Trials and tribulations

Scientists studying tuberculosis are struggling with scarce funds, layers of bureaucracy and a lack of markers that can clearly identify which treatments are working, reports **Apoorva Mandavilli**.

Salim Karim has a rare problem: he has a large grant from the US National Institutes of Health (NIH) that he doesn't want.

In 2001 Karim, who leads Caprisa, a South Africa-based consortium of AIDS and TB researchers, applied for a grant to try to pin down how best to stagger treatments for tuberculosis and HIV in those infected with both. NIH approved the study, called START, but by the time they released the funds, the dollar had collapsed and the money was not enough to start the trial.

The researchers applied a second time—but this time, their application was rejected. Eventually, NIH did give them more money. But "by then, the whole HIV-TB program had changed completely," says Karim.

For example, the original research plan had been based on TB services at clinics, but because the clinics could not cope with the numbers, shopkeepers and traditional healers had begun doling out the drugs. There were other requirements, such as how someone must be diagnosed, that narrowed the criteria for eligibility.

The trial finally began enrolling in the middle of last year and so far has just 58 of the required 592 participants. "Several studies are having this difficulty, finding patients who meet the criteria," says Karim.

For scientists who try to run clinical trials for TB prevention or treatment, this is but one tangled tale. Their list of grievances—most of them legitimate—is long, with lack of money at the very top, followed by layers of bureaucracy and regulations, evolving guidelines for treatment, and the lack of markers that can clearly identify which treatments are working.

Although TB has been around for centuries, these are to some extent growing pains. The newest drug for TB was developed in the 1960s, and the vaccine dates back to 1921—so the infrastructure and expertise for TB need to be built up from scratch.

Faced with their already outdated trial, Karim and his colleagues launched a new one, funded by Caprisa and dubbed SAPIT, that is designed to ask the same question. The new trial's criteria are much more flexible, and it has already enrolled more than a third of the 600 participants, effectively ending START before it began. "It's very unlikely that [START] will continue," says Karim.

Shoe-string budgets

TB kills nearly 2 million people each year. TB researchers like to quote this statistic, followed immediately by HIV's toll, 3 million, and the funding for research on each.

It's not an entirely unfair comparison. TB is the only one of the top three global killers—the others being AIDS and malaria—without a US presidential initiative dedicated to fighting it. Few companies are interested in TB, although that's changing (see page 265). The global funding for TB in 2006 added up to $300 million, roughly a tenth of the funds for HIV and AIDS—which is largely a result of activists' efforts—and less than the combined allotments for smallpox and anthrax (see graphic, page 273).

The TB Trials Consortium (TBTC), which manages most TB trials, runs on $9.3 million, "what can only be described as a shoe-string budget," says Richard Chaisson, director of the Johns Hopkins Center for TB Research in Baltimore.

At a meeting organized in January by Médecins Sans Frontières (Doctors Without Borders), TB experts drew up wish lists for clinical trials, then lamented that they could not do any of them without more funding.

"Even if we were to walk out of here with a unanimous opinion of what could be tested, we don't have the capacity to do it," said Ken Castro, director of the Division of TB Elimination at the US Centers for Disease Control and Prevention, which oversees TBTC.

Some of those trials are urgently needed. For example, one of the most pressing issues in TB is that the standard treatment involves multiple pills taken over six months. Cutting this time would mean that more people would finish the treatment, freeing up resources and lowering the risk of drug-resistant TB.

Researchers are eager to test some of the existing drugs, such as rifampin and rifapentine, at higher doses and in new combinations to see if they can shorten treatment time. The ideas have been around for years, but most of the money has instead been funneled into a phase 3 trial for gatifloxacin, a much needed new drug.

"That's not wrong," says Bill Burman, chair of the TBTC's core science group. "What's wrong is we should be testing a lot of drugs in parallel."

Burman gives the example of a trial site in Botswana that has already hosted one HIV-TB trial. "There are interested investigators, lots of patients, good labs, experience in clinical trials. It should be a clinical trial site, but we don't have the money," he says. "Cape Town, same thing; Thailand, same thing."

No endpoints in sight

Finding the money is only the first hurdle. TB trials face a myriad of scientific problems that need urgent solutions—such as, for example, how to tell whether a drug has successfully cured the disease.

Resource poor: This sparsely furnished room is Rwanda's national ethics office and sees about three clinical trial protocols each month.

People who take TB drugs feel better within weeks, but they have to continue to take the pills for the full six months to get rid of bacteria that may be lying dormant in their body.

That's the simple explanation.

In reality, there are several categories of the bacteria in an infected individual that to the average person sound like a string of synonyms: latent, dormant, persistent, nonreplicating, resting, metabolically inactive and quiescent, to name a few. A successful drug combination has to 'sterilize' all these subpopulations to prevent the infection from recurring.

A test called early bactericidal activity can measure whether drugs are effective against the active bacilli. But there is no good way to know whether a particular combination has succeeded in wiping out the more latent bacteria.

When new combinations are tested in trials, to be absolutely sure that drugs have worked, scientists must wait 18 months or longer and watch for a relapse. "Think about it, it's absurd," says Maria Freire, president and chief executive officer of the New York–based Global Alliance for TB Drug Development.

Because those trials also require large numbers of participants, the costs of following them quickly add up to about $50 million for each trial. "Those become expensive trials," says Burman. "For moving the field forward, to find out which dose, which combination of drugs, you can't use that [endpoint], you have to use something else."

At least up to the final stage, a large phase 3 trial, researchers should rely on the drugs' ability to kill active bacteria, Burman says. Only drugs that make it through on that basis should be tested further.

The US National Institute of Allergy and Infectious Diseases, the largest source of money for TB research, is funding projects to test other markers that could substitute for sterilizing activity, although none have yet been validated. "TB trials need a lot more thinking," says Christine Sizemore, acting chief of TB, leprosy and other mycobacterial infections at the institute.

Resistance and red tape

Scientists who want to test drugs for MDR-TB, which doesn't respond to the most common treatments, face even bigger challenges.

About 450,000 new cases of MDR-TB are detected each year, but no drug has ever been properly tested for treating it. Although all drug-resistant strains are lumped under the umbrella of MDR-TB, there is huge variability among individuals and the bacterial strains they carry.

The only way to characterize resistance is to culture the bacteria, but labs in most African countries don't have the necessary equipment. For example, there's only one lab in Kenya that can grow cultures. Trials would also need trained research assistants, rather than nurses, to guarantee scientific rigor.

The lack of infrastructure and trained personnel is a pervasive problem in many African countries. In Rwanda, for example, the national ethics office is a single, sparsely furnished room. In South Africa, one informed consent described a strain as "made from the bark of a tree in Japan" because the Afrikaans word for strain was the same.

Navigating the ethics boards in such countries can be particularly time-consuming.

For one Brazilian study, led by Chaisson and his colleagues, the researchers first submitted their proposal in February 2005. Getting Brazil's local and national institutional review boards and the drug approval agency to review the application took 16 months, hundreds of hours of paperwork and two flights to Brasilia to lobby in person. The trial finally began in May 2006.

Even in the US, the regulatory requirements are exhaustive and exhausting, and often more complicated than they need to be.

Chaisson once got a trial application back from the NIH with 178 comments. The second version, which had complied with the first round of queries, came back with 120 comments. "The regulatory process is a real killer and unbelievably bureaucratic," he says.

As frustrating as these obstacles can be, however, the real tragedy is that they further delay urgently needed new drugs and diagnostics, Chaisson says. "In the 16 months our [Brazil] study was delayed, 2.5 million died of TB."

Spotlight on... Mario Raviglione

When Mario Raviglione joined the World Health Organization (WHO) in 1991, tuberculosis (TB) control was a global patchwork of ineffective treatments, poor surveillance and disconnects between researchers, doctors and health agencies. Some countries ignored TB altogether.

Much has changed 16 years on. The WHO's main strategy against TB, directly observed treatment short-course, or DOTS for short, was launched in 1995 and is being implemented in 183 countries. Case detection rose from 12% in 1995 to 53% in 2004, and yearly TB deaths dropped from 3 million to about 2 million.

But Raviglione, who became director of the WHO's Stop TB department in 2003, says this is just the start. When others in the global health community were content with DOTS, he was already pushing for more. "In the beginning, the focus was on DOTS," Raviglione says. "People would say, 'Don't insist on anything else, because we have to do the basics first.'"

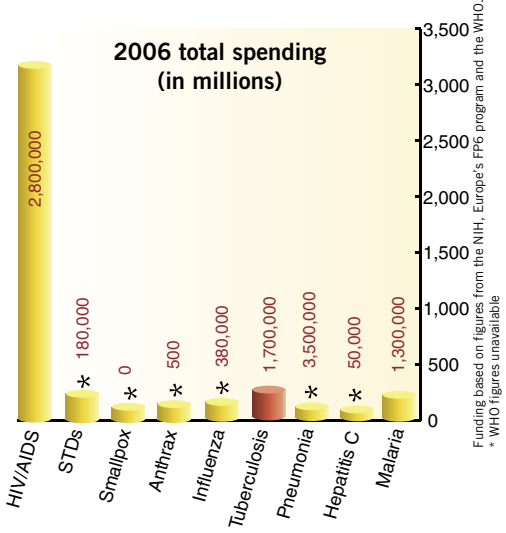
Under the new Stop TB strategy, DOTS is one element of a much larger plan. The strategy addresses problems DOTS ignores, such as the rapid spread of TB in those infected with HIV and the disconnect between researchers and public health officials. It also asks companies and local communities to play a larger role in TB control.

"DOTS was a biomedical intervention," Raviglione says. "This is a health system intervention."

Much of the new strategy is uncontroversial, but convincing the TB and HIV public-health communities to cooperate may prove difficult. Raviglione, who started out in HIV research, says those in charge of fighting HIV haven't yet acknowledged "that TB kills up to half their patients."

"If only one community pushes it, and you're talking about joint interventions that require participation from doctors in programs dealing with both," says Raviglione, "you can't do anything."

Brandon Keim, New York



Empty coffers: The global funding for tuberculosis is less than for anthrax or smallpox, although those diseases kill far fewer people (see numbers in red, above).