

What Will It Take for the Failing TB Elimination Plan to Succeed?

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Key Messages

- The plan to eliminate TB in the US by 2010 failed, and is projected to require over 90 years
- The failure to implement the U.S. plan leaves TB and drug-resistant TB as a growing, yet largely ignored global microbial threat
 - Major advances in diagnostics have been made, but slowly implemented
 - Treatment regimens remain weak, poorly tolerated and toxic
 - Major governmental funding will be required

Timeline for TB Elimination & Case Rate per Million*

Year	Rate	Landmark
'89	95	Advisory Council for the Elimination of TB plan: 2010 goal of 1 per M: 1. Better use of current tools 2. <u>Rapid develop and implementation of new tools for TB & LTBI</u> 3. <u>Rapid transfer to private and community clinics</u>
'92	104	Nat. Action Plan to Combat MDR TB; MDR 3% US, 19% NYC
'94	92	DTBE budget increased to \$140 M from \$23 M in '90; TBTC started
'99	63	MDR 1.1%; ACET reaffirmed TEP: 1. <u>Rapidly develop & implement new tools</u> 2. <u>Expand partnerships for LTBI diagnosis & treatment</u>
'00	63	Interim goal of 35 not met IOM Ending Neglect, new target 2035, same recommendations LTBI coined in targeted tst & tx guideline, 2RZ recommended

Adapted from Reves R, Nolan C, AJRCCM 2012;186:i-iii.

Timeline for TB Elimination & Case Rate per Million (cont.)

Year	Rate	Landmark
'01	56	TBESC initiated
'02	52	TB Elimination Plan implementation cost estimated: increase \$140 → \$528 per year recommended
'03	51	TBTC #22 trial: INH+rifapentine for continuation TB Tx, not HIV+ 2RZ retracted due to hepatic injury & deaths
'05	48	TB control statement recommends <u>broad implementation of LTBI Tx</u>
'06	46	TBESC 13: 92% of LTBI treated in TB, immigrant, correctional clinics
'08	42	RCT shows better completion, less toxicity of 4RIF vs 9INH Comp TB Elimination Act signed: funding not increased to \$200 M
'09	38	CDC guideline for NAA testing released & MDDR service initiated
'10	36	TB rate 36-fold higher than original ACET goal for 2010 CDC guideline recommends IGRA to replace TST
'11	34	TBTC #26 recommends 12-dose LTBI regimen after 10-yr CDC announces “ Winnable Battles” with NO mention of TB

Rapid development & implementation of new tools for diagnosis & treatment of TB & LTBI

... does not come to mind when the regimen of IRZE was:

- developed in the 1980's
- approved in US recommendations in 1993, the same year 407 U.S. residents had MDR-TB, a form of TB for which:
 - the new standard regimen was impotent
 - treatment for 18-24 is poorly tolerated & expensive
 - continues to be transmitted globally and in the U.S.
 - TBESC #8 20/20/40 percent imported, secondary, from LTBI; 350 infected contacts (Moonan P, et al. Lancet /Infection Vol 13 2013)
 - Elementary school outbreak Orange County, CA: (Adler-Shohet, Felice C. MD, on-line Ped ID Journal 2014)

Evaluation of 118 contacts of teacher with MDR TB

- Teacher's Classroom: 21 of 31 (68%) infected (+TST); 10% risk for developing MDR-TB
- Other school contacts: 10 of 87 (11%) infected
- Treatment for MDR-TB infection (unproven benefit)
 - Levofloxacin plus PZA daily for MDR LTBI
 - Started in 26 infected contacts
 - Completed 9 months in 58%
 - No other TB cases developed by 2 years

What should have happened?

- Prompt diagnosis & drug susceptibility results
- Safely return to work in 2- 4 weeks
- Cure of TB with “short-course” 6 month regimen (why not 2 or 4 months?)
- Protection of contacts with 9 months treatment (why not 2-4 months?)
- Safe travel without exposure to MDR-TB

Why not?

TB is not appropriately recognized as a global threat: my experience at the IOM

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Meeting

Sustaining Public Health Capacity in an Age of Austerity

When: September 10, 2012 - September 11, 2012 (8:30 AM Eastern)

Topics: Diseases, Global Health, Public Health

Activity: Forum on Microbial Threats

Board: Board on Global Health

The one reference to TB in 2011 Ready or Not?

2007

Major Public Health Emergencies

- **May** — CDC announced that a patient with suspected **extensively drug resistant- Tuberculosis (XDR-TB)**, which is spread through the air traveled to Europe and back, prompting an international public health scare. The patient did not turn out to have the disease, but problems in the response raised concerns among public health experts about preparedness for managing a real multidrug resistant TB patient.¹²⁷

Public interpretation: “only MDR”, not really that bad

TB is the mastodon in the room

Year	Event	Deaths in US	US TB Cases	MDR	TB annual deaths*
1993	TB Peak		25,107	407	1,639
2001	Al Qaeda	3,000	15,945	148	764
2003	SARS	Zero in US 800 global**	14,835	115	711
2011	Joplin tornado CO lysteriosis Hurricane	140 30 56	10,521	124 6 XDR	505-915

*Death certificate data – not available for 2011, but 505 if 4.8% or 915 if 8.7%, the proportion dead at diagnosis or before treatment completed.

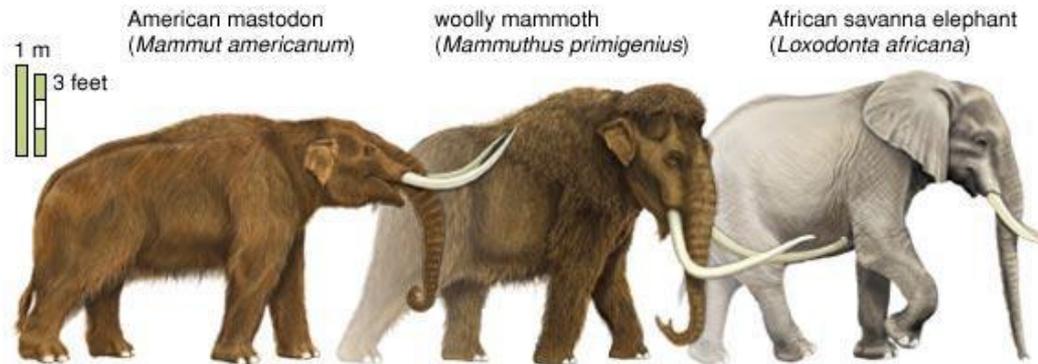
Global TB deaths over one million per year.

**Of 8,000 global infections, none in US. None infected left with future risk (e.g. latent).

. . .unlike the mastodon, TB thrives & the progeny are even worse

Global survey of 1,278 MDR cases treated 2005-8

- Resistance to at least one 2nd-line drug in 44%, injectable in 20%, fluoroquinolone in 13%
- XDR in 6.7% - currently “untreatable” globally
 - Range in 8 countries: 0.8% Philippines, 15% Korea



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Conclusions:

- The failure to “rapidly develop and implement new tools for diagnosis and treatment of TB and latent TB infection” as recommended in 1987 has left local and state health departments:
 - Inadequately prepared for MDR-TB
 - Unprepared for XDR
- This is not a theoretical risk:
 - MDR/XDR TB transmission does occur
 - Potential for super-spreaders exist for MDR-TB as shown in school exposures

The forum provided an opportunity to speak for local public health departments

- IOM presentation, “The failure to implement the plan to eliminate tuberculosis in the United States: Implications in the era of declining resources.”
- <http://www.iom.edu/Activities/PublicHealth/MicrobialThreats/2012-SEP-10.aspx>
- This lead to a commentary:
<http://www.iom.edu/Global/Perspectives/2013/High-School-Outbreak-TB.aspx>

We need to get the word out that school outbreaks of MDR will continue to occur

A High School Outbreak of Multidrug-Resistant or Extensively Drug-Resistant Tuberculosis: Is Your Local Health Department Ready?

Randall Reves, M.D., Denver Health*

April 12, 2013

The obvious answer of “no” to the question of readiness is not just due to the ongoing loss of experienced staff. Loss of infrastructure is bad enough, but even an well-staffed health department needs safe and effective treatment tools when more than 100 high school students become infected with Mycobacterium tuberculosis following exposure to an infected student and/or staff member at school. There are no

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United States in 1993.³ Tuberculosis was developed after more than 4

Otherwise, the news will be dominated by theoretical global threats

White House Declares MERS Coronavirus “Threat To Public Health.” (The Hill 6/5)

- HHS Secretary Kathleen Sebelius and the Obama Administration designated the Middle East respiratory syndrome coronavirus as a “threat to public health and national security.”
- The disease has infected at least 54 people since last April, according to the WHO.

- **Fauci Downplays Severity Of MERS. (USA Today 5/30)**
- Dr. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases said there has “only been a total of 50 cases” of the MERS virus, and it is “difficult to spread from one person to another.”
- “Right now if it stays the way it is, and goes no further than it is, than it’s obviously not a threat to the world.
- However, we know from experience with emerging and reemerging infectious diseases that there is a possibility...that the virus can change, evolve or mutate so that it does become more efficient in going from person to person.”

Meanwhile WHO estimates there were 28,000 XDR TB cases globally.

Could Increased Funding for Drug
Research & Development Make a
Difference?

Could Funding for R&D Doses Make a Difference?

- Compare the regimens currently in use for HIV and TB
- Compare the management of routine and drug resistant HIV and TB

Once-daily, single-pill combination HIV regimens in use 2014



Once-daily, 11-pill/capsule TB regimen in use since 1993

- BIW IRZE – 21 units per dose
- TIW IR – 17 units per dose



Daily

BIW : twice-weekly

Using New HIV Drugs: Man with History of Disseminated Histoplasmosis

Yr	Nucleoside	PI	NNRTI	Int. Inhib	Other
95	D4T, 3TC				
96	D4T, 3TC	IDV			
02*	D4T/ABC, 3TC	NLF/LOP, RTV			
03		AMP/RTV	EFV/NVP	ENF	
04	3TC	FOSAM/RTV	NVP		
05^	3TC, AZT, TDF	FOSAM/RTV	ETR		
06	D4T, FTC, TDF	DAR/RTV		RAL	
08	FTC,TDF	DAR/RTV		RAL	
10^	D4T, FTC, TDF	TIP/RTV	NVP		FOSC 2/52
12	FTC, TDF	DAR/RTV	ETR	DOL	IBALIZUMAB

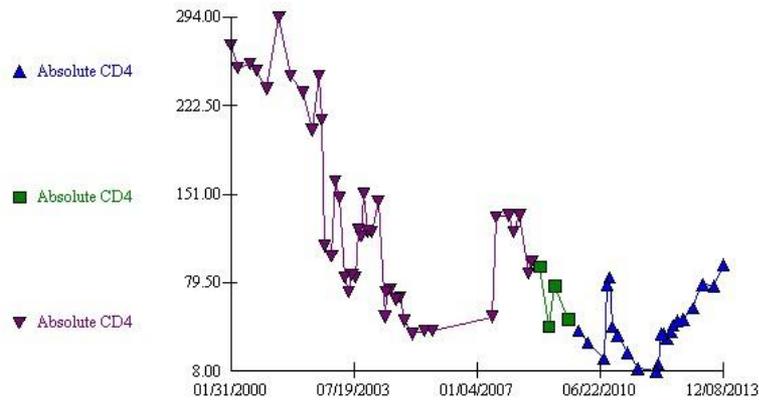
*Persistent viremia during 6 yrs on D4T, 3TC, IDV

^Resistance to 3 drug classes in 2005, 4 classes in 2010

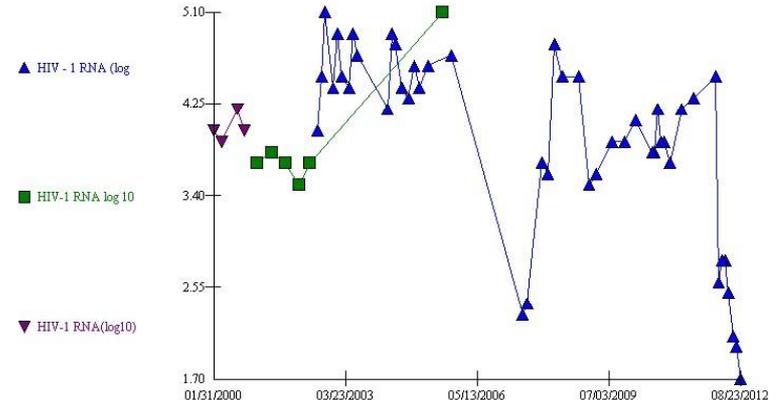
Total of 22 different drugs!

Immunologic & Virologic Response, 2000 - 2013

Absolute CD4 count



HIV-1 RNA log 10



Note: different colors reflect changes in laboratory providers over 13 yrs

Frequent History During Visits to MDR-TB Treatment Sites, Uganda in 2013

- Treated with Category 1 regimen then repeatedly with Category 2 over 3 years with no improvement
- Travels 7 km daily for DOT with L, Km, Cy, Ethio, PZA
- Finally improving, but going deaf, unable to work



The Challenge: How Can We Achieve Visionary Leadership by Politicians in Our Countries?

Tuberculosis 2013: 5



Drug-resistant tuberculosis: time for visionary political leadership

Ibrahim Abubakar, Matteo Zignol, Dennis Falzon, Mario Raviglione, Lucica Ditiu, Susan Masham, Ifedayo Adetifa, Nathan Ford, Helen Cox, Stephen D Lawn, Ben J Marais, Timothy D McHugh, Peter Mwaba, Matthew Bates, Marc Lipman, Lynn Zijenah, Simon Logan, Ruth McNerney, Adam Zumla, Krishna Sarda, Payam Nahid, Michael Hoelscher, Michel Pletschette, Ziad A Memish, Peter Kim, Richard Hafner, Stewart Cole, Giovanni Battista Migliori, Markus Maeurer, Marco Schito, Alimuddin Zumla

Two decades ago, WHO declared tuberculosis a global emergency, and invested in the highly cost-effective directly observed treatment short-course programme to control the epidemic. At that time, most strains of *Mycobacterium* Lancet Infect Dis 2013; 13: 529-39

The Way Forward

- US reauthorization of the TB Elimination Act with ATS (Nuala Moore) support and leadership – increase the Division of TB Elimination budget from \$134M to \$200M – just a start
- Achieve appropriation of the authorized funds
 - Major increased governmental funding will be needed since the profit motive is inadequate: NIH and/or other mechanisms
- Maintain local/state public health funding for TB control and cost of new tools - despite declining case-loads

How can we succeed – some thoughts on communication

- Use every opportunity to communicate the threat and the needs:
 - “We were fortunate this school TB exposure was to drug-susceptible TB – we still don’t have an approved treatment for MDR-TB infection.”
 - “I apologize for the treatment that we have to use for your TB – we should have had a better regimen 20 years ago, but TB research has been inadequately funded”.
- Partnerships with organizations – great example with TAG, the TBTC Community Research Advisory Group and rifapentine

I believe we can eliminate TB – here is why

- 1990 I moved to Denver to be the medical director of the ID/AIDS Clinic started by David Cohn
- By 1993 with about 1,000 AIDS patients
 - HIV treatment was weak, predictably failed, drug-resistance was expected
 - 12-15 death certificates/month
 - It was much easier to treat TB, even MDR, than AIDS:
 - CMV retinitis – life-long IV gancyclovir
 - disseminated MAC
 - cryptosporidiosis, cryptococcosis, microsporidiosis
 - KS, lymphoma, etc.
 - Peripheral neuropathy, dementia, progressive multifocal encephalopathy

Why I believe we can eliminate TB (2)

In 2013 the ID/AIDS Clinic is a different place

- Monthly deaths down from 12 to 3, often from cancer, cirrhosis, cardiac disease, some advanced AIDS
- We no longer teach young physicians how to manage AZT toxicity with blood transfusions or erythropoietin, and are challenged to teach about management of now-rare AIDS complications –they often go to African countries to see what was once common
- With robust R & D funding this was accomplished for a disease recognized first in 1981

With voices we are hearing today we must, can and will affect policies

- To finally accelerate the development of the treatment tools we needed in 1993, when treatment was already inadequate for some of our citizens & residents
- To bring those words, “you can take off your mask” to the usual 2nd week, not 6nd month of treatment
- To put “us” out of the business of teaching how to treat MDR TB the old way – one of the greatest gifts the United States could provide the world
- We need the full support of the entire CDC & HHS – TB must be a “winnable battle”