Thinking about TB elimination at home and abroad

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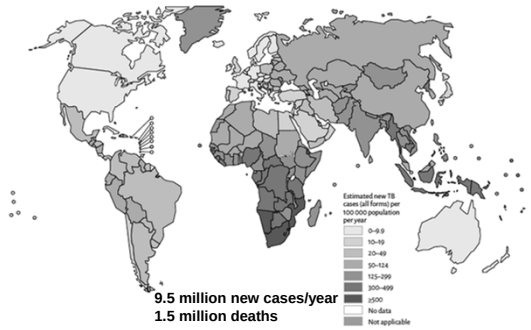
Global tuberculosis incidence



9.5 million new cases/year
1.5 million deaths

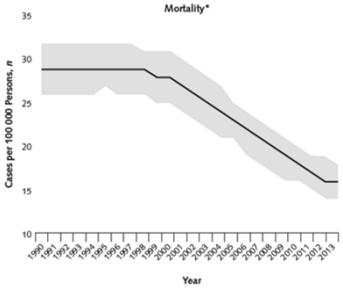
WHO, Global Tuberculosis Report 2015

Leading causes of death in the world, 1990-2103

1990	2013
Ischemic heart disease	Ischemic heart disease
Stroke	Stroke
Lower respiratory infections	COPD
COPD	Lower respiratory infections
Diarrhea	Lung cancer
Tuberculosis	Tuberculosis
Preterm birth complications	HIV/AIDS
Lung cancer	Diarrhea
Malaria	Road injury
Road injury	Diabetes

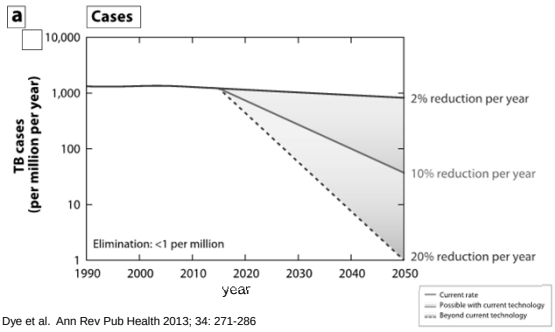
Global Burden of Disease Project, Lancet 2014; 380: 2095
WHO Global TB Report 2015

Global tuberculosis mortality trends



Dirlikov, Raviglione, Scano, 2015; Ann Int Med 163: 52-58

Trajectory of the global TB epidemic

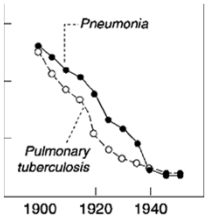


Dye et al. Ann Rev Pub Health 2013; 34: 271-286

What we need to do to eliminate tuberculosis

- Address the social determinants of disease
- Invest in public health
- Take MDR-TB seriously
- Invest in research
- Treat latent TB on a massive scale (?)

Trends in TB mortality in the pre-antibiotic era



NYC

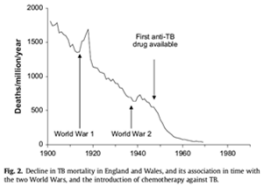


Fig. 2. Decline in TB mortality in England and Wales, and its association in time with the two World Wars, and the introduction of chemotherapy against TB.

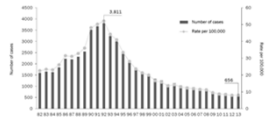
Europe

Risk factors for progression to tuberculosis disease in high-burden countries: social determinants of disease in the 21st century

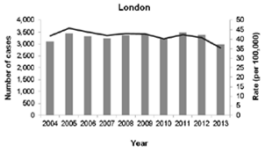
Risk factor	RR for active TB disease	PAF in adults	PAF in total population
HIV infection	20.6-26.7	16%	11%
Malnutrition	3.2	27%	27%
Diabetes	3.1	10%	7.5%
Alcohol use (>40g/day)	2.9	13%	9.8%
Active smoking	2.0	21%	16%
Indoor air pollution	1.4	22%	22%

Lonnroth et al. Lancet 2010; 375: 1814-1829

Having a good public health TB control program is important. Really.



TB Incidence 2013: 8.6/100,000
Source: NYC DOHMH

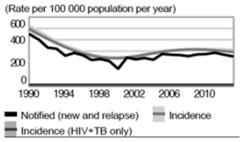


TB Incidence 2013: 37/100,000
Source: Public Health England

I'm not kidding.

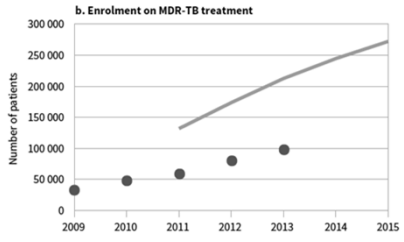
TB Incidence 2013: 3.1/100,000

TB, Republic of Korea, 1990-2013



TB Incidence 2013: 97/100,000
Source: WHO

Treatment of patients with MDR-TB in the world



WHO, Global Tuberculosis Report 2014

TAG Treatment Action Group

Stop TB Partnership

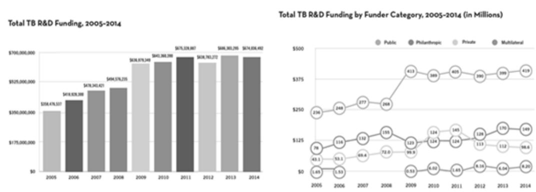
2015 Report on Tuberculosis Research Funding Trends, 2005–2014: A Decade of Data

November 2015

Treatment Action Group

By Mike Frick

Total TB R&D funding, 2005-2014



2005–2013 NIH Funding for Selected Infectious Diseases (in USD millions)

Research Area	2005	2006	2007	2008	2009*	2010*	2011	2012	2013
Tuberculosis	$158	$150	$188	$142	$216	$224	$209	$218	$207
HIV/AIDS	$2,921	$2,902	$2,906	$2,928	$3,338	$3,407	$3,059	$3,074	$2,898
Malaria	$104	$98	$112	$142	$121	$148	$145	$152	$147
Smallpox	$187	$149	$142	$94	$98	$97	$41	$40	$30
Anthrax	$183	$150	$160	$134	$115	$130	$87	$84	$70

Drugs in the clinical pipeline for the world's leading causes of mortality

Leading causes of global mortality:

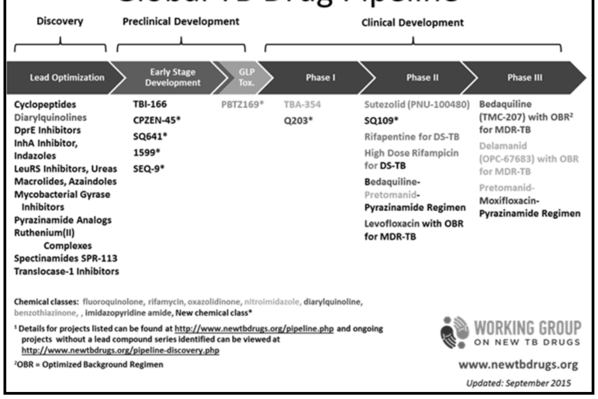
1. Ischemic heart disease
2. Stroke
3. COPD
4. Lower respiratory infection
5. Lung cancer
6. HIV/AIDS
7. Diarrhea
8. Road traffic accidents
9. Diabetes
10. Tuberculosis
11. Malaria

Drugs in clinical development:

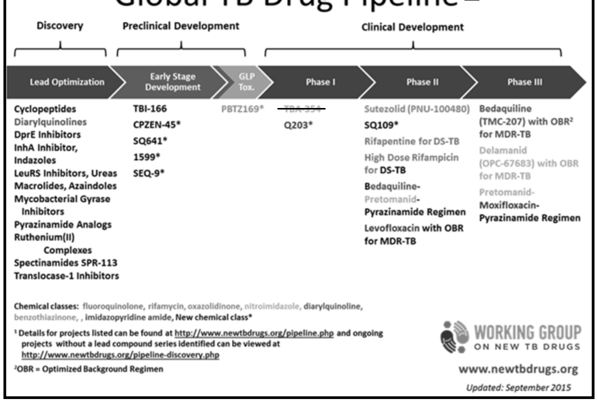
- Heart disease and stroke: >200
- COPD: >50
- Antibacterials and antivirals: 394 (drugs and vaccines)
  - ("124 for pneumonia and TB")
- Cancer: 800
  - Lung Cancer: 121
  - Breast Cancer: 111
- HIV/AIDS: 44 (includes vaccines)
- Diabetes: 180
- Anti-tuberculosis: 5-8
- Anti-malarials: 6

Sources: The Global Burden of Disease Report
The Pharmaceutical Research and Manufacturers of America (www.pharma.org), accessed Feb. 25, 2015

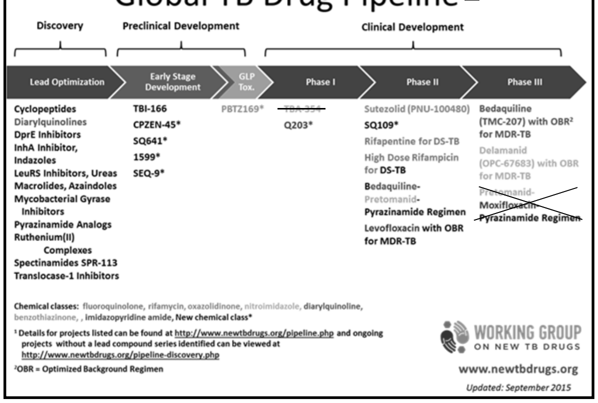
Global TB Drug Pipeline



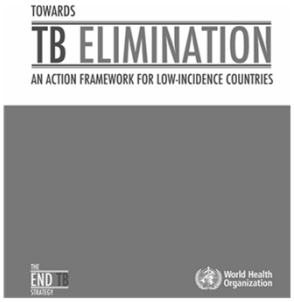
Global TB Drug Pipeline



Global TB Drug Pipeline



Can treating TB help eliminate TB?



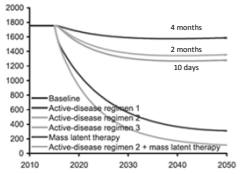
The basic reproductive rate: R_0

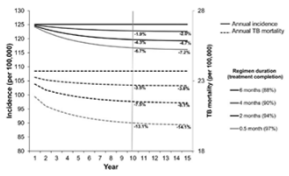
- R_0 is the average number of individuals directly infected by an infectious case during his/her entire infectious period when he/she enters a totally susceptible population
- R_0 is the product of the effective contact rate and the average duration of infectivity
  - If R_0<1, the disease will eventually disappear
  - If R_0=1, the disease becomes endemic
  - If R_0>1, the disease becomes epidemic
- The net reproductive rate is a function of R_0 and the proportion of the population that is immune
  - $R=R_0(1-p)$

Reducing TB transmission by lowering R_0

- Lowering b, the risk of transmission per contact
  - Having sick persons wear masks to prevent spread of airborne illness
  - Having contacts wear respirators to prevent spread
- Lowering k, the number of susceptible contacts
  - Social distancing (isolation/quarantine)
  - Infection control in hospitals
  - Treat HIV-infected persons with ARVs
  - Vaccination
- Lowering D, the duration of infectivity
  - Prompt diagnosis and treatment of sick persons
  - Lower the rate of development of active tuberculosis

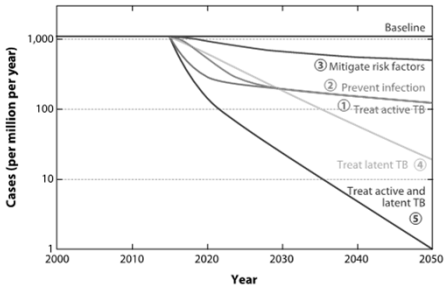
Will shorter treatment for active disease lead to lower incidence of TB?





Abu-Raddad et al. PNAS 2009; 1-06: 13980-13985
Fofana et al. PLoS One 2014; 9: e96389

Interventions and their effect on TB cases



Dye et al. Ann Rev Pub Health 2013; 34: 271-286

What would we like new regimens for active to do?

- Shorten overall treatment duration
  - Generally associated with higher adherence and completion rates
  - Easier for patients
  - More efficient use of resources for TB control programs
- Lower relapse rates
- Have fewer adverse effects, particularly less hepatotoxicity
- Be given easily and safely in combination with antiretroviral therapy
- Be effective in treating MDR-TB/XDR-TB
- Stop transmission of TB

Phase 3 treatment-shortening trials with quinolone-based regimens

Trial	Experimental regimen	Experimental regimen failure/relapse rate	Control failure/relapse rate
Chennai[1]	$2QHRZ_3/2QHR_3$ Q = G or M	10-16%	6%
RIFAQUIN[2]	$2EMRZ/2P_2M_2$	17%	5%
OFLOTUB[3]	2HRPG/2HRG	14.6%	6.9%
REMox[4]	2MHRZ/2MHR	15-20%	7%

1. Jawahar et al. PLoS One 2013; 8: e67030
2. Jindani et al. N Engl J Med 2014; 371: 1599-1608
3. Merle et al. N Engl J Med 2014; 371: 1588-1598
4. Gillespie et al. N Engl J Med 2014; 371: 1577-1587

TBTC trials of novel regimens for active tuberculosis: rifapentine

TBTC Study	Patients enrolled	Novel regimen	Standard regimen	Improvement in 2 month culture conversion
29[1]	389	HPZE (10 mg/kg)	HRZE	3.0%
29X[2]	334	HPZE (15-20 mg/kg)	HRZE	Significant at 15 and 20 mg/kg

1. J Infect Dis. 2012; 206: 1030-40
2. AJRCCM 2015; 191:333-343

TBTC Study 31: randomized, controlled trial of two 4-month, daily 1200 mg rifapentine-containing arms compared to standard therapy in patients with smear positive, drug-susceptible pulmonary tuberculosis

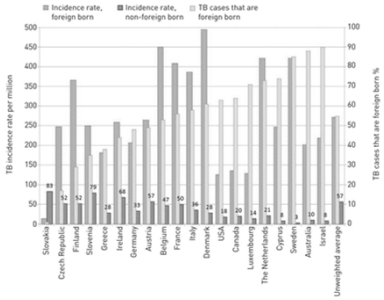
4HPZE

4HPZM

2HRZE/4HR

Coming soon to a theater near you
Study completion 2019 (please)

Distribution and incidence of TB cases in low-burden countries, by birthplace

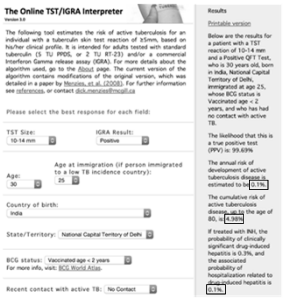


Lonnroth et al. ERJ 2015; 45: 928-952

TB among the foreign-born in the U.S.

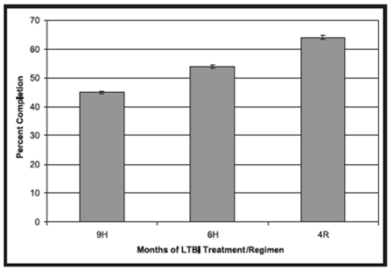
- Foreign-born population of the U.S.: roughly 42 million
- Prevalence of LTBI in the foreign-born is 16-19%
- Most TB in foreign-born persons occurs in people who have lived in the U.S. for more than three years
- A large number of foreign-born persons would have to be tested and treated for LTBI to lower TB rates in this country
- The risk of development of active TB in any individual person with LTBI is very small

Risk of TB in a 30 year old person from India living in the U.S. for 5 years



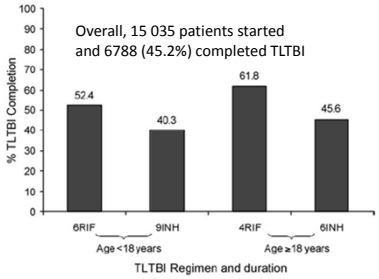
http://www.tstin3d.com/en/calc.html

Shorter regimens for LTBI appear to be associated with increased completion



Horsburgh et al. Chest 2010: 137: 401-409

Completion of treatment for LTBI in the NYC TB Control Program, 2002-2004



Li et al. Int J Inf Dis 2010; 14: e292-e297

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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

Shorter, easier, safer regimens for LTBI

- Regimens to treat LTBI will have to be very short and very safe if they are to be acceptable to large numbers of low-risk persons
- Study 26 (Prevent TB) was a giant leap forward
- We need to do even better

What we need to do to eliminate tuberculosis

- Address the social determinants of disease
- Invest in public health
- Take MDR-TB seriously
- Invest in research
- Treat latent TB on a massive scale (?)