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The Growing Tuberculosis Threat

Can India control drug-resistant tuberculosis?



COURTESY WHO / DAVID ROCHKIND

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(I)

ON THE MORNING OF 14 OCTOBER 2011, Zarir Udwadia, one of India's foremost chest physicians, sent an email halfway around the world, to the Boston offices of the medical journal *Clinical Infectious Diseases*. The message was a brief one: just 15 sentences of precise, academic prose, submitted to the correspondence section of one of the most prominent journals in its field. The letter, jointly authored by Udwadia, microbiologist Camilla Rodrigues, and their research registrars, Rohit Amale and Kanchan Ajbani—all colleagues at Mumbai's PD Hinduja Hospital—recounted their

struggles to treat patients suffering from increasingly drug-resistant forms of tuberculosis. As the letter stated, “We describe the first patients from India with TDR Tuberculosis.”

This sentence, innocuous to untrained eyes, spawned the sort of reaction rarely seen in the measured world of the medical sciences. The letter was first published online on 21 December, and immediately caught the attention of the medical community: doctors, health officials and scientists put aside their post-Christmas ennui to debate the implications of this dramatic announcement. But this was just the calm before the storm.

Two weeks later, on 7 January 2012, Udwadia’s findings were splashed across the front page of the Mumbai edition of *The Times of India*, under the headline ‘New, deadlier form of TB hits India’. Correspondents for foreign newspapers immediately picked up the story, and soon the news was zipping through wire services and hitting front pages across the world.

Udwadia became something of a celebrity, at least in medical circles—he joked that his career “peaked in January”—as requests for reprints of his letter poured in from doctors and journalists. Health authorities also began to take note: within 10 days of the *Times of India* report, India’s Central TB Division, part of the Union health ministry, sent a three-member fact-finding team to Mumbai. A few months later, tuberculosis was declared a notifiable disease, a designation that requires private doctors to inform the health ministry of all tuberculosis patients they treat.

In March, Udwadia travelled to Geneva to discuss his findings at a meeting convened by the WHO with experts from around the world. Included in the agenda were various issues related to nomenclature that his results brought to the fore.

The TDR in “TDR Tuberculosis” stands for Totally Drug-Resistant; it denotes the existence of a strain of tuberculosis that is resistant to currently available first- and second-line drugs. There had been previous reports of what had been called TDR-TB—in 2003 from Italy and 2009 from Iran—before Udwadia and Rodrigues presented their own findings to the world. But this time, the use of the word “Totally”—with its sense of absolute incurability—sufficed to transport a short letter from the correspondence pages of a medical journal to front pages and television screens worldwide. Most people know that tuberculosis is an infectious disease, and that it passes through the air from person to person heedless of class and caste, particularly over periods of prolonged contact. Now, four doctors working in Mumbai, a city most often viewed in global culture through the prism of its ever-expanding slums, said they had isolated cases that weren’t responding to tested treatments for tuberculosis. Across the world, the headlines wrote themselves.



A woman walks home in Ashok Nagar, a slum neighbourhood far from the centre of Mumbai. The distance to the health clinics discourages many poor patients from making their daily visits for medication. COURTESY WHO / DAVID ROCHKIND

When follow-up reports began to appear, indicating that other doctors had seen similar cases, both in Mumbai and elsewhere, health officials in the city began to deliberate over how to respond. Their first reaction was to address the fear of contagion: in the week after Udwadia's findings hit the newspapers, Mumbai health authorities sought to manage public anxiety over the spread of what was being reported as "TDR-TB". They announced plans to locate and test the friends, families and neighbours of the 12 confirmed patients, and began to discuss plans for a quarantine facility for the affected patients—a move that was announced with certainty by several people affiliated with state health programmes. Yet within two weeks of the initial *Times of India* report, after health officials in Delhi began to examine Udwadia's findings, a second and radically different reaction emerged. The official position seemed to change to one of sceptical attack: questions were raised about Udwadia's conclusions, about the laboratory in which Rodrigues had conducted her tests and the type of tests they had employed, and about the motivations of the doctors, because they had presented their results to an international audience instead of going to the government first.

The argument emanating from Delhi was that Udwadia and colleagues had been irresponsible in their use of the term Totally Drug-Resistant—for the reasons listed above, but also because the very term "Total Drug Resistance" had not been agreed upon internationally, and had the potential to spark panic among the general population. Whereas Mumbai's TB authorities and Maharashtra state health officials had initially discussed plans to curtail the spread of this dangerous new strain of TB, now the Union health ministry asserted that existing programmes and procedures were sufficient to handle these cases. The reasons for this shift in position have not been made clear, but several experts critical of the government's reaction suggested that one motivation was to protect the country's reputation—and its status as a desirable destination for international capital and tourism.

The debate about how to handle TDR-TB had quickly shifted to an argument about whether TDR-TB was real—and if it wasn't, about what to call the strain Udwadia and his colleagues had observed. The government saw vindication for its position in a decision taken by the WHO after the publication of Udwadia's letter—the WHO declared that it did not recognise the term “totally drug resistant”. Citing this, the Union Health Ministry stated that there was no such strain as TDR-TB, and added that there was no need for anything more than a slight modification to the current regime of TB control, but the nomenclatural battle has continued. Many medical experts, including Udwadia, argue that the widening spiral of drug-resistance is a stark indication that the procedures already in place are not sufficient to prevent the emergence of deadly new forms of TB or treat those patients suffering from drug-resistant strains—and that the rigidities of these existing programmes, and inefficiencies in their implementation, may in fact be a major cause of worsening drug-resistance.

While health officials may have attempted to discredit the news of a “totally drug-resistant” strain of tuberculosis as needlessly alarmist and based on faulty science, in an editorial published in the medical journal *Thorax*, Udwadia wrote that tuberculosis “remains India's biggest public health problem. India bears a disproportionately large burden of the world's TB, one a developing country can ill afford”. The WHO estimated that in 2010, India had a total of 3.1 million people infected with TB, of which 2.3 million were new cases of incidence from that year. In his editorial, Udwadia wrote that tuberculosis kills 300,000 every year. “That is one death every 2 minutes,” he added, “a grim statistic that has changed little over the decades.”

One of the biggest problems researchers and doctors face is that tuberculosis remains a problem of the downtrodden. Overwhelmingly, tuberculosis is a disease of the developing world, and in the developing world, a disease of the poor—one reason the disease garners little attention in both the local and international media. The poor are especially vulnerable to infection because they're forced to live in overcrowded, substandard housing, often without proper sanitation and ventilation. Nutrition is a vital factor in staving off tuberculosis infection, so the conjunction of poverty and malnutrition further deepens the vulnerability of the poorest Indians, as do domestic migratory patterns, which often deposit poor migrants into the heart of communities teeming with tuberculosis.

There is also a significant social stigma attached to tuberculosis; this has been true through history, and remains the case today, despite the great advances that have been made in our treatment and understanding of the disease. This is due in part to the association between tuberculosis and poverty, but even within poor communities, tuberculosis patients face a very real threat of excommunication. Researchers tell innumerable stories of wives thrown out of their houses by husbands after being diagnosed with tuberculosis; fearing this stigma, many women infected with TB choose not to report the disease.

Both Udwadia and Mini Khetrpal—the TB officer at the Brihanmumbai Municipal Corporation (BMC), who now oversees the care of the patients originally diagnosed with TDR-TB at Hinduja Hospital—were therefore understandably wary of revealing too many details about the affected patients. But when I met Udwadia in August, he did offer a broad profile. “They were all impoverished—there wasn't anyone from the middle class,” he said. “But remember, this is a disease that trickles across social strata. TB does not respect social status or even physical boundaries. One of these patients hops on a plane and you have it in a different country. One of these patients is a driver for a rich industrialist and he gets it. But yes, these people, they were very impoverished, from the most marginalised sections of society—that is what was common to them, if you want the [archetype] of a typical TDR patient.”



Patients, mostly with TB and lung problems, in the waiting room of Hinduja Hospital in Mumbai. Due to the scale of the disease, private partnership in the government's programmes is vital for meeting the demands for testing and treatment centres. CHIARA GOIA FOR THE CARAVAN

Udwadia, who has not been in contact with any of the patients since the end of January, when the BMC took over their care, told me there were now 15 reported cases of what he had identified as TDR-TB. "And I know that the fifth just died," he said. "My research registrar just updated me."

When I spoke to Khetrapal on the telephone in late August, she confirmed that five of the original patients had died. "There were twelve patients in all, and five patients have expired," she said. "Five are with us [under BMC treatment], and two were from Maharashtra state, so we at the BMC don't look at them. We follow up on a regular basis on each of the five remaining patients. The treatment is going well."

If five of the original patients have now died, that leaves at least seven people infected with this new strain of tuberculosis, and the question of further contagion remains an issue. Doctors estimate that a person with active tuberculosis infects between 10 and 20 other people in a year, and the additional complication of increased drug resistance in the afflicted patients may suggest an incipient crisis.

Tuberculosis has been a persistent and deadly ailment for most of recorded human history because the bacterium, *Mycobacterium tuberculosis*, travels through the air. Camilla Rodrigues, the microbiologist at Hinduja Hospital, explained that TB is an airborne transmission disease, like measles or chicken pox. "The other two aren't nearly as dangerous, of course," she said. One of the reasons we now see TB as a socio-medical problem is because of its transmissibility: if I have TB, my neighbours will be pretty worried, because I'm coughing out TB bacilli all the time, and that wafts through the air. That is the worst part—particles become airborne, and they don't settle. Say I have a respiratory viral infection. If I cough, within three feet of my cough, the droplets will settle. With TB, some particles do of course settle, but lots of particles get wafted off on tiny little particles of dust, and they remain in the air at breathing level. So an innocent visitor can easily inhale that."

One way to stop the spread of a new strain of drug-resistant tuberculosis would be to quarantine the infected patients; the patients would be treated in negative pressure isolation rooms, which are used in hospitals to prevent the transmission of airborne contagious diseases. But it seems that is simply not an option in India. “Where would you quarantine them anyway?” Udwadia said. “In the West—in the US or the UK—they would have been quarantined right away, compounded, in a sense. Even involuntarily, if that was necessary.” Health officials had discussed such measures in the first days after Udwadia’s findings, even as activists raised concerns about the legal and ethical implications; the idea was eventually shelved. “The government was talking about a facility that they were opening up—somewhere in Sangli, I think—but I have heard nothing since,” Udwadia told me. “So they’re out there roaming the community, like every other TB patient in India is as well.”

(II)

IN THE MONTHS SINCE UDWADIA and his colleagues identified what they described as Totally Drug Resistant Tuberculosis, the strain’s nomenclature has been hotly debated. According to the definitions issued by the WHO, there are two forms of drug-resistant tuberculosis: Multi-Drug-Resistant (MDR-TB), which is defined as tuberculosis resistant to the two most powerful first-line anti-TB drugs; and Extensively Drug-Resistant (XDR-TB), defined by resistance to the first-line drugs and several of the most effective second-line drugs. In March, following the meeting of tuberculosis experts in Geneva, the WHO concluded that while all signs pointed to a worrying level of drug resistance, there was insufficient data to establish an entirely new case designation for the strain Udwadia had written about. The WHO also rejected the term “totally drug-resistant” as unclear and unscientific and recommended that the high resistant strain being observed be classified as “extensively drug-resistant”. Some medical professionals, like Ashok Kumar, the head of the Central TB Division, had described the resistant strain as “XXDR” or Extremely Drug Resistant, when the first reports appeared—but even this term was rejected by the WHO, which insists that the strain be classified as XDR. But whatever the name, the strain—like those reported earlier in Italy and Iran—represents the latest challenge in a long and evolving war, dating back several centuries, that pits doctors and medical researchers against resilient, proliferating and mutating bacteria.

References to the disease we now know as tuberculosis have been found in texts from more than 3,000 years ago (including the *Rigveda*). But the first definitive breakthrough in tuberculosis control came on a wintry Berlin morning in 1882, when a doctor with the German Imperial Health Office, Robert Koch, used a new staining technique to identify and describe the bacillus *Mycobacterium tuberculosis*. Koch received the Nobel Prize for medicine in 1905 for his discovery, and humanity at last knew precisely what was causing a disease that would go on to claim more than 100 million lives in the 20th century.

The first vaccine for tuberculosis, known as BCG (Bacille Calmette–Guérin) after its French creators, Albert Calmette and Camille Guérin, was introduced in 1921; it remains the only vaccine for TB in use today, though its efficacy varies widely. Until 1943, when the first anti-TB drug, streptomycin, was isolated, the only curative options doctors possessed were sanatorium treatments dating back to the 19th century and crude surgical interventions where infected parts of the lungs or pockets of bacteria were removed. The initial deployment of streptomycin was a great success, and it quickly entered wide-scale use. But almost immediately, *Mycobacterium tuberculosis* began to fight back. In this regard, bacteria are a moving target: as they multiply, tiny copying errors—mutations—creep into their genetic code. Most of the time, these mutations don’t help the bacteria, but on occasion a mutation occurs that confers beneficial new traits, such as resistance to an antibiotic.

It may sound implausible, but consider the numbers: if you are infected with TB, there are approximately one trillion *Mycobacterium* cells living inside you. The odds of a single bacterium having a streptomycin-resistant mutation are about one in 100 million—equal to or worse than your chance of winning a lottery jackpot. But given a trillion bacteria, even with these odds, 10,000 could survive streptomycin treatment. And now that you've effectively wiped out their competition, these bacteria can thrive. The solution to this conundrum is what's known as combination therapy—hit the tuberculosis bacteria with three different antibiotics at the same time. To survive, a bacterial cell needs mutations that protect against all three drugs. It's like winning three different lotteries all in one go—a tall order even for a trillion bacteria.

But for combination therapy to succeed, both in terms of curing the disease and preventing the development of new forms of drug-resistance, patients must adhere to a comprehensive treatment regime and, crucially, they must complete a full course of treatment even if their symptoms abate. To do otherwise risks encouraging the most resistant bacteria to flourish by eliminating their competitors. Over time, incomplete or ineffective drug regimens essentially breed resistant strains of bacteria, which is why drug-resistant tuberculosis is considered an iatrogenic disease—meaning that it is caused by errors or failures in medical treatment.

In the early 1990s, the WHO developed a new anti-TB strategy, known as DOTS (Directly Observed Treatment, Short-Course), intended to improve treatment outcomes, prevent the spread of TB and arrest the development of new forms of drug-resistance. The programme has five major components, among them the administration of a standardised drug regimen under the supervision of a health worker—hence “directly observed”, which ensures that patients actually take their medicine and complete their course of treatment.

The Indian government began pilot-testing its Revised National Tuberculosis Control Programme (RNTCP), which incorporates the principles of DOTS, in 1993. The initial results were promising, and in 1997 the RNTCP was implemented nationwide. The programme involves the delivery of anti-tubercular drugs free of cost, through an extensive network of government primary health centres and participating private-sector providers.

It is a massive undertaking, and a major organisational achievement, one that has rightly been hailed as a global success story. Since 2006, RNTCP has covered 100 percent of India's territory (though it still hasn't reached 100 percent of the population); the programme has consistently maintained a treatment success rate of greater than 85 percent, and a detection rate close to the global target of 70 percent. But while the RNTCP has successfully met WHO targets for case detection and cure, its record in treating patients with Multi-Drug-Resistant Tuberculosis is less admirable: in 2010, only five percent of patients who needed drug susceptibility testing (known as the DST, such tests tell you which drugs the TB bacteria in a person is sensitive to, and therefore whether the person has Drug Resistant TB or not) were screened, and only two percent of the estimated 99,000 patients with MDR-TB received second-line drug treatment through the RNTCP.

Any large-scale national programme—particularly in a country as large as India—is likely to suffer from certain inefficiencies, but in the treatment of tuberculosis these can have especially pernicious effects. Lapses in protocol relating to cleanliness or infection control at health centres can contribute to the further spread of tuberculosis, and lead to increased drug-resistance in patients who have come for treatment. If a patient fails to complete the entire course of treatment, an opportunistic, more resistant form of the disease is likely to take over.

There is no doubt that DOTS and its localised variants have been tremendously successful, but the rising incidence of drug-resistance and the more worrisome appearance of new drug-resistant strains, particularly in the developing world, has led some critics to raise questions about the design and implementation of rigidly standardised national TB-control programmes. India and China—which has the world’s largest DOTS initiative—are, in the parlance of global health authorities, “high-burden” countries for MDR-TB, representing 38 percent of all cases worldwide in 2010, and augmenting national programmes to address drug-resistant strains has become a major priority for global TB-control efforts. Programmes that have been designed to ensure standardised treatment, critics say, may lack the flexibility to deal with a constantly shifting target like mutating bacteria, in part because these programmes are so enormous that implementing even tiny adjustments in treatment practices poses severe logistical and financial challenges.

IN AUGUST, I WENT TO MEET UDWADIA in his office at Hinduja Hospital. He is bespectacled, gangly and brisk—a man who gives the impression that he does not have a second to waste. He began to talk almost before I had sat down. “Since I came back from the United Kingdom twenty years ago, we’ve seen before our eyes the pattern of resistance slowly worsening,” he said. “When I first got back, MDR was something unusual, very rare. Then, XDR came along. The very year it was described—2006, I think—we started reporting our first cases in Hinduja. They gave us the terminology, we went back to our database and sure enough, we had these patients.” In 2011, Udwadia continued, “we started seeing these patients come in with a report that was across-the-board resistant to all possible drugs. This was coming. It was on the way, because it’s just an ominous progression of resistance. Each initial you add, whether it’s M or X or T, is just a reflection of our failure.”

Tuberculosis control in the city of Mumbai involves a labyrinthine network of agencies and acronyms. It is managed by the Mumbai District TB Control Society (MDTCS), an organ of the Central TB Division, which is in turn part of the Union Ministry of Health and Family Welfare. The MDTCS has deputed officials from the city’s municipal authority, the Brihanmumbai Municipal Corporation (BMC), to oversee matters in the city. The Central TB Division crafts the national policy through the RNTCP, which the BMC is charged with implementing in Mumbai.

On 7 January, the day that Udwadia’s findings made the front page of *The Times of India*, Maharashtra and BMC health officials contacted Udwadia and his colleagues to discuss how best to address the situation. Less than a week later, *DNA*, one of Mumbai’s largest newspapers, reported that the Maharashtra State Anti-Tuberculosis Association had also detected two cases of “TDR-TB” in 2011, according to Yatin Dholakia, the association’s secretary and technical adviser. “Drug sensitivity tests showed their illness was resistant to all the available drugs,” he told the newspaper. “Of the two, a 15-year-old girl took treatment for a while and then migrated somewhere. The other, a 25-year-old, will have to undergo surgery as part of her lung is infected and needs to be removed.”

A week later, the BMC swung into action. After a meeting between state and city officials, Manisha Mhaiskar, the additional municipal commissioner for health, announced that the BMC would begin contact tracing for each of the 12 patients diagnosed with TDR-TB—which involves going into the communities where the afflicted people live and testing close contacts like family, colleagues and friends. At this point, the state officials and Udwadia were trying to come up with a plan to work together; after officials visited Hinduja Hospital, Udwadia told the *Hindustan Times* that he had suggested the introduction of new legislation “to ensure that specialists can treat TB patients. We are looking for a public-private partnership so we could give the prescription and the state could provide the medicines.”

On 14 January, it was reported that doctors at St John's Research Institute, in Bangalore, had conducted drug susceptibility tests on 100 tuberculosis patients, and found six cases of increased drug-resistant TB, which were also described as "TDR-TB". In the same week, two of the original patients at Hinduja Hospital died—both women in their 30s who had been fighting tuberculosis for more than three years. After consulting with the Central TB Division, state health officials announced plans to isolate the surviving patients at a sanatorium in Jaysingpur, about 400 km south of Mumbai, though Union Health Minister Ghulam Nabi Azad said a decision would not be taken until the Central TB Division's fact-finding team completed its assessment. On the same day, Sanjay Oak, the BMC's director of medical education and major hospitals, told *TheTimes of India* that "isolation is the prudent way of tackling this TB variant", adding that "two of these patients are autorickshaw drivers who mingle with common people everyday".

But within a few days, it became clear that the Union and state health authorities had decided to take a different course. After 10 days in which concrete steps to prevent the further spread of increased drug-resistant TB dominated the discussion, the official line suddenly shifted to a semantic dispute. On 17 January, a Union health ministry press release declared that the term "Totally Drug-Resistant" was "non-standardised and is misleading", and that "it is neither recognised by the WHO nor the RNTCP". The press release also cast doubt on the reliability of the laboratory at Hinduja Hospital, noting that it was not accredited by the RNTCP to conduct drug-sensitivity tests on second-line drugs.

One day later, the six-member fact-finding team from the Central TB Division, led by Ashok Kumar, attended a meeting where they heard the testimonies and opinions of a number of tuberculosis experts in the city. Afterwards, Kumar announced that Udwardia and his colleagues had been "premature" in their diagnosis of a new strain of tuberculosis. "There is no situation as TDR-TB in the city," he said. "The World Health Organization does not recognise it. There is always hope with new drugs."

Near the end of January, it was decided that the BMC would take over treatment of the 12 patients who had been diagnosed with TDR-TB. The patients were taken to the BMC's tuberculosis hospital in Sewri, South Mumbai, where they began new treatment under the prescriptions of the RNTCP.



A patient at the Sewri TB hospital in Mumbai sits on his bed after receiving an injection. With a mean patient age of 32, TB badly hits young working men and women. COURTESY WHO / DAVID ROCHKIND

The Sewri TB hospital, however, has for years been something of a grisly joke among health professionals in Mumbai; its crumbling edifice and stained walls are regarded as an outward sign of its neglect by city health authorities and the inadequate training provided to its non-medical staff. To take just one example, in 2006 the hospital's operating theatres were found to be in such disrepair and staffed by so few doctors that it was decided they should stop performing surgeries altogether—an odd decision for a tuberculosis hospital in a city riddled with tuberculosis; the operating theatres lay idle for six years, though they re-opened earlier in 2012.

To make matters worse, members of the hospital's own staff publicly threatened to quit in protest over the decision to shift the patients to Sewri. Lower-rung workers at the hospital had long complained that they were not given protective items like masks and gloves while working in an obviously contagious environment. According to newspaper reports from January, roughly 30 employees at the hospital had died of tuberculosis in the previous five years; in January when the increased drug-resistance patients were being shifted to Sewri, two resident doctors and another 17 hospital staffers were undergoing their own treatment for tuberculosis. It was not hard to see why the arrival of 12 patients with an apparently untreatable strain of the disease sowed panic among the staff, especially for those who would be in closest contact with them.

Nerges Mistry, a director at the Foundation for Medical Research in Mumbai, told me that poor conditions at a facility like Sewri carried considerable risk for its staff. "For the doctor it's still relatively okay—they come in and see a patient for ten or fifteen minutes while on their rounds," she said. "Their interaction is limited. But what about the ward boys? Or the nurses? This is how TB spreads, from sustained exposure to people with active TB. So you work in that environment, and then go home, usually to a low-income community, where people already live in tightly packed conditions. To keep costs down, the authorities are putting their own workers at risk. But they're putting whole communities at risk too."



Nerges Mistry of the Foundation for Medical Research. MANOJ PATIL FOR THE CARAVAN

FOR UDWADIA, the controversy over his classification represents a distraction from the real issue, which is the increasing incidence of drug-resistance and its implications for the state of tuberculosis control in India. “These patients were resistant,” he told me in August, “but why did this cause such a stir? Partly because of the name and politics behind it, yes—but basically these patients were across-the-board resistant to all the first-line and second-line drugs that we could test them for. That’s why we chose the name Total. I’m not saying totally doomed, I’m not saying no drug will work. But for the tests we did—and we specified what those tests were—they were totally resistant. First we saw one, then we saw a second, and then, almost all at the same time, we had about five. It would have been churlish not to put them together in the form of some communication. It was important to publish this.”

“After we wrote about TDR,” Udwadia continued, “someone from Delhi popped up and said he had a patient like this. Someone from the South—Bangalore or Madras, I think—said they’d also seen patients like this. If you look hard enough, if you have a laboratory good enough, you will pick up these patients. They’re at the bottom of the barrel. They might have been classified as MDR or XDR, but they’re clearly one step beyond that, in terms of resistant profile.” Though government officials argue the media had over-reacted to the initial declaration of “TDR-TB”, Udwadia is convinced the problem is actually more widespread than news reports have suggested. “The numbers are going to be larger here as well,” he said. “If one centre is seeing fifteen cases—and I’m telling you, this problem is not unique to our centre—then there must be other patients out there.”

Irrespective of what they’re called, the existence of these cases, as Udwadia sees it, stands as an indictment of the current system, both for its failure to identify patients already carrying drug-resistant strains and its inability to prevent new strains from emerging. “These patients hold a mirror to the way this disease is mismanaged in our country,” Udwadia told me. “Their mean age was 32, so they are young bread-earners, male and female, and they’ve seen an average of four doctors and received a mean of nine drugs before they were labeled TDR-TB. Think of how sad that is—there is

nothing more soul-destroying than going through two years of treatment and getting nowhere. Two years of treatment, and only having your resistance amplified.”



Udwadia at Hinduja Hospital. CHIARA GOIA FOR THE CARAVAN

According to Udwadia, “the typical TDR patient” would already have gone through two rounds of treatment under RNTCP: the standard DOTS six-month “short course”, and then a second eight-month treatment known as DOTS Category 2. “Then they seek multiple private practitioners, who amplify resistance further,” Udwadia said. “By the end, their resistance is amplified to such a dreadful stage that they end up with TDR.”

In early September, eight months after the frantic fortnight in January when TDR panic gripped Mumbai, I went to see Ashok Kumar, the head of the Central TB Division. Kumar, a doctor who is also a deputy director general in the Union health ministry and the project director of the RNTCP, has worked in government health services for 32 years; since February 2011, he has run the nation’s mammoth TB-control enterprise. Sitting in his impressively large office at Nirman Bhawan, in the heart of Lutyens’ Delhi, Kumar maintained that the drug-resistant strains should never have been described as TDR-TB.

“Bacteria build resistance to every drug in the world. That is the nature of disease,” Kumar said. “Now the cases in Mumbai in January that you asked me about—they used the term Total Drug Resistance, a term on which no technical committee agrees. Neither WHO nor anyone else. Why do they not agree? When Hinduja Hospital reported these eight cases, immediately we sent a Central team from Delhi. I also went there. My first move was to conduct an investigation. So we called all the experts from Mumbai in one place: chest specialists, clinicians, laboratory people, more than 60-70 people, including this gentleman who reported these findings [Udwadia], the laboratory people, Dr Camilla [Rodrigues], everyone. Look, I am a public health man, I’m not a chest specialist. So I asked them—I said, you tell me. Everyone said this is not Total Drug Resistance.”



Boxes of TB medicine sit in a cabinet at a DOTS-centre. TB patients must take the medicine daily; if they take their medication intermittently or prematurely stop treatment, they are at risk of increased levels of drug resistance. COURTESY WHO / DAVID ROCHKIND

According to Kumar, the tests conducted at Hinduja Hospital had not definitively established the existence of a strain of tuberculosis resistant to all treatment—only to certain drugs, and only under laboratory conditions. “His definition was regarding results from outside the body,” Kumar said, referring to Udhwadia. “He has said that these cases were resistant to all, yet there is no technical community of microbiologists that can agree. There is a big difference between *in vivo* [in the body] and *in vitro* [in a culture] tests. The body gives absolute, good environment, whereas a culture may not be able to give that.”

“If you say it is Total Drug Resistance, you are giving wrong information to the public,” Kumar continued. “Everyone is not a scientist. The first thing is, there are ten or eleven drugs available, and all these drugs are not given to these patients. By saying ‘Total’ you are saying that strain will never respond to anything, that this strain will kill everybody. You are creating a panic.”

For Kumar, there was no doubt that Udhwadia and his colleagues had jumped the gun, a sentiment that was vindicated when the WHO declined to issue a new classification for the cases Udhwadia had reported. “How do we get to a definition in the scientific world? These things have to be agreed upon after examination of evidence, lots of review,” Kumar said. “Science does not go by one man’s opinion.”

Kumar’s final argument, delivered with great gusto, was that further treatments—known as ‘salvage regimes’, because they employ drugs not typically prescribed for tuberculosis—had actually delivered some progress for Udhwadia’s former patients. “All the cases he reported are stable and responding to treatment!” Kumar said. “We have investigated. The rickshaw puller still pulls his rickshaw. The labourer continues to work as a labourer. They are responding! For most of them, in their sputum, the microbacterials were not found.”

At this point I interjected, noting that five of the patients had actually died since they entered the RNTCP. “No, no,” he said. “Where have you got this information from? Two have died, and one fellow is untraceable.” When I explained that my source was Mini Khetrapal, the BMC’s TB-control officer, Kumar was unruffled. “Let me tell you, we are not worried by this,” he said. “Death can happen to anybody—death is associated with TB, that is why TB is important. If you are not taking early, regular, complete treatment, death is bound to happen, because it affects your lungs—a vital organ. Your brain is not getting oxygen. You are bound to die.”

(III)

"OUR MISSION MUST BE TO TREAT THE SICK—not just the sick who can pay. Our mission must be to treat TB regardless of resistance pattern,” Udwadia told me in one of his characteristic bursts. “Paul Farmer said that—do you know who he is? He’s one of my heroes.” Farmer is a towering figure in modern medicine: a physician and medical anthropologist, chairman of the Harvard Medical School’s Department of Global Health and Social Medicine, and one of the founders of Partners in Health, a humanitarian NGO that has established hospitals and community clinics to provide primary care to some of the world’s poorest and most neglected populations, in places like Haiti, Rwanda, Russia and Lesotho.

Farmer is the best-known figure in a growing movement, led by medical anthropologists, to reorient thinking about diseases like tuberculosis away from a strictly “bio-medical” approach and towards a more holistic understanding of the social and economic aspects of illness, in order to remove barriers that prevent impoverished populations from seeking or obtaining proper care. In May, I met Nora Engel in Mumbai—a professor at Maastricht University in the Netherlands who has spent years researching innovations in MDR-TB treatment in India, Engel’s work follows in the path of academics like Farmer and his collaborator Jim Yong Kim (whom Barack Obama recently nominated to head the World Bank), who have argued that tuberculosis is not just a medical problem, but also a social problem. Engel’s research in India focuses on the difficulties of improving treatment services and how actors and innovators try to cope with the structural violence and social inequalities that cause treatment failures.

“If you view tuberculosis as strictly a biomedical problem, you’re defining it only in medical terms, and so the solutions to it can also only be biomedical,” Engel said. “One of the reasons drug-resistance is growing is because patients are unable to complete their treatments. But why are they unable to complete the course? You cannot see these as medical problems in isolation, they are problems of society.”

The great success of India’s implementation of the DOTS programme through RNTCP has been rightly celebrated, but its possible contribution to rising drug-resistance is only now being understood. The emphasis on “directly observed” treatment, as previously mentioned, is the key element in DOTS, designed in response to decades of research documenting the failure of patients to complete the required six months of treatment. To this end, RNTCP has set up a network of thousands of sites across India, called DOTS-centres, where a healthcare worker or designated volunteer is required to watch every patient actually consume their medication. The drugs for tuberculosis work much in the same way many common antibiotics do—if the course is not completed, or the drugs are of poor quality, there is a good chance the bacterium has not been expunged from the patient’s body. And it is when the patient, for whatever reason, is not able to completely defeat regular TB that it returns with increasing levels of resistance: hence, in the last decades, the spawning of MDR, XDR and strains of disputed classification like XXDR and TDR.

So the great challenge for health authorities, as they seek to curtail the proliferation of drug-resistant tuberculosis, is that they must provide good quality medicine to a vast network of clinics and establish standard practices for treatment at hundreds of thousands of sites, while at the same time ensuring that their primarily poor and uneducated patients complete their lengthy courses of treatment. Once a patient begins to feel better, he may decide it's more important to return to work—or if he lives in a rural area, that it's too difficult to make the regular journey to the DOTS-centre. The contribution of medical anthropologists has been to push these issues towards the foreground of debates on TB-control—by examining the real-world conditions in which patients, whether wilfully or because of compulsion, discontinue their treatments.

For years, the standard response of health authorities—in India and elsewhere—has been to place the burden for these delivery failures on the patients themselves. The prevailing reasoning, broadly speaking, was that patients are either too uneducated to recognise the importance of completing their course, or too poor to be able to do so. But a number of recent studies have begun to look at how treatment strategies and policies have contributed to the failure to complete regimens. In a study looking at innovations in tuberculosis control, Engel notes that “the underlying assumption of the emphasis on DOTS is that patients cannot be trusted to act for the good of the community and therefore need to be controlled in order to avoid treatment failure and protect the drugs from losing their power”. But, Engel writes, if the real reasons for treatment failures are factors like poverty or gender inequality, which “structure patients’ vulnerability to the disease and their access to care, but are often beyond their control”, then those treatment failures will not be addressed by focusing our attention exclusively on observation protocols or patient compliance.



Tuberculosis patients take their daily medication at the Mahatma Nagar DOTS-centre run by Maharashtra Janavikas Kendra, a local NGO. The stigma attached to the disease often prevents women from seeking medical care. COURTESY WHO / DAVID ROCHKIND

THE FOUNDATION FOR MEDICAL RESEARCH was established as a trust in 1975 by donations from two of Mumbai's wealthiest industrialists, Naval Godrej and the shipping tycoon Vasant Sheth, with a

mission to examine health issues that affect the most vulnerable sections of society. Though it began with a focus on leprosy, it now concentrates on drug-resistant tuberculosis and waterborne diseases. Nerges Mistry, the foundation's joint director, has spent the past three decades looking at how health policies are implemented and how they affect the poorest people in Mumbai.

When we met in May, at the foundation's offices in Worli, Mistry described the myriad ways in which conditions at TB-control centres fall short of the prescribed standards. "In the Bombay RNTCP, there is a total lack of infection control practices," she told me. "I only look at Mumbai, so I don't know about the rest of the country, but here in Bombay the health posts [the DOTS-centres] are in abysmal condition. I don't know how the doctors and staff work there. They work in filthy conditions, and more sick people come in everyday."

"In one health post we went to, there was a single glass for about 70-80 patients to drink from," Mistry said. "They were drinking from it one by one. One glass! Does that control infection or spread it? These are the simple things they don't take care of—it's not always about the grand design. If you're asking me if our health posts are functional in every way they should be—we're a far cry off."

Beyond issues of basic hygiene, there has also been criticism of the manner in which drugs are administered at these health centres, particularly regarding the unsympathetic attitudes of some staffers towards their often-impoorished patients—which, as a number of experts have observed, creates additional disincentives for completion of treatment. Even more worryingly, Mistry said, actual practices often fall well short of DOTS guidelines: the tenets of direct observation are followed "on paper", Mistry said, with a wry smile, "but in practice it's somewhat different". In some cases, she continued, this is a matter of misplaced priorities. "For years, they thought they were getting TB under control. So imagine there is a polio drive happening. The entire staff disappears to do the polio drive. Now you have a situation where the patients who come to the health post are given drugs for fifteen days and trusted to take the medicines themselves—which rather defeats the purpose of 'directly observed'—they end up shooing the patients away!"

"We've looked at the figures," Mistry continued. "Most of the RNTCP funding goes on salaries and the drugs required. The allocation for first-line drugs and staff is very high, about 61 percent of the budget. The allocation for MDR-TB is very low—only one percent—considering we're supposed to be dealing with 100,000 cases or so. There is also little funding for capacity-building with the health workers in the RNTCP: training, updates, orientation. Almost all of that is missing."



The chest X-Ray of a patient at the BMC's tuberculosis hospital in Sewri, South Mumbai, hangs in the surgical ward. COURTESY WHO / DAVID ROCHKIND

WHEN I ASKED ASHOK KUMAR about the dispiriting figures for MDR-TB in India, his response was twofold: first, that the numbers are not as bad as they appear, and second, that plans are being put in place to address the problem. “Look, India has such high population, and so much normal tuberculosis already,” he said. “If you say we are a high-burden MDR country, you have to compare it to the population we have. When two to three percent of my new TB cases are MDR, and we have 20 or 21 percent of the global cases for normal TB—in proportion to our population, we do not have a big MDR problem.”

Kumar said health ministry figures indicate that there are about 64,000 cases of MDR-TB, in India. “India has a very good, well-run DOTS programme, so our MDR incidence is not very high when compared to other countries like China,” he said. (The exact number of MDR-TB cases is subject to debate, but according to some studies, India has as many cases as China, though the proportion of MDR-TB to overall TB cases is much lower.) “According to the reports I have received,” Kumar added, “we have about 50 or so cases of XDR.”

However one interprets the numbers, it seems clear that drug-resistant tuberculosis now represents a major public health problem—and one that continues to grow each year. Kumar explained that the health ministry has introduced new measures that he believes will effectively counter the spread of drug resistance, as described in the ministry's recently released National Strategic Plan for TB control. In addition to proposed general improvements to RNTCP and an emphasis on “universal focus”, Kumar listed several concrete steps that have already been taken. “We have made TB notifiable, so all those private practitioners who were till now mistreating patients will have to inform us,” he said. “We have banned all serology tests,” he added, referring to widely used commercial diagnostic kits that often deliver inaccurate results and impede proper treatment. Finally, Kumar said, the ministry has sent “repeated entreaties to the Drugs Controller General” to implement strict monitoring of prescriptions for TB drugs. The government, Kumar said, is also building new diagnostic labs. “Right

now, all over India, we have 42 accredited DST [drug-susceptibility testing] labs. When I took over in February, there were eighteen or nineteen,” he said. “By March 2013, we will have established another thirteen labs.”

Kumar, charged with controlling tuberculosis across a population of 1.2 billion people, must have one of the most complex jobs in the world—one that is not made any easier by India’s historically low per capita spending on health and the proportionately low expenditure on tuberculosis control. “The costs are very high here,” Kumar said. “We’re talking about billions and billions. But the government has been very generous, they have really enhanced our financial situation.” According to Kumar, the RNTCP budget, which totalled R14.7 billion over the past five years, will be increased to more than R60 billion over the next five years. And despite taking one last swipe at Udwardia, he seemed to concede that the alarm over TDR-TB had brought new urgency to the fight against tuberculosis. “So you see, some people might have wanted to create a scare for their own advancement in the scientific community,” he said. “But it has done a good thing also. It has brought attention to TB. Now we must use this opportunity to benefit the country.”

THE STEPS THAT KUMAR outlined seem likely to produce some improvement in treatment of MDR-TB, but two serious challenges remain: first, the poor existing record of RNTCP in treating drug-resistant patients, and second, the daunting task of reforming private-sector treatments, which are outside the ambit of RNTCP and bear considerable responsibility for the increasing incidence of drug resistance.

With regard to the RNTCP, some experts, like Udwardia, argue that it fails the vast majority of patients infected with MDR-TB: those infected with drug-resistant tuberculosis are put through the standard six-month DOTS treatment before receiving a proper diagnosis for MDR-TB. Instead of being given a drug-susceptibility test after the failure of first-line drug treatment, they are put on the DOTS Category 2 regimen, though there is limited evidence for its effectiveness among patients already infected with MDR-TB. In many cases, this second eight-month regimen only amplifies resistance further, and patients are not given drug-susceptibility tests until both courses have failed—14 months after beginning their first round of treatment—and the results are not known for another two months. That means a 16-month delay before an MDR-TB patient is given an accurate diagnosis: even if you set aside the suffering of the individual patient, you get 16 months during which resistant strains can be spread among the patient’s family and neighbours, while his own resistance becomes more severe.

Once MDR-TB has finally been diagnosed, the RNTCP offers treatment, through a select number of pilot projects called DOTS-Plus, to roughly one percent of its drug-resistant patients. Treating MDR-TB is significantly more expensive than normal tuberculosis—as Udwardia told me, “you can treat several hundred normal-TB patients for the cost it takes to treat one MDR patient”. He characterised the government’s failure to provide adequate care for MDR-TB as a kind of “public health *realpolitik*”, justified by claims of their financial circumstances. “There’s an ethical dilemma posed by allowing these patients to languish when you have successful treatments available,” Udwardia said. “It’s wrong on clinical grounds, wrong on epidemiological grounds—because they will spread the disease—and wrong on economic grounds, because it is cheaper to act now than later. But most importantly, it’s wrong on moral grounds.”

Patients with MDR-TB who aren’t able to obtain proper treatment through RNTCP often turn to the private sector. “The vast majority,” Udwardia has written, “are left to fend for themselves, and desperately seek out a variety of private practitioners, exhausting finances, running up loans which devastate families, till MDR is further amplified to XDR, and finally, and most grimly, to TDR-TB.”

In fact, a great proportion of tuberculosis treatment in India takes place in the private sector—which encompasses everything from top hospitals like Hinduja down to inexpensive doctors operating in high-TB zones like slums. Some of these low-cost doctors are good, some are barely qualified, and some are completely unqualified. But they are involved, at some point or the other during the course of a patient's treatment, in the majority of tuberculosis cases in India.

It is not only the poor who seek care from private doctors. Despite the free treatment and drugs available under RNTCP, about half of all patients are estimated to turn first to the private sector—for issues like convenience (a private clinic might have more flexible opening hours) or confidentiality. The problem for the poorest tuberculosis patients is that the private doctors to whom they have access are far less likely to accurately diagnose and treat their infections.

The other problem with low-quality private-sector care, of course, is the indiscriminate prescription of ineffective medication, which worsens drug-resistance in individual patients and contributes heavily to the overall evolution of increasingly drug-resistant strains. There is an absence of regulation for prescriptions from private doctors, and critical second-line drugs are sometimes indiscriminately prescribed, even by homeopaths and Ayurveda specialists.

In 2010, Udwadia and several colleagues published a study they had conducted in Dharavi, which audited the MDR-TB prescription practices of 106 private doctors in the slum. Out of 106 doctors, they judged that only five were capable of making appropriate prescriptions for drug-resistant TB, “in that they contained a minimum of three new second-line drugs in the right doses and for the right duration. The majority of prescriptions were inappropriate and served only to amplify resistance.”

Camilla Rodrigues, the microbiologist at Hinduja Hospital, observed that it was natural for people to turn to private doctors, even of dubious qualification—and that tuberculosis bacteria would, in a manner of speaking, take maximum advantage of this tendency. “Why is Mumbai the hub of this disease in India? Because it's a commercial city,” Rodrigues said. “People have to be well, they have to be working and moving about. You can't sit home a single day—some of these people don't have a home to stay in—so they have to look at quick fixes, whoever can sort them out as fast as possible. If you're going to doctor A, and within a week you're not improving, you just drop him and go to doctor B.”

“There is a lot of doctor shopping in the private sector, which is one of the worst things you can do with TB,” Rodrigues continued. But, she added, many drug-resistant patients don't have any better options; the DOTS-Plus programme for MDR-TB, she said, “came in late—it only kicked in in Mumbai in 2010. Until then, patients had to go to the private sector because the public sector didn't have the programme. And this is in Mumbai, where there are 29,000 people per square kilometre!” Given these conditions, Rodrigues said, “drug resistance is bound to happen. Bacteria aren't going to sit back and allow themselves to be killed. They're going to mutate, they're going to change form.”

While some blame for the rising tide of resistance must fall on the vast number of private doctors indiscriminately prescribing ineffective drugs, the state also bears some responsibility for turning a blind eye to this problem for too many years, even as government TB-control officials were surely aware of the possible consequences. In the wake of the worldwide attention to the Mumbai TDR-TB story, the government finally took some measures to regulate and monitor private-sector TB treatment, beginning with making tuberculosis a notifiable disease (reactivating a British law dating back to the 19th century). This means that all private practitioners and clinics are required by law to notify the relevant district health officer of *every* case of tuberculosis they see and treat. It's a vital

step, but one that should have been taken many years ago, when MDR-TB cases first began to appear.

(IV)

IT'S TOO SOON TO TELL whether the changes Kumar intends to implement in the hope of halting the growth of drug-resistance will be effective, or whether they are too little and too late. For critics of the RNTCP's approach, a larger reorientation would be required to make serious inroads against MDR-TB.

"In terms of the grand picture, whatever we're doing is only firefighting," Nerges Mistry said. "There is a lot of TB in vulnerable populations that we're not seeing, and institutions where we don't look for TB at all, such as prisons, mental health homes, orphanages—these are all places where TB takes hold and spreads. But there is no planning in the RNTCP to bring these organisations under their ambit." At the same time, Mistry suggested, so much of what causes the persistence of tuberculosis is well beyond the reach of RNTCP. "Unless the government steps in to involve slum conditions, you're never going to get TB under control," she said. "Look at how we manage our waste. Unless we improve living standards in the slums, we'll continue to face these problems."

One of the problems for large-scale programmes like the RNTCP is their inability to adapt quickly—which is often precisely what's required to deal with a disease that is rapidly evolving. They seek procedural sanction from international bodies like the WHO, which invariably slows things down: even if solutions are found, and new WHO guidelines are produced, these have to be disseminated through an enormous bureaucratic structure.

So by the time procedures are put in place to deal with MDR-TB, we're facing a new threat from XDR-TB—and well before any programmatic approach has been adopted for XDR-TB, a new mutation has emerged, which appears to resist all standard drugs. As studies by experts like Paul Farmer have demonstrated, the uncritical application of standard drug regimens in areas where levels of MDR-TB are not known will only amplify existing resistance.

"Because it's such a huge system, it's an inflexible system," Mistry said. She noted that nutrition is important for the control and treatment of tuberculosis, and argued that the RNTCP could significantly improve its performance if it also paid attention to what its patients were eating. "But the RNTCP say they cannot do anything about that, that it is not their area," Mistry said. "They are to some extent fossilised. It's so big that any change you want to bring in means huge inputs and management, resources and so on. They're so exhausted by the process of reaching out to the entire country that they don't at the moment have the resources to expand their ambit in any way."

Nine months later, the storm over TDR-TB mostly seems to have dissipated. This is excellent news for the government, which would otherwise have been faced with the economic consequences of being branded a hotspot for drug-resistant tuberculosis. During our interview, Ashok Kumar addressed this point, referring to a 1994 outbreak of plague in Gujarat that attracted enormous attention in the local and international press. "I was at the NICD [National Institute for Communicable Diseases] when you media reported on the plague in Surat," Kumar said. "What does that do to the country? I know what that did to investment, to tourism. Everything shut down." But as he himself admitted, the shock of the January headlines did serve to bring the country's TB problem into prominence.



Zarir Udwadia's mail regarding a new strain of drug-resistant TB created a wave of panic in the media and among health officials. CHIARA GOIA FOR THE CARAVAN

While the return of tuberculosis to the government's agenda is unquestionably positive, one final question remains: what will become of the surviving patients Udwadia and his colleagues had diagnosed with TDR-TB? What can be done for them, and for the people they have likely infected? Of the seven surviving patients in the care of the Mumbai RNTCP, some, according to Khetrapal, were responding to treatment.

Doctors like Udwadia approach these cases on an individual basis, trying to piece together new courses of drug therapy designed for each patient. "We use what are called 'salvage drugs'—literally last-resort drugs, scraped from here or there," Udwadia said. "You need a whole new regime. Even if a new 'wonder drug' came out today, it would be worthless, because you'd be adding it to a failing regime. So from here and there, we think what we can give—some drugs you can't even test for, so we hope they are sensitive, and put together an individual cocktail for each patient."

Then, just as quickly as he had started it, he ended our conversation: "In a sense, it's almost like going back to the sanatorium days, when you talk about good food, rest and things like that—things we didn't need to think about when the drugs were so effective. That is what we're left with."

Mistry, however, believes that it is essential for the government and health officials to stay abreast of the latest developments in the field, and confront new challenges without growing defensive of the country's reputation. "The system is always in denial mode, like most systems in the public domain," she said. "For years they denied there could be any MDR-TB in the country. Then they said it's not in such alarming proportions. It's the same with 'TDR'. They say it is just another type of MDR, that there might be some exotic drugs that will curtail it. Udwadia was not trying to say there was an epidemic of 'TDR', but the fact remains there is a proportion of patients who are likely to be resistant to all the drugs available for MDR. What are you going to do about them?"

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