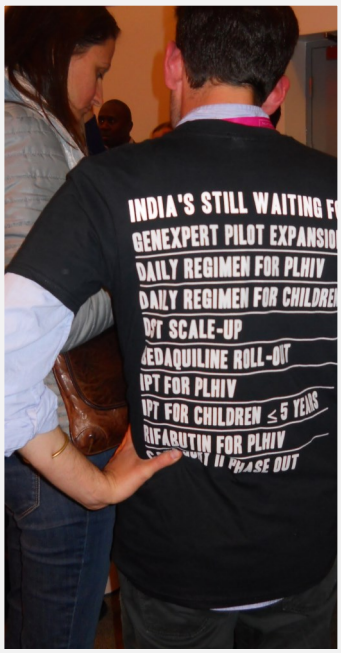
47th Union World Conference on Lung Health
Confronting Resistance

A report from IDSA Global Health

Resistance

The resistance that enabled tuberculosis to resurge from a sickness considered all but conquered in the last century, to one that in this century kills more people than any other infectious disease on earth, goes beyond the mutations of the bacteria that survive initial treatment. It is encompassed in the reluctance of research institutions to continue the fight against the disease after initial victories, of industry to develop tools and treatments needed in settings of limited resources, and of governments, funders and international agencies to fill the resulting gaps. In late October 2016, the 47th Union World Conference on Lung Health convened in Liverpool with a theme of confronting resistance with realities, research, and responses, to once again turn back the toll of a curable disease.



Realities

A World Health Organization-sponsored day of presentations that included current global tuberculosis data, as well as summaries of responses and unmet needs with a scope of challenges encompassing diagnosis, surveillance, policy, treatments, prevention, and research to confront the disease, set the stage for sessions throughout the conference. Weeks before, the agency had released a report of corrected tuberculosis incidence and mortality surveillance data showing that even with a slight drop from the previous year's tally of illnesses and deaths, the toll of tuberculosis in 2015 exceeded estimates previously provided for 2014. The new numbers reflect stalled progress against tuberculosis in the 30 countries with the highest burden of disease, and rising rates in others. The gravest impacts, presenters emphasized, are being felt by the most vulnerable populations worldwide: children, people who are incarcerated, the rural poor, and residents of urban slums. Both a cause and effect of disease among populations with the least resources to combat it, drug-resistant tuberculosis — disease that does not respond to the first, most effective treatments — has been found in every country where capacities to identify it exist. The report, speakers noted, provides the first snapshot of tuberculosis impacts for the period during which the international targets known as the Sustainable Development Goals call for a 95 percent reduction in tuberculosis incidence in the next two decades, with a 35 percent drop by 2020. Meeting that goal, or the one that follows, to reduce rates of tuberculosis globally by 75 percent, speakers concluded, will call for a "radical intensification of efforts."

Advances in diagnostic technologies and treatments that open new possibilities for those efforts would be highlighted during the days that followed. But, a preview of funding data from the Treatment Action Group showed, funding that would further that research has stalled in recent years, while efforts to ensure that the effective tuberculosis prevention, diagnostic and treatment tools that exist now are available to the people who need them, continue to fall short.

The costs of being a patient remain devastating but largely untallied

"Poverty is a major driver of disease," Dame Margaret Whitehead of WHO's Social Determinants of Health Centre noted in a conference session. But then, she added, "disease is a major cause of impoverishment."

The costs of being a TB patient, from cash laid out while seeking diagnosis, to money spent traveling long distances to clinics, to work hours lost during travel, treatment and recovery, enumerated by speakers at three sessions during the 2016 Union World Conference on Lung Health, ripple across households, communities and economies. In some countries they include the patient-borne expense of an X-ray to confirm diagnoses, and in communities across countries with the greatest tuberculosis burdens they include the costs of medicines — of questionable origin and effectiveness — from private sector and traditional practitioners. Over the course of treatment that can span two years or more, the costs of being sick with tuberculosis can include exorbitant interest on loans, and the sale of assets, including livestock, tools, and other equipment, needed for future income and employment.

The impacts of these costs are well enough known to be encompassed in WHO's End TB Strategy, with the goal that no household incur catastrophic costs due to the disease. But as a health economist at the London School of Hygiene and Tropical Medicine said, "We've known for a long time that TB patients have high costs, but we haven't known how much, and where."

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Anna Vassall,
London School of Hygiene and Tropical Medicine

An actual tally of those costs is just beginning with a WHO-sponsored project, launched in 2015, and joined by 34 countries, to survey tuberculosis patients on the financial impacts of their illness. Preliminary data from two countries presented during the conference gave a glimpse of the price of the disease. In Vietnam, lost income for patients and their family caretakers alone account for nearly 70 percent of the cost of being a tuberculosis patient, causing at least 59 percent of people there treated for the disease to incur financial losses WHO categorizes as catastrophic. Other preliminary data presented from Myanmar indicated 64 percent of TB-affected families there incurred catastrophic costs, with the greatest impacts among patients with the lowest incomes and among patients with multidrug-resistant tuberculosis that can exponentially multiply the time, costs and impacts of treatment.

International research support peaked, and now lags

But even as a measure of the economic impacts of tuberculosis begins, a measure of international support for science and innovation that would alleviate those impacts showed that interest and involvement in TB research and development among both public and private sectors is lagging. In fact, in the last year, according to the Treatment Action Group's *2016 Report on Tuberculosis Research Funding Trends: No Time to Lose,* funding toward new medicines, diagnostics, and a vaccine to control tuberculosis fell to its lowest level in eight years, with just a third raised of $9.84 billion that the Stop Tb Partnership projected would be needed between 2011 and 2015 to support development of the tools necessary to control tuberculosis.

The report, released at the WHO pre-conference event, showed that after a climb in the first years of this century, funding has never exceeded 2009 levels, before its drop last year, and is largely dependent on two donors: the United States, and the Bill and Melinda Gates Foundation, with only three major pharmaceutical companies remaining in the field of TB research.

The report noted that research advocates have called upon some of the countries hit hardest by tuberculosis Brazil, Russia, India, China, and South Africa – the BRICS – as well as Indonesia, to triple their investments in TB research and development, a suggestion reiterated throughout the conference on attendee's T-shirts.

Research

If the greatest cost of being a patient comes over the time required by current treatments, the benefits to patients, communities and health systems that can come with new treatments are significant to economies as well as to individual and public health. With only two new medicines released in recent years, research presented at the conference focused on maximizing access and effectiveness of existing treatments.

Simpler, safer, regimens offer shorter treatment for drug-resistant and drug-sensitive disease

Marking a potential turning point, trial results presented at the conference indicated the possibility of effective tuberculosis treatment with just five drugs, in two treatment regimens, both of shorter durations than previous regimens.

Results of the NC-005 study, across 10 sites in Uganda, South Africa and Tanzania of a combined anti-tuberculosis regimen using one of the newest approved drugs, an investigational drug, a repurposed drug and an existing tuberculosis drug showed signs of full recovery at the end of two months of treatment among nearly all patients on the experimental treatment, three times as quickly as trial participants on standard treatment regimens.

Importantly, researchers reported, the BPaMZ regimen of bedaquiline (the first new treatment in about half a century when it was approved in 2012 to treat drug-resistant disease), pretomanid — an investigational drug developed by TB Alliance, moxifloxacin — a repurposed antibacterial medicine, and pyrazinamide, a drug used in first-line tuberculosis treatment, was as effective among patients with multidrug-resistant disease as among patients with disease responsive to first-line medicines.

Equally encouraging were results of the NIX-TB regimen trial of a regimen for patients with extensively drug-resistant tuberculosis — XDR-TB — for whom other treatments had failed. Defined as tuberculosis that is resistant to at least two first-line drugs used to treat the disease, and to at least two drugs used to treat patients with strains of disease resistant to multiple drugs, XDR-TB is so difficult to cure that only about one in five XDR TB patients survive the illness beyond five years, the researcher presenting data on the experimental regimen noted. But of 33 patients who had completed the NIX-TB experimental regimen, of bedaquiline, pretomanid and linezolid, a drug previously used to treat other resistant infections, none showed evidence of tuberculosis in laboratory samples after four months. After completing six months of treatment, 20 patients, followed for six more months showed no evidence of illness. Side effects, termed manageable by researchers, were linked only to the use of the last drug, linezolid, for which researchers continue to adjust dosages and durations.

Together, the results hold hope for regimens that end treatment, illness, and infectiousness earlier. They would, in the process, facilitate management of tuberculosis programs currently struggling to stock as many as 20 medications, and potentially alleviate the financial impacts of lengthy complicated regimens on patients, families, communities and health systems.

Findings support recommendations for shorter MDR-TB treatment course

One morning four months into her treatment for multidrug-resistant tuberculosis, Phumeza Tisilie went into the bathroom turned on the tap and realized she couldn't hear the water running. A doctor confirmed that the then 22-year-old South African woman had suffered significant hearing loss, sustaining one of the most debilitating permanent side-effects caused by treatment for drug-resistant tuberculosis.

United Nations Special Envoy on Tuberculosis Dr. Eric Goosby, South Africa tuberculosis survivor Phumeza Tisile, and Dr. Mario Raviglione of the World Health Organization

Her exposure to the toxic drug that caused her deafness would have been shorter, possibly allowing her to complete treatment without sacrificing her hearing, under a regimen recommended by the World Health Organization in May 2016, and validated once again by results of a study released at the 47th Union World Conference on Lung Health. The findings from a study carried out across nine francophone countries in Africa showed a nine-month regimen led to an 82 percent cure rate among 1006 patients with multidrug-resistant tuberculosis, representing a substantial improvement over a previous standard treatment regimen of at least twice that duration and leading to cure rates only a little higher than 50 percent.

While the findings also confirmed similarly encouraging results presented the year before at the 46th Union conference in Cape Town, presenters expressed hope that the new results would prompt countries to hasten efforts to adopt the WHO guidelines.

Partnerships form to bridge gaps between treatment and the most neglected patients

With help, new drugs make it over rough terrains, through prison walls

While approvals of bedaquiline and delamanid in the last several years offered new options for patients for whom previous treatments had proven ineffective, it took the efforts of a collaboration of national health ministries and nonprofit organizations to prove the medicines could be supplied effectively to patients deemed the hardest to reach.

Preliminary results from ENDTB Initiative pilot projects to make the drugs available to 750 patients across four countries, presented at the conference told stories of obstacles overcome to get the medicines to people in prisons, in remote rural areas, and among populations with high rates of injecting drug use, hepatitis C and HIV. The projects, in Lesotho, Georgia, Armenia and Peru, proved that use of the newest drugs is possible in a range of settings, presenters said, and demonstrated how obstacles could be overcome with combinations of community engagement and technology. The initiative aims to make bedaquiline and delamanid available to 2600 patients across 15 countries within the next four years.

A soft drink company steps up for the youngest patients

And while the challenges facing children with tuberculosis remain numerous and strewn across the landscape of health responses, from detection to diagnosis, and finally to treatment, a partnership between the TB Alliance and the company that makes Pepsi Cola, will rise to the challenge of developing medicines appropriate to the youngest victims of the disease. Pepsi will lend its expertise — on how to make tasty products healthier, as well as how to make health products more desirable, for free, and will give open access to its findings to nonprofit efforts to make drug regimens to fight tuberculosis accessible worldwide.

"We have a bigger animal to fight, but we do it the same way we did when we thought it was smaller . . ."

Dr. Lucica Ditiu, Executive Director of the Stop TB Partnership

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