, 20 million pills, bottles, and sachets of counterfeit and illegal medicines were seized in a five-month operation coordinated by the International Criminal Police Organization (INTERPOL) across China and seven of its Southeast Asian neighbors (WHO, 2016). These counterfeit drugs exacerbated resistance to many infectious diseases. Asia accounted for the biggest share of the trade in counterfeit medicines where most of the new cases of MDR-TB emerged (Cockburn et al., 2005). An important obstacle to tackle AMR was the lack of regulatory enforcement in many countries due to the illegal drug industry's political influences (Sachs, 2012). Among different kinds of pharmaceutical products, drugs for treating TB infection attracted widespread attention among large pharmaceutical companies, particularly those in India and South Asia (Bate et al., 2014). Further, there were also quality issues with the Indian pharmaceutical firms on antibiotics and TB drugs produced by the Indian pharmaceutical firms and sold in Africa, India and other five middle income non-African countries (Udwadia and Moharil, 2014; Fojo and Dowdy, 2017; Law et al., 2017). This might have increased multi-drug resistant TB cases.

### World Trade Organization and TRIPS Agreement

Efforts were made by international organizations, such as World Trade Organization (WTO), International Trade Organization (ITO), and World Health Organization (WHO) to regulate pharmaceutical drug trade among countries. For instance, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement was a multilateral agreement on intellectual property under the WTO. TRIPS had been in effect since 1995 with the aim of promoting intellectual property rights and international actions against counterfeit merchandises (Udwadia et al., 2012). Not only did TRIPS focus on patented products, the agreement also covered other forms of intellectual properties, including copyrights, trademarks, and industrial designs. However, emphasis was placed on patented products, which

were essential to medical and technological innovation. It was expected that technological advances would help supply poor countries with affordable and effective medical products. In other words, TRIPs laid down ground rules on intellectual property rights, which were seen as a way to introduce a system in which disputes over the intellectual property right issues can be settled systematically.

**Challenges to the Campaign against Counterfeit Drug Trade**

Protection and enforcement of the intellectual property rights varied widely around the world (Maron et al., 2013; Hoffman et al., 2015). As they became more important in trade, the variations became a source of tension in international economic relations. Prior to TRIPS and during TRIPS negotiations, developing countries opposed the protection for patented pharmaceutical products due to fear of an increase the prices for patented pharmaceutical products, accessibility to the pharmaceutical technology, and strong social movements led by international NGOs and diverse interest groups (Azam, 2015; Price et al., 2015).

In 2005, the Indian government adopted an amendment to the patent protection legislation to comply with TRIPS, which required patents to be granted on new medicine. The introduction of the TRIPS agreement became devastating for countries that relied on India as a source of affordable quality medicines. Low-income countries unable to grant patents on pharmaceutical products faced technical and financial difficulties to produce their own generic medicines. As such, TRIPS-related legislation in India and other manufacturing countries effectively cut the lifeline of affordable drugs for low-income countries. Evidence suggested that new drug prices would increase by 200% due to the TRIPs patent requirement (WHO, 2013). However, the TRIPS Agreement was interpreted and implemented in a manner that protected public health and, in particular, to promote access to medicines for all. The impact of patents on access remains a complex issue and an area of particular focus. Although the policy options was to minimize barrier to access, but equally the absence of an enforceable patent right does not guarantee effective access (Udwadia et al., 2012).

In response to the AMR situation around the world, WHO came up with a global action plan for the prevention, caring, and control of MDR-TB. The plan aimed to end the global TB epidemic by reducing the TB-induced deaths by 95% and by cutting new cases by 90% between 2015 and 2035 (WHO, 2016). The strategy included integrated, patient- centered care, and preventive approach focusing on early detection, treatment, and prevention for all TB patients, including children. It was to ensure that all TB patients had equal, unhindered access to affordable services and early diagnosis of TB, including the universal drug susceptibility test and systematic screening of contacts for high-risk populations. Also, the WHO guidelines also aimed to ensure the quality and standards of MDR-TB drugs by requiring that its member states produced quality medicines and control counterfeit drugs.

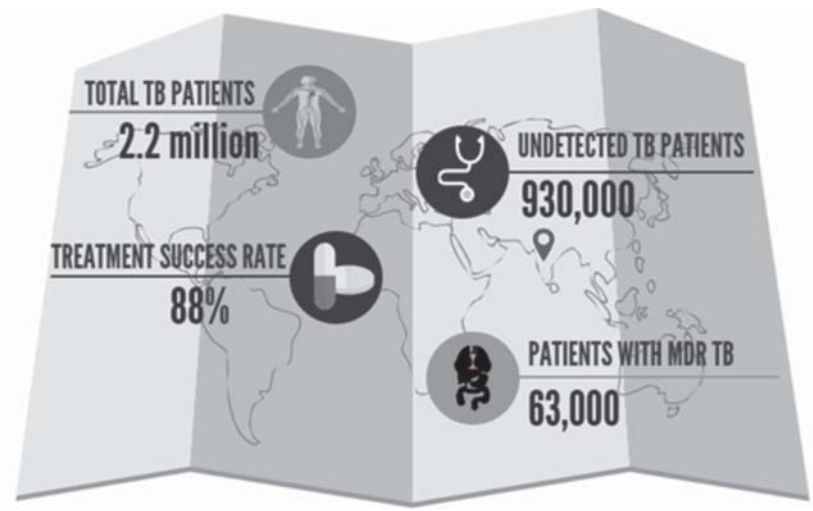
**Rise of Medical Technology to Combat "Superbugs"**

Recent developments showed that nanotechnology appeared to be most promising way to fight against the so-called "superbugs" (Varshney and Shailender, 2012). The use of nanoparticles was a promising strategy to reduce AMR because nanoparticles could overcome existing drug resistance mechanisms, including decreased uptake and increased efflux of drug from the microbial cell, biofilm formation, and intracellular bacteria. Finally, nanoparticles could target antimicrobial agents to the site of infection, so that higher doses of drug were given at the infected site, thereby overcoming resistance (Ghasemi et al., 2009). However, the use of nanotechnology in developing new drugs to combat against the superbugs experienced low success rates with the poverty-related diseases, such as TB. These diseases came as a challenge for the pharmaceutical sector due to high prevalence rates of patient non-compliance (Pelgrift and Friedman, 2013). An ideal drug delivery system should be able to target and to control the drug release. Targeting and controlled release would increase efficiency of the drugs and reduce their side effects (Andrade et al., 2013; Aruguete et al., 2013; Natan and Banin, 2017). Therefore, the nanotechnologically-driven drug delivery system might offer a number of advantages over the conventional dosage forms by improving drug

efficacy, reducing toxicity and side effects, enhancing bio-distribution, and enhancing patient compliance (Varshney and Shailender, 2012).

**India's National Efforts against the TB Epidemic**

Globally, about nine million people were infected with TB each year. In this figure, one-and-a-half million died. Low- and middle-income countries, in particular, bore the greatest burden of the TB epidemic with 95 percent of TB cases in 2013. One-quarter of all TB patients in the world were reported in India alone (2.2 million people) (Figure 2). Several conditions within India increased its citizens' risk of TB infection: rapid urbanization, high population density, and poverty. The WHO estimated that approximately one million TB patients in India were not aware of their status. Despite high treatment success rate of 88%, the current number of patients with MDR-TB was 63,000 in 2013 (Figure 2).




*Source*: Jha (2015)

**Figure 2:** TB Epidemic in India

The "WHO End TB" campaign involved policy formulation and implementation to combat the TB epidemic in poor countries (WHO, 2013). In India, the campaign resulted in health and social policies, including universal health coverage, social protection, and safety nets (Sharma et al., 2008). These measures were designed to tackle an increase in MDR-TB cases among poor and vulnerable populations, people living with HIV-AIDS, and migrant workers (WHO, 2016). Politics, however, played an instrumental role in regulating the pharmaceutical sector in both developed and developing countries (Nair, 2008). Ineffective law enforcement mechanisms led to illegal drug manufacturing and marketing, which consequently exacerbated the global AMR situation (Azam, 2005). In India, the rise of MDR-TB was due to the lack of a comprehensive public health policy (Nair, 2008). Also, because of a weak regulatory system, the country's pharmaceutical industry suffered from transparency issues from a variety of fronts, including drug licensing, coordination among regulatory agencies, and patent protection. As a result, WHO banned the TB drugs produced by several Indian pharmaceutical companies because these drugs did not meet the international manufacturing standard (O'Neil, 2016).

After the emergency of TRIPS, the Indian pharmaceutical industry woke up to the challenges of new intellectual property regime (Nair, 2008). Research programs, such as the Drug Discovery Program, were set up to keep up with the new international regulatory system. As the WTO member states, India adopted TRIPS and strengthened the patent protection standard on pharmaceutical drugs (WHO, 2016). Yet, scientific studies consistently found the large gap in the prices between generic and brand-name pharmaceutical drugs. As such, India adopted the long-term vision of "TB Free India" with the goal of establishing universal access to quality TB diagnosis and treatment (WHO, 2016).

## Vulnerable Populations and MDR-TB

Low- and middle-income countries faced challenges in the availability of drugs, diagnostics, clinical expertise, laboratory capacity, financial constraints, and law enforcement. The emergence of new scientific knowledge, such as nanotechnology, helped improve accessibility, affordability, and availability of essential drugs. Yet,

although the Indian government allocated more resources for disease prevention and outbreak control in recent years, research and development for the MDR-TB drugs and other antimicrobial medicines in India remained relatively underfunded compared to other government projects. This resulted in low-quality antimicrobial drugs that were too expensive for the poor households who could not afford to buy an adequate supply of the necessary medications. Even if a new drug was introduced, the low-income households in India might not be able to afford it since the second- and third-line antimicrobial drugs were still too expensive for them. This reflected the public sector's limited resource allocations for health and healthcare services in India, which in turn was linked to the country's widening gap between the rich and poor households.

Several attempts were made at the international level to deter the counterfeit drug trade, such as TRIPS. For instance, TRIPS aimed to make the global economy more conducive to intellectual property by prohibiting counterfeit goods, protecting intellectual property rights, and providing legal basis for effective enforcement of such rights. In addition, international agreements like TRIPS helped countries enforce the intellectual property rights in their respective territories. Not only did these legal measures intend to foster innovation and create incentives for the pharmaceutical companies to invest in research and development, they also sought to empower national governments to mitigate the AMR situation. Further, emphasis on the long-term drub patents encouraged the pharmaceutical companies to invest in research and development of new drugs.

Due to the WHO monitoring and surveillance of TB drugs in 2016, the TB drug made by an Indian pharmaceutical company—Svizera Laboratories—was suspended. Svizera Laboratories were manufacturing the TB drugs, which were supplied to developing countries. It was discovered they were not up to the international manufacturing standards and quality. This reflected the low quality of regulatory frameworks and governance in India, especially with regard to the control and monitoring of the pharmaceutical sector, which led to the proliferation of ineffective medicines throughout the developing world and emergence of the TB epidemic in India.

Regardless, the multilateral efforts made by the WHO, WTO, ITO helped countries and partner organizations in promoting the universal health coverage (UHC) and social safety net protection, which are integral to an effective response to MDR-TB (Forrest, 1999). In many country contexts, MDR-TB was addressed within the UHC and social safety net protection mechanisms. Further, the WHO provided training services and methodologies of how to measure the medical expenses, costs of seeking/staying in care, and income loss from MDR-TB. These methodological tools helped to identify and overcome the underlying causes of stopping treatment before complete cure. However, the hidden interests of large pharmaceutical companies were aggravating the MDR-TB situation in India and other developing countries. These large pharmaceutical companies argued that poor countries did not have adequate financial resources to pay for the imported drugs, even at discounted prices. More than 95% of TB cases were reported in developing countries, and this statistics explained why the large pharmaceutical companies did not have much interest in developing new and affordable TB drugs. This lack of interest in TB drug development was neglected worldwide, including in India. At the same time, the enforcement of TRIPS agreement and patent right helped to increase the prices of MDR-TB drug. Currently, India was attempting to amend the Patent Right Act to prohibit new forms or different formulations of known medicines and to enable other companies to patent new anti-microbial drugs.

## What is the Next Step?

International organizations and national governments around the world have made several efforts to deal with the AMR issue. It remained a challenge, however, in certain countries to implement those policy measures. Scholarly works showed that a single intervention had limited capacity to effectively mitigate the adverse consequences of AMR. Instead, intersectoral collaboration was regarded as a solutionto fight drug resistance. The adoption of new technologies—such as a nanotechnology—was believed to help develop new drugs—particularly the anti-TB drugs—and to improve diagnostic tools for infectious diseases.

Yet, an important question remained: how could the Indian government and the governments of developing countries address the structural issues of accessibility, affordability, and availability of essential drugs for vulnerable populations. A simple answer was that there was an urgent need to consider the social determinants of health, including poverty, living conditions, work environment, and education.

Specifically, the Indian government ought to ensure that the vulnerable and marginalized groups had access to anti-TB drugs. In a majority of poor countries, public expenditures to meet the basic drug needs fell below the WHO recommendation of $2 per head per year. In India, for instance, where personal incomes were less than $2 a day, sustainable public health financing were required from the government appropriations and social security budgets. Yet, even with heavily subsidized prices, the anti-TB drug uptake rates remained low in India where there are fewer public health service providers than private (for-profit), not-for-profit, and community-based care providers. Thus, subsidized drug prices should not be restricted to the government sector, but also cover the non-governmental sectors and minority communities. The worst-case scenario was if no action was taken, things would go back to the times before invention of antibiotics where morbidity and mortality rates were high as a result of minor infections. Drug resistance was therefore a silent tsunami.

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