Mycobacterium tuberculosis revisited
Challenges in 21st Century

Dr CC Leung
TB & Chest Service
Public Health Services Branch
Centre for Health Protection
Department of Health
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Outline

• Epidemiology

• Control strategies and limitations

• Drug resistance and implications
Mycobacterium tuberculosis complex

• Longstanding co-existence
  – Genetic sequence study: 70,000 years of co-evolution with *Homo sapiens* (Comas et al. Nat Genet. 2013;45:1176-82)
  – Fragments of the spinal column from Egyptian mummies show evidence of tuberculosis (TB) over 4000 years ago.

• Large-scale TB epidemics peaking asynchronously in different continents in recent centuries
  – Epidemic curve spanning roughly 300 years in Europe
  – Natural decline observed before chemotherapy
    • TB mortality dropped by 1.71% per year in UK from 1853 to 1910: ? socio-economic improvement and / or natural selection (Davies et al. Int J Tuberc Lung Dis. 1999; 3:1051-4)
Natural history of tuberculosis

Exposure → Infection → Disease

- **Primary TB**: 5% (5 yr)
- **No disease, but latent infection with TST +ve**: 95%
- **Infection remaining latent for life**: 90%
- **Reactivation and developing disease ~ 5% life-time risk**

• 10.4 million cases (estimated)
  – Including 1.2 million HIV+TB
  – 60% of TB cases in
    • China, India, Indonesia, Nigeria, Pakistan, South Africa

• 1.8 million deaths
  – Including 0.4 million death in HIV+TB

• Latent TB Infection
  – 1/3 of global population
Global TB Situation 2015
(From WHO Global TB Report 2016)

Estimated TB incidence rates, 2015

- Estimated new TB cases (all forms) per 100,000 population per year
- 0-24.9
- 25-99
- 100-199
- 200-299
- ≥300
- No data
- Not applicable
Post-2015 Targets

• 2015 (West Pacific and Southeast Asia)
  – TB death rate: $\sim 15 / 100,000$
  – TB incidence: $\sim 135 / 100,000$

• 2025
  – 75% reduction in TB deaths
  – 50% reduction in TB incidence ($< 55 / 100,000$)

• 2035
  – 95% reduction in TB deaths
  – 90% reduction in TB incidence ($< 10 / 100,000$)

• 2025 / 2035
  – No affected families face catastrophic costs

• 2050: ?? Elimination (TB incidence $< 1 / 1,000,000$)
WHO END TB Strategy: Projections

- Current global trend: -1.5%/year
- -10%/year by 2025
- -5%/year
- -17%/year

Optimize use of current & new tools emerging from pipeline, pursue universal health coverage and social protection.

Introduce new tools: a vaccine, new drugs & treatment regimens for treatment of active TB disease and latent TB infection, and a point-of-care test.
BCG vaccination coverage

Infant mortality rate (All causes)

Infant mortality rate (TB)

Year

Percentage

BCG vaccination coverage over time in Hong Kong.
TB Vaccines

• Vaccines as a control tool
  – Easier to apply on a huge population scale and NOT affected by the emerging drug resistance

• Existing BCG vaccine: partial and unreliable protection against pulmonary TB in adults, the crucial transmission link.

• Require major breakthroughs
  – Natural infection: No long-lasting immunity
  – Conventional “Identify, Inactivate / Attenuate, Administer” approach does NOT work
Screening and Treatment of LTBI (HK)

• With the limitations of current diagnostic and treatment tools, a targeted approach is adopted for high-risk groups as defined locally
  – High disease risk / consequence (epidemiological data)
  – To screen = Intention to treat if positive

• TST: varying cutoffs
  – Household contacts (smear+ source), esp<35
    • 15mm, 5mm if under 1 yr
  – HIV (5mm)
  – Silicosis (10mm)
  – Immunosuppression/TNF blocker (10mm before/5mm on Rx)
    • usually not considered necessary after adequate curative TB Rx

• IGRA
  – Selected cases (avoid BCG interference / ? elderly)
NNT to prevent 1 TB case in 5 years

Leung CC et al. Eur Respir J. 2011;37:690-711

The graph illustrates the number needed to treat (NNT) to prevent 1 TB case in 5 years, depending on the cumulative incidence in 5 years. The graph shows three lines, each representing a different relative risk (RR): RR=0.4 (solid line), RR=0.25 (dashed line), and RR=0.1 (dotted line). The x-axis represents the cumulative incidence in 5 years, ranging from 0.5 to 10.0%, and the y-axis represents the number needed to treat, ranging from 0 to 350.
Benefit versus Risk
Leung CC et al. Eur Respir J. 2011;37:690-711
Preventive Treatment

• Targeted screening and treatment of LTBI with the currently available immunodiagnostic tools and treatment regimens aims mainly for personal protection.

• Even with possible future tool refinements, the need to screen the entire global population and treat 1/3 of them would be formidable.
Current Control Strategy

• With limitations in available tools, the current emphasis is on **Source Control by Case-finding and Treatment**
  – 70% detection of infectious (smear-positive) TB cases and 85% treatment success required to reduce TB burden progressively:
    – **Partial** treatment
      • Reduces case-fatality but
      • Increases chronic excreters and
      • Emergence of drug resistance
Prompt treatment rapidly controls infectivity

  - Before treatment: $10^6$ to $10^7$ bacilli per ml of sputum
  - 7 days → viable bacilli fall by 2 log
  - 14 days; < $10^4$ bacilli

- Studies using guinea pigs to quantify the transmission risk in hospital wards demonstrated that effective treatment terminates transmission within days of initiation Riley R, et al. Am Rev Respir Dis 1962; 84: 511–525

- Wells Riley equation
  \[ P = 1 - e^{-Jqpt/Q} \]
  \[ \downarrow J = \text{no of infectors} \]
  \[ \downarrow q = \text{quantum of infectious particles} \]
  \[ \downarrow t = \text{time} \]
Limitations

• Diagnosis
  – Variable presentation + overlapping clinical and radiological features with other diseases
  – Sputum microscopy lacks sensitivity (~50%)
    • Esp in Children / HIV-infected
  – Conventional culture and drug susceptibility test
    • Slow (4-8 weeks + 2-4 weeks)

• Treatment
  – Long duration and complex regimen
    • adherence problem / medication errors, resulting in failure / relapse and resistance
With Successful Control of Transmission by DOTS, Endogenous reactivation now accounts for majority of TB cases in most Intermediate Burden Areas.
TB from Recent Transmission

Molecular and Conventional Epidemiology of Tuberculosis in Hong Kong: a Population-Based Prospective Study

Moira Chan-Yeung,¹ Cheuk-Ming Tam,² Harriet Wong,¹ Chi-Chiu Leung,² Julie Wang,¹ Wing-Wai Yew,³ Chak-Wah Lam,⁴ and Kai-Man Kam⁵

Hong Kong Government Tuberculosis and Chest Service² and Tuberculosis Reference Laboratory, Public Health Laboratory Centre,⁵ Department of Health, Division of Respiratory and Critical Care Medicine, Department of Medicine, The University of Hong Kong,¹ Tuberculosis and Chest Unit, Grantham Hospital,³ and Ruttonjee and Tang Shiu Kin Hospital,⁴ Hong Kong, Special Administrative Region, People’s Republic of China

Received 12 November 2002/Returned for modification 16 January 2003/Accepted 24 February 2003

A prospective population-based molecular and conventional epidemiological study of 65.4% of bacteriologically confirmed cases of tuberculosis was carried out on the island of Hong Kong from May 1999 to Oct 2000 by the IS6110-based restriction fragment length polymorphism technique. Eleven of the isolates had five or fewer bands; 24.5% of the remaining 691 isolates belonged to clusters. The estimated proportion of recently transmitted disease was 15 to 20%.
Estimated Infection Rate (HK)

*Estimation based on: Incidence (smear-positive cases) = ARI * Styblo ratio
Notification by Gender & Age

TB Notification Rate by Age & Sex 2004, 2013 & 2014

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>0-5</td>
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<td>10-14</td>
<td>10-14</td>
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<td>15-24</td>
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<td>25-34</td>
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<td>35-44</td>
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<td>55-64</td>
<td>55-64</td>
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<tr>
<td>65-74</td>
<td>65-74</td>
</tr>
<tr>
<td>75+</td>
<td>75+</td>
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</tbody>
</table>

Notification Rate per 100,000 Population

### Co-existing medical diseases

(Leung CC el. al. J Am Geriatr Soc. 2002;50:1219-26)

<table>
<thead>
<tr>
<th></th>
<th>Age ≥ 65 (n = 457)</th>
<th>Age &lt; 65 (n = 413)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>67 (14.7%)</td>
<td>38 (9.2%)</td>
<td>.014</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>43 (9.4%)</td>
<td>5 (1.2%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>19 (4.2%)</td>
<td>2 (0.5%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>43 (9.4%)</td>
<td>3 (0.7%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cerebro-vascular disease</td>
<td>25 (5.5%)</td>
<td>3 (0.7%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>8 (1.8%)</td>
<td>4 (1.0%)</td>
<td>.486</td>
</tr>
<tr>
<td>COPD* / silicosis</td>
<td>87 (19.0%)</td>
<td>26 (6.3%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (9.8%)</td>
<td>15 (3.6%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>18 (3.9%)</td>
<td>4 (1.0%)</td>
<td>.010</td>
</tr>
<tr>
<td>Dementia</td>
<td>14 (3.1%)</td>
<td>0 (0%)</td>
<td>.001</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>8 (1.8%)</td>
<td>0 (0%)</td>
<td>.008</td>
</tr>
<tr>
<td>Gout</td>
<td>9 (2.0%)</td>
<td>2 (0.5%)</td>
<td>.098</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (2.2%)</td>
<td>2 (0.5%)</td>
<td>.062</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>2 (0.4%)</td>
<td>4 (1.0%)</td>
<td>.431</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>2 (0.4%)</td>
<td>3 (0.7%)</td>
<td>.673</td>
</tr>
</tbody>
</table>
Field Hurdles

• Social determinants
  – Social and economic disparities / health inequities between and within countries
  – Mobile populations (migrants/refugees/travellers)
  – HIV and other risk factors

• Drug resistance complicates control
  – MXR-TB and XDR-TB
Global: Drug Resistant TB

- **MDR/RR-TB**
  - 580,000 (MDR-TB: 480,000 + RR-TB: 100,000)
    - 45% in India, China and Russian Federation.
    - New cases: 3.9%; Previously treated: 21%

- **Extensively drug-resistant (XDR-)TB:**
  - MDR-TB with additional resistance to any fluoroquinolone and at least one of the second line injectables
    - Reported in 117 WHO member states
    - 9.5% of MDR-TB
Clinical drug resistance: Man-made phenomenon

Wild M. tuberculosis strain
(Mainly in human reservoir)

Spontaneous mutation (Chromosomal)
(NO extra-chromosomal transferable factors)

Drug-resistant strain

Selection by inadequate regimen,
erratic drug supply or poor adherence

Acquired drug resistance

Transmission from SOURCE,
esp. if diagnostic delay,
overcrowding, vulnerable host,
poor infection control

Primary drug resistance

Hypothetical bacterial populations

A: Continuous growth
- ISONIAZID (rifampicin, streptomycin)

B: Acid inhibition
- PYRAZINAMIDE

C: Spurts of metabolism
- RIFAMPICIN

D: Dormant

Rate of bacterial growth:
- HIGH
- LOW
Factors Affecting Response to Treatment

- **Unimportant:**
  - rest
  - sanatorium accommodation
  - diet
  - nursing care

- **Relatively important:**
  - severity of disease
  - initial or acquired drug resistance

- **Important:**
  - Chemotherapy
  - Compliance
FINDINGS: From 1990 to 2010, the prevalence of smear-positive tuberculosis decreased from 170 cases (95% CI 166-174) to 59 cases (49-72) per 100,000 population. During the 1990s, smear-positive prevalence fell only in the provinces with the DOTS programme; after 2000, prevalence decreased in all provinces. The percentage reduction in smear-positive prevalence was greater for the decade after 2000 than the decade before (57% vs 19%; p<0.0001). 70% of the total reduction in smear-positive prevalence (78 of 111 cases per 100,000 population) occurred after 2000. Of these cases, 68 (87%) were in known cases-i.e., cases diagnosed with tuberculosis before the survey. Of the known cases, the proportion treated by the public health system (using the DOTS strategy) increased from 59 (15%) of 370 cases in 2000 to 79 (66%) of 123 cases in 2010, contributing to reduced proportions of treatment default (from 163 [43%] of 370 cases to 35 [22%] of 123 cases) and retreatment cases (from 312 [84%] of 374 cases to 48 [31%] of 137 cases; both p<0.0001).
National survey of drug-resistant tuberculosis in Mainland China

<table>
<thead>
<tr>
<th></th>
<th>New cases</th>
<th>Previously treated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR-TB</strong></td>
<td>5.7% (4.5%-7.0%)</td>
<td>25.6% (21.5%-29.8%)</td>
</tr>
<tr>
<td><strong>XDR-TB</strong></td>
<td>0.5% (0.2%-0.8%)</td>
<td>2.1% (0.6%-3.5%)</td>
</tr>
</tbody>
</table>

95% confidence interval in brackets

Apparent Paradox: Possible Reasons

- Irregular treatment before effective coverage of quality DOTS in national programme: emergence of isoniazid and rifampin resistance
- No regular culture / DST-guided use of secondline drugs: MDR-TB not detected or effectively treated
- Standard 5-drug retreatment programme amplified resistance, especially in failure cases
- Uncontrolled use of secondline drugs outside programme settings: XDR-TB
- Transmission of drug-resistant TB within community
Immigrants and tuberculosis in Hong Kong

CC Leung *, CK Chan, KC Chang, WS Law, SN Lee, LB Tai, Eric CC Leung, CM Tam

ABSTRACT

Objective: To examine the impact of immigrant populations on the epidemiology of tuberculosis in Hong Kong.

Design: Longitudinal cohort study.

Setting: Hong Kong.

Participants: Socio-demographic and disease characteristics of all tuberculosis notifications in 2006 were captured from the statutory tuberculosis registry and central tuberculosis reference laboratory. Using 2006 By-census population data, indirect sex- and age-standardised incidence ratios by place of birth were calculated. Treatment outcome at 12 months was ascertained from government tuberculosis programme record forms, and tuberculosis relapse was tracked through the notification registry and death registry up to 30 June 2013.

Results: Moderately higher sex- and age-standardised incidence ratios were observed among various immigrant groups: 1.06 (Mainland China), 2.02 (India, Pakistan, Bangladesh), 1.59 (Philippines, Thailand, Indonesia, Nepal), and 3.11 (Vietnam). Recent Mainland migrants had a lower sex- and age-standardised incidence ratio (0.51 vs 1.09) than those who immigrated 7 years ago or earlier. Age younger than 65 years, birth in the Mainland or the above Asian countries, and previous treatment were independently associated with resistance to isoniazid and/or rifampicin. Older age, birth in the above Asian countries, non-permanent residents, previous history of treatment, and resistance to isoniazid and/or rifampicin were independently associated with poor treatment outcome (other than cure/treatment completion) at 1 year. Birth outside Hong Kong was an independent predictor of relapse following successful completion of treatment (adjusted hazard ratio = 1.76; 95% confidence interval, 1.07-2.89; P = 0.025).

Conclusion: Immigrants carry with them a higher tuberculosis incidence and/or drug resistance rate from their place of origin. The higher drug resistance rate, poorer treatment outcome, and excess relapse risk raise concern over secondary transmission of drug-resistant tuberculosis within the local community.

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CC Leung *, MB, BS, FHKAM (Medicine)
CK Chan, MB, BS, FHKAM (Medicine)
KC Chang, MB, BS, FHKAM (Medicine)
WS Law, MB, ChB, FHKAM (Medicine)
SN Lee, MB, ChB, FHKAM (Medicine)
LB Tai, MB, ChB, FHKAM (Medicine)
ECC Leung, MB, BS, FHKAM (Medicine)
CM Tam, MB, BS, FHKAM (Medicine)

Tuberculosis and Chest Service, Department of Health, Wanchai Chest Clinic, 1/F, 99 Kennedy Road, Wanchai, Hong Kong

* Corresponding author: cc_leung@dh.gov.hk
Incident MDR/RR-TB cases in 2015
(From WHO Global TB Report 2016)
# Rate of Drug-resistant Tuberculosis

Among cases (mainly cases seen at chest clinics) registered during the period January to December 2012 (Data from Programme Forms)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Category</th>
<th>E</th>
<th>R</th>
<th>H</th>
<th>S</th>
<th>1 drug</th>
<th>2 drugs</th>
<th>≥ 3 drugs</th>
<th>MDR-TB</th>
<th># Total % resistance</th>
<th>Total no. of cases analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 19</td>
<td>New cases</td>
<td>1.32</td>
<td>2.63</td>
<td>7.89</td>
<td>9.21</td>
<td>6.58</td>
<td>1.32</td>
<td>3.95</td>
<td>2.63</td>
<td>11.84</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Previously treated cases</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>1.30</td>
<td>2.60</td>
<td>7.79</td>
<td>9.09</td>
<td>6.49</td>
<td>1.30</td>
<td>3.90</td>
<td>2.60</td>
<td>11.69</td>
<td>77</td>
</tr>
<tr>
<td>20 - 39</td>
<td>New cases</td>
<td>0.34</td>
<td>1.02</td>
<td>3.75</td>
<td>10.56</td>
<td>10.22</td>
<td>1.70</td>
<td>0.68</td>
<td>0.85</td>
<td>12.61</td>
<td>587</td>
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<tr>
<td></td>
<td>Overall</td>
<td>0.81</td>
<td>1.78</td>
<td>4.37</td>
<td>10.84</td>
<td>10.03</td>
<td>1.78</td>
<td>1.29</td>
<td>1.46</td>
<td>13.11</td>
<td>618</td>
</tr>
<tr>
<td>40 - 59</td>
<td>New cases</td>
<td>1.01</td>
<td>1.44</td>
<td>5.60</td>
<td>10.49</td>
<td>9.05</td>
<td>2.87</td>
<td>1.01</td>
<td>1.29</td>
<td>12.93</td>
<td>696</td>
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<tr>
<td></td>
<td>Previously treated cases</td>
<td>2.63</td>
<td>5.26</td>
<td>13.16</td>
<td>21.05</td>
<td>17.11</td>
<td>2.63</td>
<td>6.58</td>
<td>5.26</td>
<td>26.32</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>1.17</td>
<td>1.81</td>
<td>6.35</td>
<td>11.53</td>
<td>9.84</td>
<td>2.85</td>
<td>1.55</td>
<td>1.68</td>
<td>14.25</td>
<td>772</td>
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<tr>
<td>60 up</td>
<td>New cases</td>
<td>0.66</td>
<td>0.47</td>
<td>4.32</td>
<td>8.26</td>
<td>7.50</td>
<td>2.35</td>
<td>0.47</td>
<td>0.19</td>
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<td>1066</td>
</tr>
<tr>
<td></td>
<td>Previously treated cases</td>
<td>0.00</td>
<td>1.61</td>
<td>8.60</td>
<td>10.75</td>
<td>10.22</td>
<td>3.76</td>
<td>1.08</td>
<td>1.61</td>
<td>15.05</td>
<td>186</td>
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<tr>
<td></td>
<td>Overall</td>
<td>0.56</td>
<td>0.64</td>
<td>4.95</td>
<td>8.63</td>
<td>7.91</td>
<td>2.56</td>
<td>0.56</td>
<td>0.49</td>
<td>11.02</td>
<td>1252</td>
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<tr>
<td>All</td>
<td>New cases</td>
<td>0.70</td>
<td>0.95</td>
<td>4.66</td>
<td>9.48</td>
<td>8.58</td>
<td>2.31</td>
<td>0.78</td>
<td>0.74</td>
<td>11.67</td>
<td>2425</td>
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<tr>
<td></td>
<td>Previously treated cases</td>
<td>1.70</td>
<td>4.08</td>
<td>10.54</td>
<td>13.95</td>
<td>11.56</td>
<td>3.40</td>
<td>3.74</td>
<td>3.74</td>
<td>18.71</td>
<td>294</td>
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<tr>
<td></td>
<td>Overall</td>
<td>0.81</td>
<td>1.29</td>
<td>5.30</td>
<td>9.97</td>
<td>8.90</td>
<td>2.43</td>
<td>1.10</td>
<td>1.07</td>
<td>12.43</td>
<td>2719</td>
</tr>
</tbody>
</table>

Notes:
- E = ethambutol; R = rifampicin; H = isoniazid; S = streptomycin
- * % resistant to one, two or more than two of the four drugs E, R, H and S
- # Total % resistance: resistant to at least one of the four drugs E, R, H and S
- New cases: for cases with no past history of anti-tuberculosis treatment
- Previously treated cases: for cases with past history of anti-tuberculosis treatment
- Overall: for all cases
Critical Concern: Drug-Resistant TB

• Major (5 or more fold) risk differentials of MDR-TB between HK and some neighboring areas

• Increasing use of secondline drugs outside programme settings:
  – Rapidly emerging resistance to injectibles, fluoroquinolones and pyazinamide (besides isoniazid and rifampicin)
  – Cases resistant to ALL first and secondline drugs

• Intensified population movements affecting drug adherence and promoting cross transmission across all age bands including children and elderly

• Overcrowded local environment and institutions including schools, elderly homes and hospitals.
Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city

(Leung EC, et al. Eur Respir J. 2013;41:901-8)

ABSTRACT: Multidrug-resistant (MDR)-tuberculosis (TB) and extensively drug resistant (XDR)-TB reportedly lead to increased household transmission.

This is a retrospective cohort study of active TB occurring among household contacts exposed to MDR-TB.

Of 704 contacts in 246 households, initial screening identified 12 (1.7%) TB cases (prevalent cases) and 17 (2.4%) contacts that subsequently developed active TB (secondary cases) after a median (range) duration of 17 (5–62.5) months. Eight prevalent cases and three secondary cases had MDR-TB. TB incidence rates per 100 000 person-years were 254.9 overall and 45.0 for MDR-TB. XDR-TB in the index MDR-TB patient significantly increased the odds of identifying a prevalent TB case to 4.8 (95% CI 1.02–22.5), and the hazard of finding a secondary TB case to 4.7 (95% CI 1.7–13.5). Molecular fingerprinting confirmed household transmission of MDR-TB. Of 20 retrievable isolates from 27 XDR-TB index cases, restriction fragment length polymorphism analysis showed clustering among 13 (65%), with 11 (55%) due to recent transmission by n-1 method and an identifiable household source in only three (27.2%) of the 11 cases.

XDR-TB relative to MDR-TB significantly increases household transmission of TB, probably reflecting prolonged/higher infectivity, and indicating a need for prolonged household surveillance. XDR-TB may largely transmit outside of the household settings.
Age Profile: MDR-TB 2005-2014

![Age Profile Chart](chart.png)
### Notification Sources (2004-2014)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>East Kowloon Chest Clinic</td>
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<td><strong>Sub-total</strong></td>
<td>2,535</td>
<td>2,401</td>
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</table>

- **Grantham Hospital**: 257, 165, 176, 215, 209, 214, 180, 163, 138, 148, 140
- **Haven of Hope Hospital**: 137, 127, 124, 124, 87, 103, 65, 60, 66, 77, 95
- **Kowloon Hospital**: 205, 113, 142, 108, 120, 64, 108, 92, 97, 64, 74
- **Ruttonjee Hospital**: 263, 256, 254, 218, 165, 130, 176, 165, 127, 140
- **Wong Tai Sin Hospital**: 189, 184, 140, 90, 104, 62, 105, 57, 58, 86, 69

#### Other Govt. Institutions (a) 87, 84, 60, 66, 78, 54, 64, 62, 54, 51, 61

#### Other H.A. Hospitals 2,301, 2,543, 2,538, 2,530, 2,648, 2,472, 2,425, 2,364, 2,497, 2,377, 2,578

#### Private Practitioners 136, 155, 154, 90, 83, 57, 101, 100, 109, 118, 129

#### Private Hospitals 116, 131, 143, 185, 332, 348, 283, 253, 226, 223, 206

### Total Cases

| Total Cases | 6,226 | 6,160 | 5,766 | 5,463 | 5,835 | 5,103 | 5,093 | 4,704 | 4,856 | 4,664 | 4,205 |

#### % of cases from Chest Clinics among the total

- 40.7%
- 39.0%
- 34.9%
- 33.6%
- 32.1%
- 30.7%
- 31.3%
- 30.2%
- 29.6%
- 29.8%
- 25.8%

#### % from Chest Hospitals (b) 16.3%

#### % from Other Public Hospitals 38.4%

#### % from Private Sector 4.0%
Infection control for TB in HCF

Hierarchy of controls

1. **Administrative controls**
   - Assessment of risk
   - Infection control plan
   - HCW training
   - Early identification, diagnosis, isolation, and treatment
   - Patient education
   - Triage
   - Evaluation of infection control programme

2. **Engineering controls**
   - Maximise natural ventilation
   - Mechanical ventilation
   - UV (germicidal) light
   - HEPA filters

3. **Personal controls**
   - Masks and respirators
   - BCG vaccination
   - TST/ preventive therapy

**Importance**

- Early diagnosis and treatment leads to rapid fall of sputum bacillary count.
- This MAY NOT APPLY to MDR- or XDR-TB and early detection of rifampicin resistance is therefore crucial in high risk settings.
Combating Drug Resistance

• Control at SOURCE
  • Early detection of TB and drug resistance through deployment of rapid molecular tools, especially in high risk scenarios
    – Prompt initiation of APPROPRIATE treatment
      • Drug-sensitive TB: avoid fluoroquinolone unless rifampicin resistance excluded
      • Rifampicin-resistant TB: genotypic test for further resistance isoniazid, fluoroquinolone and injectible, followed by phenotypic test +/- MIC / TDM to guide choice of drugs (including also repurposed or new drugs)

• Prevent further drug resistance
  – Seeking appropriate source of advice for difficult scenarios
  – Do not add a single drug to a failing regimen (addition phenomenon)
  – Intensified case-holding efforts till treatment completion
    • DOT and defaulter tracing
    • Cross-jurisdiction notification
    • Statutory enforcement (generally as last resort)
### Genetic basis of DR-TB

<table>
<thead>
<tr>
<th>Table: Mechanisms of drug resistance in <em>M. tuberculosis</em></th>
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</thead>
<tbody>
<tr>
<td><strong>Drug (year of discovery)</strong></td>
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<tr>
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</tr>
<tr>
<td>Isoniazid (1952)</td>
</tr>
<tr>
<td>Rifampicin (1966)</td>
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<tr>
<td>Pyrazinamide (1952)</td>
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<tr>
<td>Ethambutol (1961)</td>
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<tr>
<td>Streptomycin (1944)</td>
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<tr>
<td>Amikacin/kanamycin (1957)</td>
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<td>Capreomycin (1960)</td>
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<td>Quinolones (1963)</td>
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<td>Ethionamide (1956)</td>
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<td>PAS (1946)</td>
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</tbody>
</table>

MIC = minimum inhibitory concentration; ACP = acyl carrier protein; PAS = para-aminosalicylic acid.

Examples of commercial products

- **rpoB mutations**
  - INNO-LiPA Rif.TB
  - Xpert MTB/RIF:
    - automated
    - heminested real-time PCR assay
    - molecular beacons for probing rpoB mutations

- **rpoB and katG mutations**
  - GenoType MTBDR (Hain test)

- **rpoB, katG, and inhA mutations**
  - GenoType MTBDRplus

- **gyrA, rrs, and embB / gyr B, eis mutations**
  - GenoType MTBDRsl (v1 / v2)
Phenotypic DST for TB
Bottger EC. Clin Microbiol Infect 2011; 17: 1128–1134

• Classifies clinical isolates as either drug-‘resistant’ or drug-‘susceptible’ by their ability to grow in the presence of a ‘critical concentration’ (lowest concentration of drug that inhibits 95% of wild-type strains of bacilli, not related to achievable serum level) of the test drug.

• Drug resistance in *M. tuberculosis* is heterogeneous:
  – low-level, moderate-level and high-level drug resistance phenotypes, associated with different mutations
  – Decrease in drug susceptibility does not inevitably exclude the drug from treatment regimens

• Quantitative measures, e.g. MIC, may help to:
  – reflect the biological complexity of drug resistance,
  – optimally exploit the compounds available for treatment.
Therapeutic Drug Monitoring (TDM)

• **Individual pharmacokinetic variability**: difficult to predict without TDM

• Methods:
  – One or two samples:
    • 2-h post-dose sample: approximates peak serum drug concentration (Cmax)
    • 6-h sample: distinguish between delayed absorption and malabsorption.
  – Promptly centrifuged, serum harvested and frozen
    • Isoniazid and ethionamide not stable at room temperature
  – Dried blood spots and prepackaged multidrug plates for MIC: ↑ access

• **Clinical role requires further validation**:
  – Concentration response seen in vitro and animal model data
  – In human studies, standard dosing not consistently achieving target concentrations for first-line drugs, but not necessarily associated with poor response
TB Drug Groups

(3HO. Treatment of Tuberculosis Guidelines 4th edn)

- **First-line anti-TB drugs**
  - **Group 1 (oral first-line drugs)**: isoniazid, rifampicin (rifapentine or rifabutin), pyrazinamide, ethambutol,
- **Second-line anti-TB drugs**
  - **Group 2 (injectables)**: aminoglycosides (streptomycin, kanamycin, amikacin) and injectable polypeptides (capreomycin, viomycin)
  - **Group 3 (oral and injectable fluoroquinolones)**: ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin.
  - **Group 4 (oral bacteriostatic)**: para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide.
- **Third-line anti-TB drugs**
  - **Group 5 (unclear role)**: clofazimine*, linezolid*, high dose isoniazid*, thioacetazone, amoxicillin plus clavulanate, imipenem plus cilastatin, clarithromycin.

* Recent evidences supporting use of these drugs for difficult MDR-TB
TB Chemotherapy in Hong Kong

Chemotherapy 藥物治瘉 (from 1950s)

Annual decline: 4.7% (1952-1990)
Annual decline: 2.3% (1990-2013)

Supervised treatment

Fluoroquinolones for MDR-TB
Linezolid for difficult MDR-TB / XDR-TB

DOTS / DOTS Plus

Delamanid
Fluoroquinolone (FQ): a word of caution

- Essential for treatment of MDR-TB
  - Inadvertent FQ monotherapy should be avoided
    - With the relatively high TB incidence in HK, there is a need to exclude TB when FQ is used for common chest infections
    - Avoid using FQ as supplementary fourth drug (like ethambutol or streptomycin) in firstline regimen unless rifampicin resistance reasonably excluded.

- Beware of food and drug interactions
  - Absorption of fluoroquinolones is reduced by dairy products, and drugs (antacids, sucralfate, chewable didanosine, vitamins) containing divalent cations (such as Zn, Fe, Ca, Mg)
Thank You