Urgent Need to Address the Realistic Challenges of Drug Resistant Tuberculosis
Perceptions versus Realities

IOM (Institute of Medicine) Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge, Workshop Summary. Washington, DC:

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STEMMING THE TIDE OF MULTIDRUG-RESISTANT TUBERCULOSIS:

MAJOR BARRIERS TO ADDRESSING THE GROWING EPIDEMIC

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Magnitude of Problem  Grossly Underestimated

Certain to exceed 500,000 new cases estimated to occur each year

Only half of 22 countries with highest TB burden participate in WHO MDR-TB survey

Surveys most often represent data at least four to five years old

Many countries data derived by modeling not surveillance

Few countries have capacity for testing susceptibility to second line drugs

Less than half of African Region population represented in surveillance data
Only 10% of new MDR-TB cases are treated each year

< 2% receiving verifiable, quality assured, second-line anti-TB drugs

Even in the small proportion of patients that are being treated, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective.
Human-to-Human Spread More common than Previously Appreciated

Until recently assumed drug resistant strains too weak to achieve human-to-human transmission

Therefore, infection control was not a public health priority

Unlike pattern in 1970s and 1980s, wherein most MDR-TB appeared to result from lack of patient compliance or sequential treatment regimens, today transmission of MDR and XDR-TB strains appears to dominate, ie Shanghai data; Tomsk and Lima experience.
Enhancing laboratory capacity may improve surveillance but not likely to impact individual patient treatment and thus failure to impact epidemic spread of drug resistant strains.

Unrealistic to think in countries where there are currently fewer than one laboratory per 10 Million population (which is the case in most high-burden countries), that sufficient resources and time are available to scale up quickly enough to have a major impact upon rapid diagnosis and treatment, especially given that most patients are in remote settings.

Recently introduced diagnostics and those in late stage development increase speed and sensitivity unfortunately they still require laboratory infrastructure.

Technology for detection of MDR and XDR-TB at point of care is available but requires further evaluation.
Countries need one culture facility per 5 million population and one DST facility per 10 million population.

- Out of 22 select high-burden countries:
  - Only six had one culture facility per 5 million population (China, South Africa, the Russian Federation, Brazil, Thailand, and Cambodia)
  - Only nine had one DST facility per 10 million population (China, Indonesia, South Africa, the Russian Federation, Viet Nam, Uganda, Brazil, Thailand, and Cambodia)

- Excess capacity exists in economically developed nations
Bottlenecks in Procurement and Distribution of High Quality Drugs

Procurement problems
Drug Quality Issue
Need for Better Data on Drug Quality
Quality Enforcement
Quality Strategies
Need for Accurate Demand Forecasting
Conclusions:

Must separate general perceptions from realities. First, we must accept the fact that TDRTB (Totally Drug Resistant TB) strains are rapidly growing in numbers. No one is actively looking and thus actual burden is totally unknown.

New image of drug resistant TB dictates that revolutionary and rapid changes must be made in infection control and making existing drugs matter.

Major difference today is high prevalence of HIV threatens to make infection with drug resistant strains, a more contagious, rapidly progressing and highly lethal disease.
Personal Reflections:
Need for Urgency:

Currently there are no consistent policies to deal with patients whose TB is untreatable.

What we do know is that proof that disease in these patients is untreatable may take months during which time they may spread their resistant organisms to family members and others in the community, including health care workers.
Even under the best of circumstances (Tomsk and Peru) 30 to 40% of cases of XDRTB are untreatable with existing drugs. Do they represent TDR?

Currently there are NO good data on TDRTB. We all know it exists but no one systematically looks for it and no one talks about it. One of the most urgent needs is to get accurate data so we can realistically address the challenge.

Treatment of drug sensitive TB requires a cocktail of 3 or more antibiotics. “Successful treatment of XDR and TDR TB requires not one or two new antibiotics but 3-4 new classes of antibiotics simultaneously thus representing a HUGE technical and financial challenge.”
Putting Challenges into Perspective: The Realities of Drug Discovery

- 90% failure rate from target identification to regulatory approval
- 50% failure approval rate even in Phase III. Thus to get a single new drug the pipeline must be full at each stage.
- Average time for drug discovery and development from target ID to approval 10-14 years (probably considerably longer for TB due to follow-up).
- Average costs for a single new drug from discovery to approval and not including post-launch surveillance for adverse events, manufacturing compliance, drug delivery, etc = >$1.5billion (probably higher for TB due to lack of infrastructure, point of care diagnostics, surrogate markers)
Realities of New TB Drug Development:

Technical and financial challenges in development of new drugs are so large that no one government, institution, or company has enough resources or expertise to adequately address the challenges. To put it in perspective, the total R&D budget for large companies on average across therapeutic areas is $2-3 billion with average launch of a single new product of 1 in 4 years. Total global investment in TB drug R&D, including the Gates Foundation in 2009 was $176 million.
Public Perception:

-TB remains a problem but we have drugs to successfully treat it. Some countries have almost eliminated it using existing tools.

-Only 500,000 new cases of MDR-TB per year which is not large compared to other unmet medical needs besides these are caused by inappropriate treatment, lack of patient compliance, and impure drugs.

- No worries, MDR/XDR TB not spread from person to person.
Failure to acknowledge the new realities of drug resistant TB and to act rapidly will be catastrophic for many countries and will greatly jeopardize the public health of all others (immigration and international travel).

We must start communicating the realities of drug resistant TB and translating the data into policies commensurate with the magnitude and urgency of the challenges we face.
Opportunities to Collaborate

May 26-27, 2010     Moscow, Russia
“IOM/NAS and RAMS Workshop on Drug Resistant TB”

2011     India IOM/Indian Academies
China    IOM/NAS and CAS

NIAID preceding workshop on TB Research Priorities