Predictive values of IGRAs and TST for progression to active disease in TB contacts in Singapore

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3rd Global IGRA Symposium
12-15 January 2012

Background

• Singapore: an intermediate TB incidence country
  – Since 1950s: universal BCG-vaccination at birth
  – 1950s - 2001: BCG re-vaccination policy for school leavers (at 12 or 16 years of age)

• 1987-1997: Stagnation of TB rate at 50-55 /100,000 population (citizens/permanent residents)

• 1998: National TB Programme implemented targeted TST screening of close contacts for preventive therapy (PT)

• 2004: Availability of commercial IGRAs
Two cohorts of adult non-HIV contacts tested with an IGRA and TST (2TU RT23 PPD)

- 961 community contacts (household, workplace)
  - Screened with T-SPOT.TB® and TST from January-September 2005;
  - Decision for PT based on T-SPOT result in the majority
  - PT regimen: Isoniazid for 6 months, self-administered

- 1122 contacts in congregate settings (prisons, nursing homes, mental institute)
  - Screened with QuantiFERON Gold In-tube® (QFT-IT) and TST from November 2005-May 2007
  - Decision for PT based on QFT result
  - PT regimen: Isoniazid for 9 months, directly-observed

- Of eligible contacts, 81% in T-SPOT cohort; 85% in QFT cohort commenced PT
  - Completion rate: 77% for T-SPOT cohort; 89% for QFT cohort

- Follow-up:
  - Contacts commenced on PT were followed 4-6 weekly until treatment completion, then discharged
  - QFT +ve contacts in congregate settings who could not take PT were reviewed 6 monthly for 2 years
  - Test-positive community contacts who did not take PT were discharged with advice
  - Test-negative contacts were discharged

- Contacts matched with National TB Notification Registry for notification of active TB as at July 2011
  - 18 cases (6 in T-SPOT group, 12 in QFT group)
  - One case with known re-exposure to active TB excluded (T-SPOT group)
Contacts screened with T-SPOT and TST
Flow-chart according to T-SPOT

![Flow-chart diagram]

Contacts screened with T-SPOT and TST
Flow-chart according to TST (10 mm cut-off)

![Flow-chart diagram]
<table>
<thead>
<tr>
<th>Number screened with both tests</th>
<th>Treatment status</th>
<th>No. who developed active TB / No. screened</th>
<th>Person-years</th>
<th>Incidence / 1000 PYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=903</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-SPOT-/TST-</strong></td>
<td>PT</td>
<td>0/1</td>
<td>5.77</td>
<td></td>
</tr>
<tr>
<td>N=141 (15.6%)</td>
<td>No PT</td>
<td>0/140</td>
<td>851.88</td>
<td></td>
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<tr>
<td><strong>T-SPOT-/TST+</strong></td>
<td>PT</td>
<td>0/27</td>
<td>162.77</td>
<td></td>
</tr>
<tr>
<td>N=364 (40.3%)</td>
<td>No PT</td>
<td>2/337 (0.9%)</td>
<td>2028.7</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>T-SPOT+/TST-</strong></td>
<td>PT</td>
<td>0/8</td>
<td>48.38</td>
<td></td>
</tr>
<tr>
<td>N=25 (2.8%)</td>
<td>No PT</td>
<td>0/17</td>
<td>102.78</td>
<td></td>
</tr>
<tr>
<td><strong>T-SPOT+/TST+</strong></td>
<td>PT</td>
<td>2/256 (0.8%)</td>
<td>1557.91</td>
<td>1.3</td>
</tr>
<tr>
<td>N=373 (41.3%)</td>
<td>No PT</td>
<td>1/117 (0.9%)</td>
<td>714.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

TST positivity cutoff >=10 mm

Contacts screened with QFT-IT and TST
Flow-chart according to QFT

1122 Contacts of 70 index cases

QFT +ve
275 (25%)

PT 191
Active TB 3

No PT*
84
Active TB 2
PPV 2.3%

QFT -ve
814 (75%)

PT 0
Active TB 0

No PT
814
Active TB 7
NPV 99.1%

* includes PT non-completers
Contacts screened with QFT-IT and TST
Flow-chart according to TST (10 mm cut-off)

1122 Contacts of 70 index cases

- TST >= 10mm
  - 645 (59%)
  - No PT
  - 490
  - Active TB
  - 6
  - PPV 1.2

- TST < 10mm
  - 444 (41%)
  - No PT
  - 408
  - Active TB
  - 0
  - NPV 99.3

12 Active cases
13 Indeterminate QFT
8 No TST

* Includes PT non-completers

<table>
<thead>
<tr>
<th>Number screened with both tests N=1089</th>
<th>Treatment status</th>
<th>No. who developed active TB / No. screened</th>
<th>Person-years</th>
<th>Incidence / 1000 PYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-/TST- N=397 (36.5%)</td>
<td>PT</td>
<td>0/0</td>
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<tr>
<td></td>
<td>No PT</td>
<td>3/397 (0.8%)</td>
<td>1990.95</td>
<td>1.5</td>
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<tr>
<td>QFT-/TST+ N=417 (38.3%)</td>
<td>PT</td>
<td>0/0</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>No PT</td>
<td>4/417 (1.0%)</td>
<td>2052.30</td>
<td>1.94</td>
</tr>
<tr>
<td>QFT+/TST- N=47 (4.3%)</td>
<td>PT</td>
<td>0/36</td>
<td>180.07</td>
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<tr>
<td></td>
<td>No PT</td>
<td>0/11</td>
<td>30.60</td>
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</tr>
<tr>
<td>QFT+/TST+ N=228 (20.9%)</td>
<td>PT</td>
<td>3/155 (1.9%)</td>
<td>758.43</td>
<td>3.95</td>
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<tr>
<td></td>
<td>No PT</td>
<td>2/73 (2.7%)</td>
<td>222.24</td>
<td>8.2</td>
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</tbody>
</table>

TST positivity cutoff >=10 mm
Limitations

• Majority of IGRA-positive subjects received LTBI treatment
  – Possible selection bias for those who did not receive Rx (more HH than non-HH contacts received PT in T-SPOT group)

• No DNA fingerprinting data of contact and source cases’ MTC isolates
  – Unable to rule out possibility of infection during follow-up period (5 cases developed active TB > 36 months after screening)

• No systematic follow-up of all contacts
  – Drop out rate (eg. death, left country) uncertain

Summary of findings

• PPV of T-SPOT.\textit{TB} : 0.7\% (vs TST 0.7\%)
• NPV of T-SPOT.\textit{TB} : 99.6\% (vs TST 100\%)
• T-SPOT+/TST+ contacts have RR of 1.417 [95\% CI 0.13-15.65] of developing active TB vs those T-SPOT-/TST+

• PPV of QFT-IT : 2.3\% (vs TST 1.2\%)
• NPV of QFT-IT : 99.1\% (vs TST 99.3\%)
• QFT+/TST+ contacts have RR of 4.231 [95\% CI 0.77-23.23] of developing active TB vs those QFT-/TST+; and RR of 5.477 [95\% CI 0.91-32.94] of developing active TB vs those QFT-/TST-
Conclusions

For TB contacts in Singapore’s intermediate burden setting:
- Both T-SPOT and QFT-IT, and TST had low PPV
  - Consistent with meta-analysis by Rengaka et al. *Lancet* 2012;12:45-55
- All three tests had high NPV

In our population, use of IGRA will reduce number considered for PT

Acknowledgements

- Nursing Officer Kwee-Yin Han, Senior Staff Nurses Pushparani and Chwee-Kim Koh & Staff of TB Control Unit Contact Clinic
- Mr Chua Sock Kiang and Staff, Singapore Prisons Service
- Dr Shen Liang, Yong Loo Lin School of Medicine, National University of Singapore
- Oxford Immunotec for providing T-SPOT.*TB* kits at a reduced price for this project
- Ministry of Health, Singapore