Thinking about TB elimination at home and abroad

Neil W. Schlager, M.D.
Professor of Medicine, Epidemiology, and Environmental Health Science
Columbia University

Leading causes of death in the world, 1990-2103

<table>
<thead>
<tr>
<th>Year</th>
<th>1990</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>Ischemic heart disease</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Lower respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Lung cancer</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Preterm birth complications</td>
<td>HIV/AIDS</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>Road injury</td>
<td></td>
</tr>
<tr>
<td>Road injury</td>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

Global tuberculosis mortality trends

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

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

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

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

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

I’m not kidding.

TB, Republic of Korea, 1996-2013

Treatment of patients with MDR-TB in the world

WHO, Global Tuberculosis Report 2014

2015 Report on Tuberculosis
Research Funding Trends, 2005-2014:
A Decade of Data
Total TB R&D funding, 2005-2014

3/23/2016

3

Total TB & R&D funding by TuD Category, each time (in $ millions)

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

Leading causes of global mortality:
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5. Lung cancer
6. HIV/AIDS
7. Diarrhea
8. Road traffic accidents
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10. Tuberculosis
11. Malaria

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

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

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>$158</td>
<td>$150</td>
<td>$188</td>
<td>$142</td>
<td>$216</td>
<td>$224</td>
<td>$209</td>
<td>$218</td>
<td>$207</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>$2,921</td>
<td>$2,920</td>
<td>$2,926</td>
<td>$2,928</td>
<td>$5,308</td>
<td>$3,407</td>
<td>$3,059</td>
<td>$2,074</td>
<td>$2,800</td>
</tr>
<tr>
<td>Malaria</td>
<td>$104</td>
<td>$98</td>
<td>$112</td>
<td>$142</td>
<td>$121</td>
<td>$148</td>
<td>$165</td>
<td>$152</td>
<td>$147</td>
</tr>
<tr>
<td>Smallpox</td>
<td>$107</td>
<td>$149</td>
<td>$142</td>
<td>$94</td>
<td>$58</td>
<td>$97</td>
<td>$41</td>
<td>$40</td>
<td>$30</td>
</tr>
<tr>
<td>Anthrax</td>
<td>$183</td>
<td>$150</td>
<td>$160</td>
<td>$134</td>
<td>$115</td>
<td>$130</td>
<td>$87</td>
<td>$84</td>
<td>$70</td>
</tr>
</tbody>
</table>

Global TB Drug Pipeline

Chemical classes: Tetracyclines, chloramphenicol, erythromycin, streptomycin, kanamycin, sulfonamides, dapsone, pyrazinamide, isoniazid, ethambutol, fluoroquinolones, new chemical entities

www.eduworld.org
September 2015

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www.eduworld.org
September 2015
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?

Interventions and their effect on TB cases

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Experimental regimen</th>
<th>Experimental regimen failure/relapse rate</th>
<th>Control failure/relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chennai1</td>
<td>2QHRZ(2QH)RQ G or M</td>
<td>10-16%</td>
<td>6%</td>
</tr>
<tr>
<td>RIFAQUIN2</td>
<td>2EMRZ/2P, A, R</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>OFLOTUB3</td>
<td>2HRPQ/2HRIQ</td>
<td>14.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>REMax4</td>
<td>2MHRZ/2MHR</td>
<td>15-20%</td>
<td>7%</td>
</tr>
</tbody>
</table>


TBTC trials of novel regimens for active tuberculosis: rifapentine

<table>
<thead>
<tr>
<th>TBTC Study</th>
<th>Patients enrolled</th>
<th>Novel regimen</th>
<th>Standard regimen</th>
<th>Improvement in 2 month culture conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZP1</td>
<td>389</td>
<td>HPZE (10 mg/kg)</td>
<td>HRZE</td>
<td>3.6%</td>
</tr>
<tr>
<td>ZP2</td>
<td>334</td>
<td>HPZE (15-20 mg/kg)</td>
<td>HRZE</td>
<td>Significant at 15 and 20 mg/kg</td>
</tr>
</tbody>
</table>

2. ARIOM 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

4HRZE

4HRZM

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. BMJ 2015; 41:928-02

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

**Shorter regimens for LTBI appear to be associated with increased completion**

![Graph showing completion rates of LTBI treatment](Image)

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

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

![Graph showing completion rates of LTBI treatment by age and regimen duration](Image)

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

**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**

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- Invest in public health
- Take MDR-TB seriously
- Invest in research
- Treat latent TB on a massive scale (?)