The impacts of IGRAs on contact tracing

- Japanese experiences -

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Our involvement in QFT

- 1996: clinical trial of QuantiFERON-TB
  (stimulants: PPD)
- 2002: clinical trial of QuantiFERON-TB Gold
  (stimulants: ESAT-6, CFP-10)
  The cut-off (0.35 IU/ml) was fixed.
  (Mori T, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. Am J Respir Crit Care Med. 2004;170:59-64.)
- 2006: clinical trial of QuantiFERON-TB Gold In-Tube
  (stimulants: ESAT-6, CFP-10, TB7.7)

The Japanese situation pre-IGRAs

- **Universal BCG vaccination and re-vaccination (until 2006)**
- **As a result, the TST has very poor specificity**
  - **Many low risk people are TST positive**
  - **Erythema measured rather than induration in Japan**
- **Contact investigations in adults largely case finding**
  - **Chest X-ray screening**
  - **TST used if less than 30 years of age**
    - **Those who show erythema diameter more than 30mm are indicated for chemoprophylaxis**
    - **But limited faith in results by both doctors and patients**
- **TB rates > 20/100,000 – so improved control needed.**

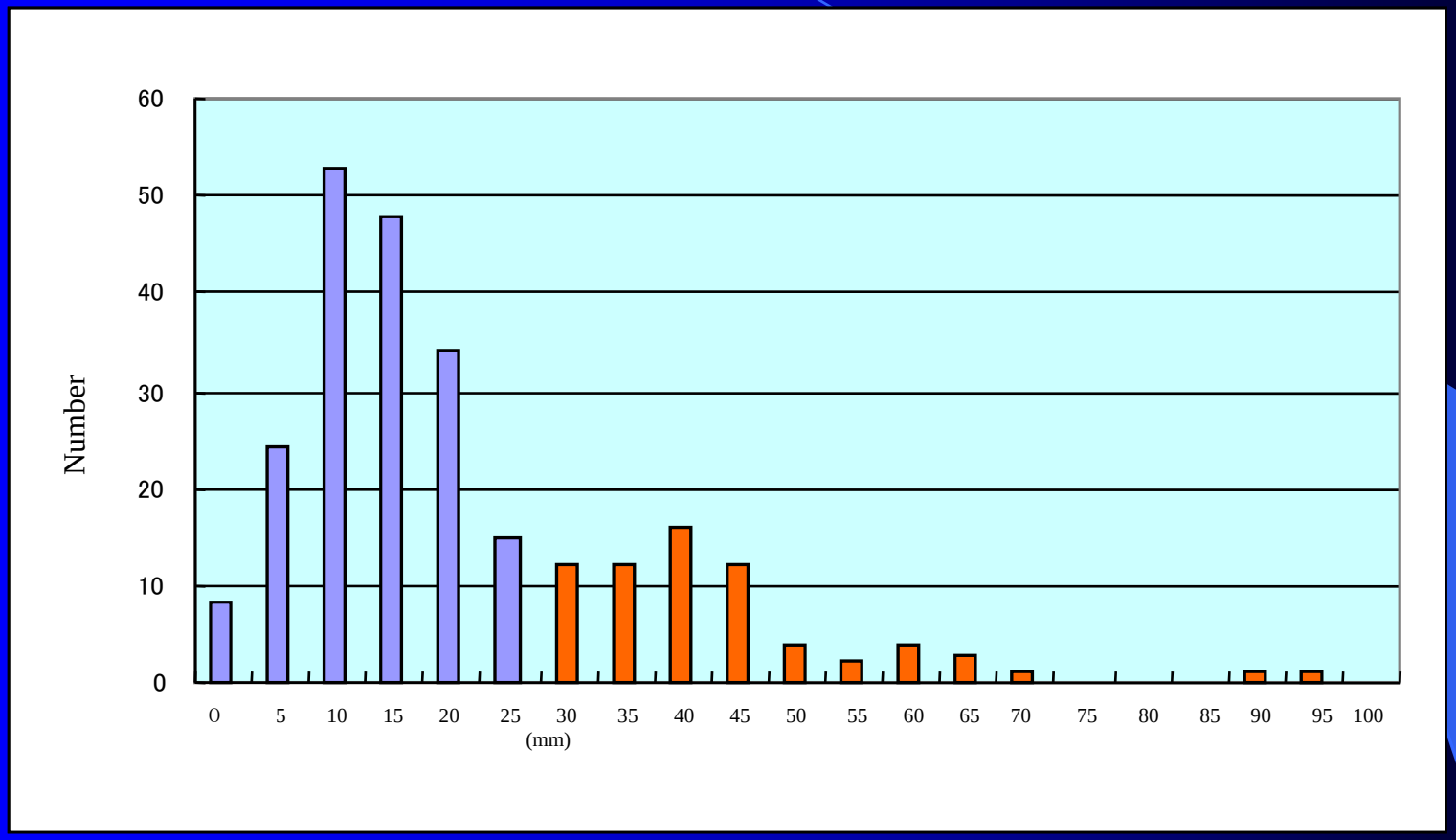
Standard of prophylaxis for contacts investigation using TST erythema in Japan

Contacts with culture positive TB patients	BCG unvaccinated	BCG vaccinated
−	More than 30mm (Re-TST:more than 20mm)	More than 40mm*
+	More than 10mm	More than 30mm*

***restricted for only persons who are suspected as TB infected**
TST was performed only for those under 30 years old.

Contact Investigation Case-1

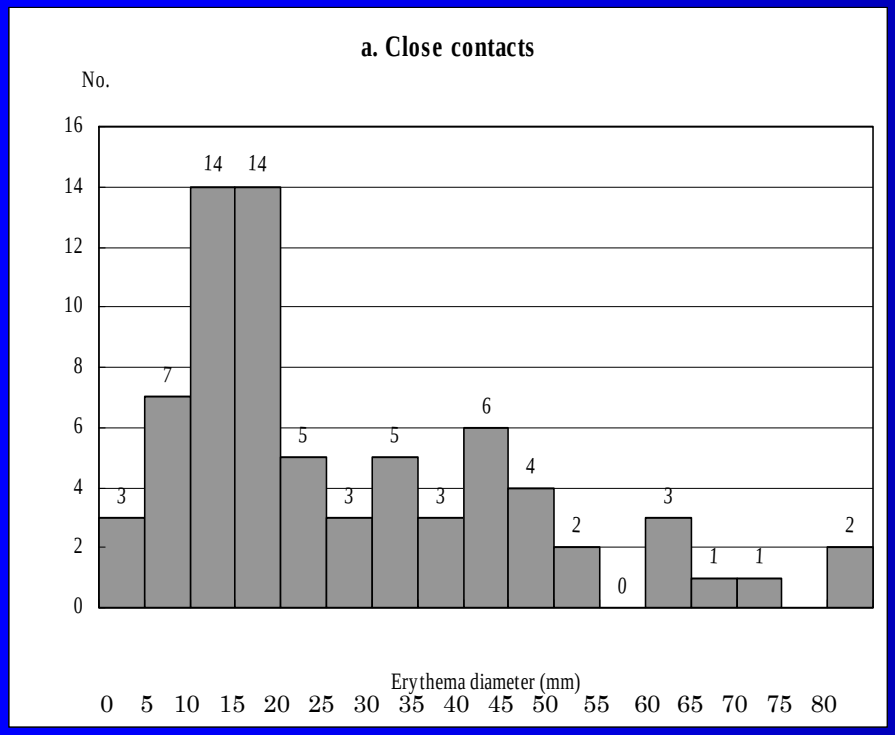
Problems with the TST

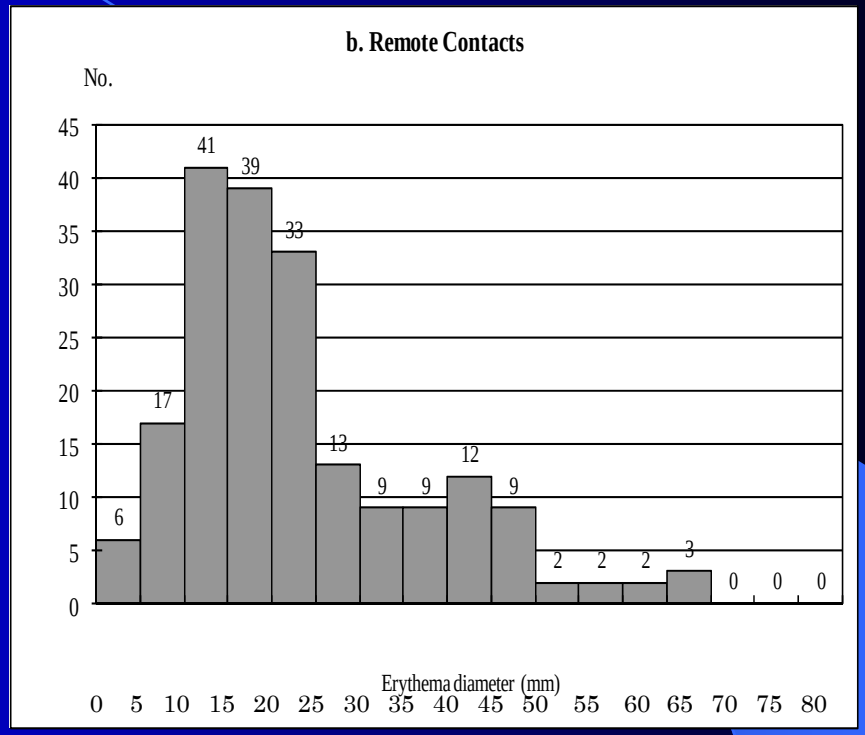


As with measuring erythema - poor discrimination between positive and negative

Harada N, et al. Usefulness of a novel diagnostic method of tuberculosis infection, QuantiFERON TB-2G, in an outbreak of tuberculosis. Kekkaku. 2004;79:637-643.

Distribution of close and casual contacts according to erythema size of TST.

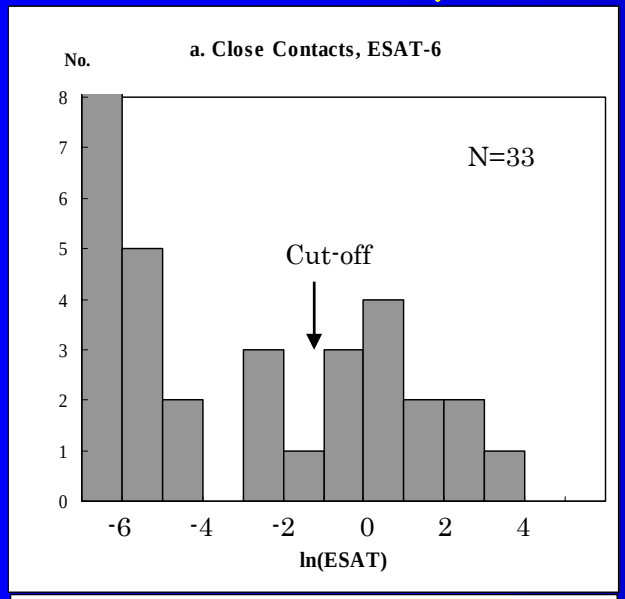


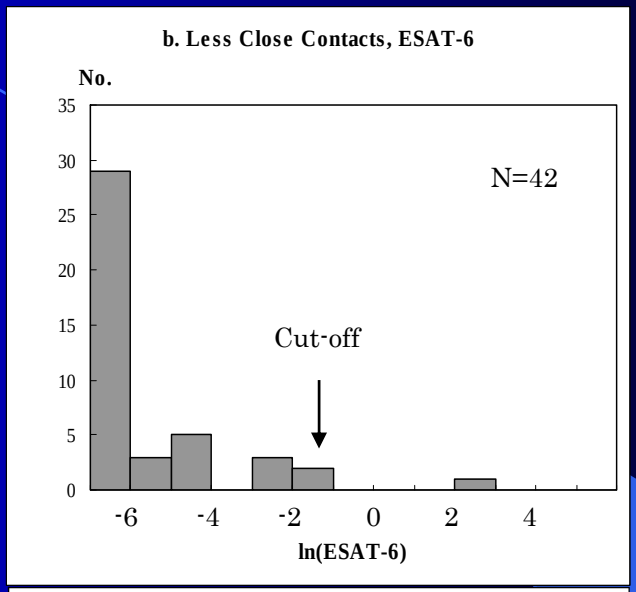


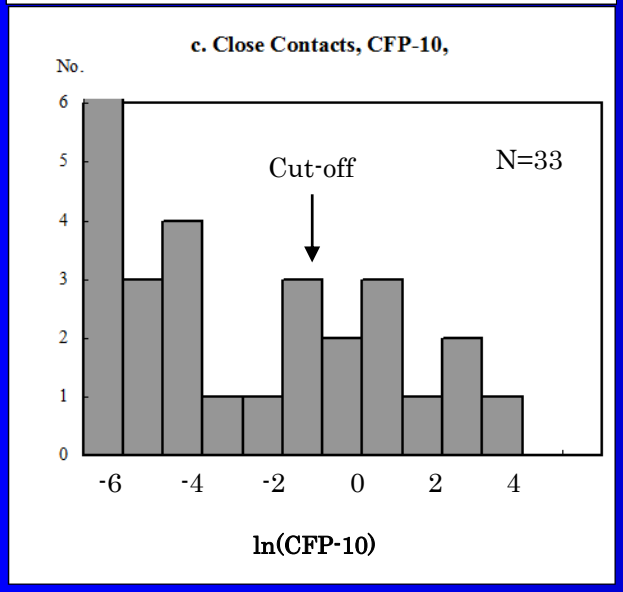
- Very similar pattern between close contacts and those with limited exposure
  - No evidence of diagnostic utility for the TST

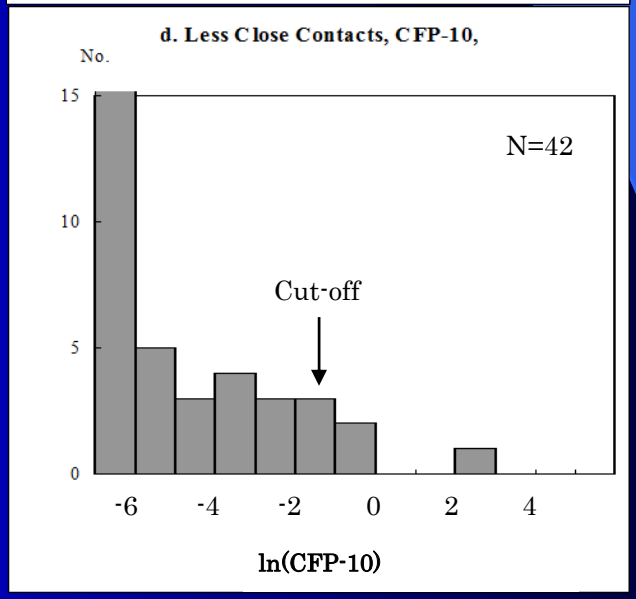
Note: “Close contacts” include those who joined an excursion to a foreign country with the index case for 5 days.

Distribution of subjects according to log-transformed values of IFN-γ (close vs casual contacts)









QFT positive rate: 45.5% (15/33)

QFT positive rate: 7.1% (3/42)

Contact Investigation Case-1

QFT in place of the TST

TB patient	A lecturer
Number of contacts	270
Number of TST positive	75
Rate of TST positive (%)	27.8%
Number of QFT positive	18
Rate of QFT positive (%)	6.7%

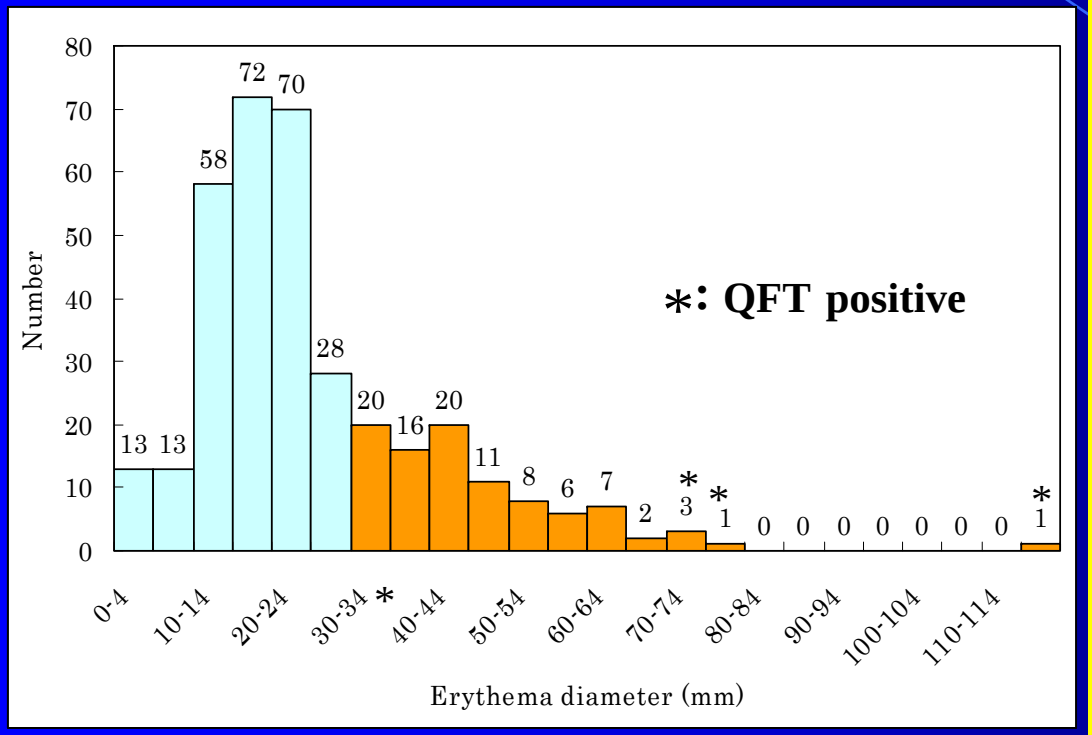
N=75
r =0.207

- QFT significantly associated with exposure – TST was not.
- QFT greatly reduced indication for INH from 27.8% based on TST to only 6.7%.

Contact Investigation Case-2

Further confirmation of the benefits of QFT

Distribution of erythema



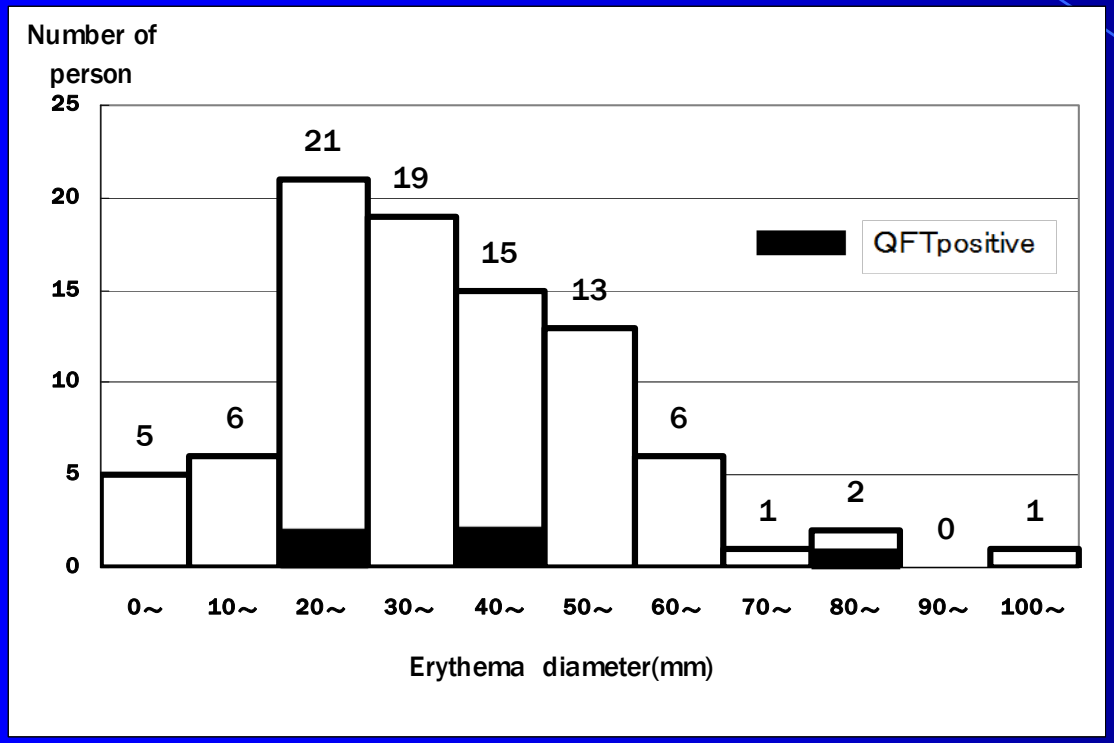
TB patient	A student
Number of contacts	349
Number of TST positive	95
Rate of TST positive (%)	27.2%
Number of QFT positive	4
Rate of QFT positive (%)	1.1%

The 91 TST-positive, but QFT-negative, students were followed for 3.5 years and none developed active TB.

Higuchi K, et al. Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. Respirology 2007;12:88-92.

Contact Investigation Case-3

Distribution of erythema



TB patient	A student
Number of contacts	116
Number of TST positive	57
Rate of TST positive (%)	49.1%
Number of QFT positive	5
Rate of QFT positive (%)	4.3%

Since the clinical isolate from the index case was INH-resistant, REP was offered as chemoprophylaxis for QFT positives. No cases of TB have developed.

Masuda M, et al. Usefulness of QuantiFERONTB-2G in a suspected case of drug resistant tuberculosis outbreak in a university. Kekkaku. 2008;83:7-11.

Contact Investigation Case-4 (Psychiatric hospital)

Characteristics	HCWs	Inpatients
Age range (mean), in years	20-81 (46.6)	20-68 (48.0)
Gender (% of female)	33.3	16.2
Active TB shadow on Chest X-ray	0% (0/9)	0% (0/37)
QFT positive rates	11.1% (1/9)	59.5% (22/37)
Age range (mean) of QFT positives	(81)	33-68 (49.1)
Age range (mean) of QFT negatives	20-69 (42.3)	20-67 (46.4)

- Many contacts with LTBI would have been missed, if they had been diagnosed based on the conventional tests.
- In these facilities, late actions would result in large outbreaks. Prior IGRAs tests would efficiently prevent such cases.

Harada N, et al. Assessment of nosocomial transmission of tuberculosis in a psychiatric hospital using a whole blood interferon-gamma assay. Jpn J Infect Dis. 2008;61:415-418.

The current Japanese situation on TB control

- Since 2007, the guideline recommends QFT in place of the TST for all contact screening.
  - Large body of evidence showing it performs better than the TST
- BCG vaccination no longer an issue.
- Targeted prophylaxis now possible.
  - INH on the basis of a positive QFT result
- QFT brings significant savings in contact screening.
  - Kowada et al. Mol Diag Ther. 2008; 12:235-51

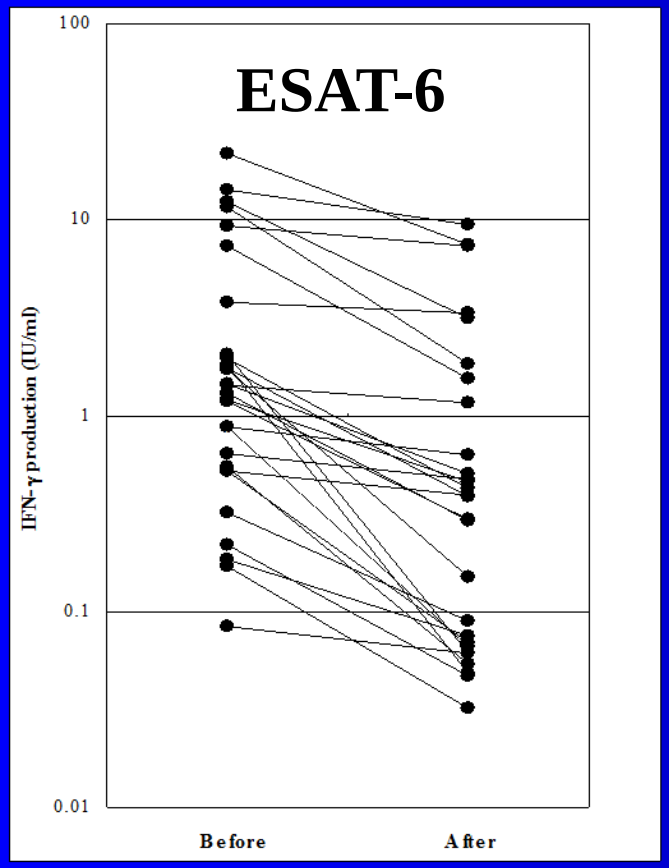
Effects of chemoprophylaxis on QFT responses:

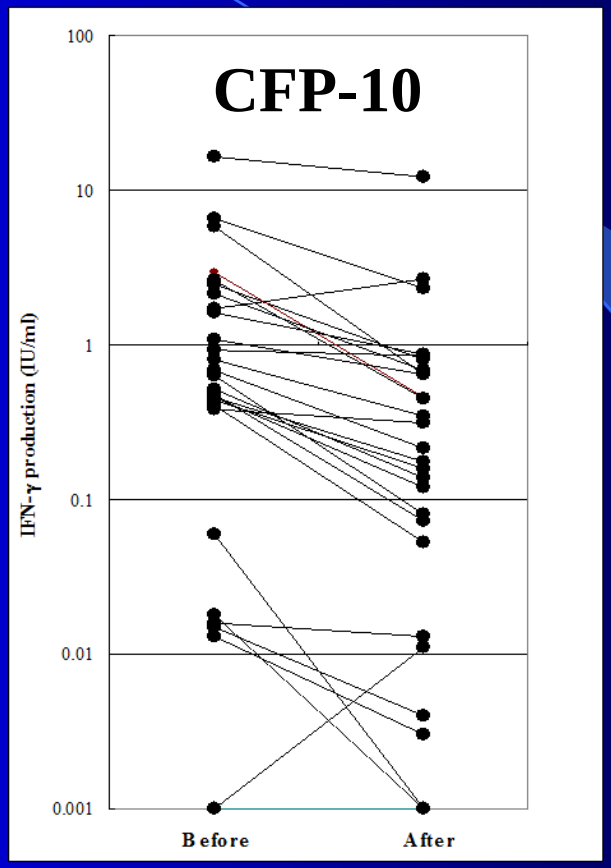
Can QFT be used to monitor treatment?

Effects of chemoprophylaxis on QFT responses

Contacts with a infectious TB patient were tested with QFT before and after (immediately and further later) chemoprophylaxis in two contact investigations. Each QFT values were compared. Compliance with taking daily INH was monitored for the 6-month period.

QFT responses before and immediately after chemoprophylaxis-case 1





Geometric mean 1.398 0.362 0.312 0.120

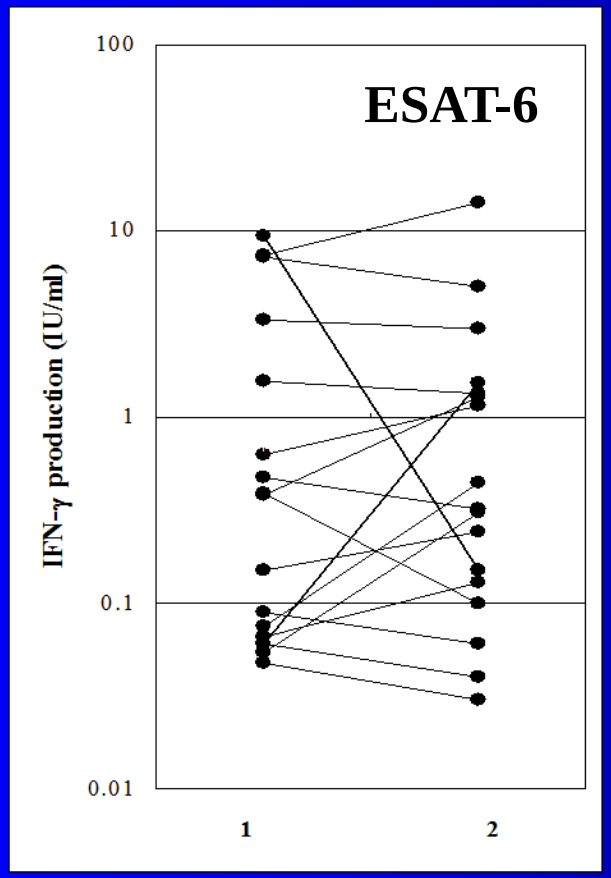
p <0.001 (Wilcoxon's rank test)

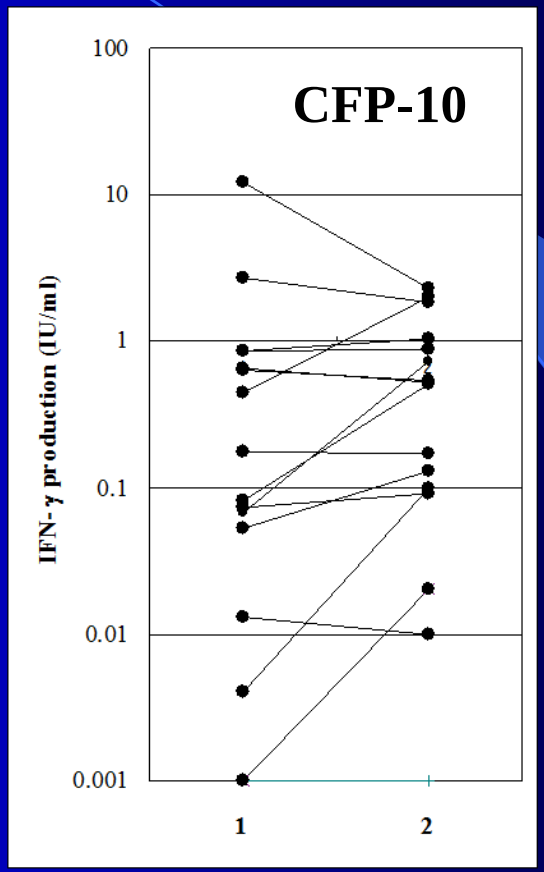
p <0.001 (Wilcoxon's rank test)

Rate of reversion (pos to neg) 25%

Higuchi K, et al. Effect of Isoniazid Chemotherapy for Latent Tuberculosis on Whole Blood Interferon-γ Responses. Respirology 2008; 13: 468-472.

QFT responses at one and half years after chemoprophylaxis



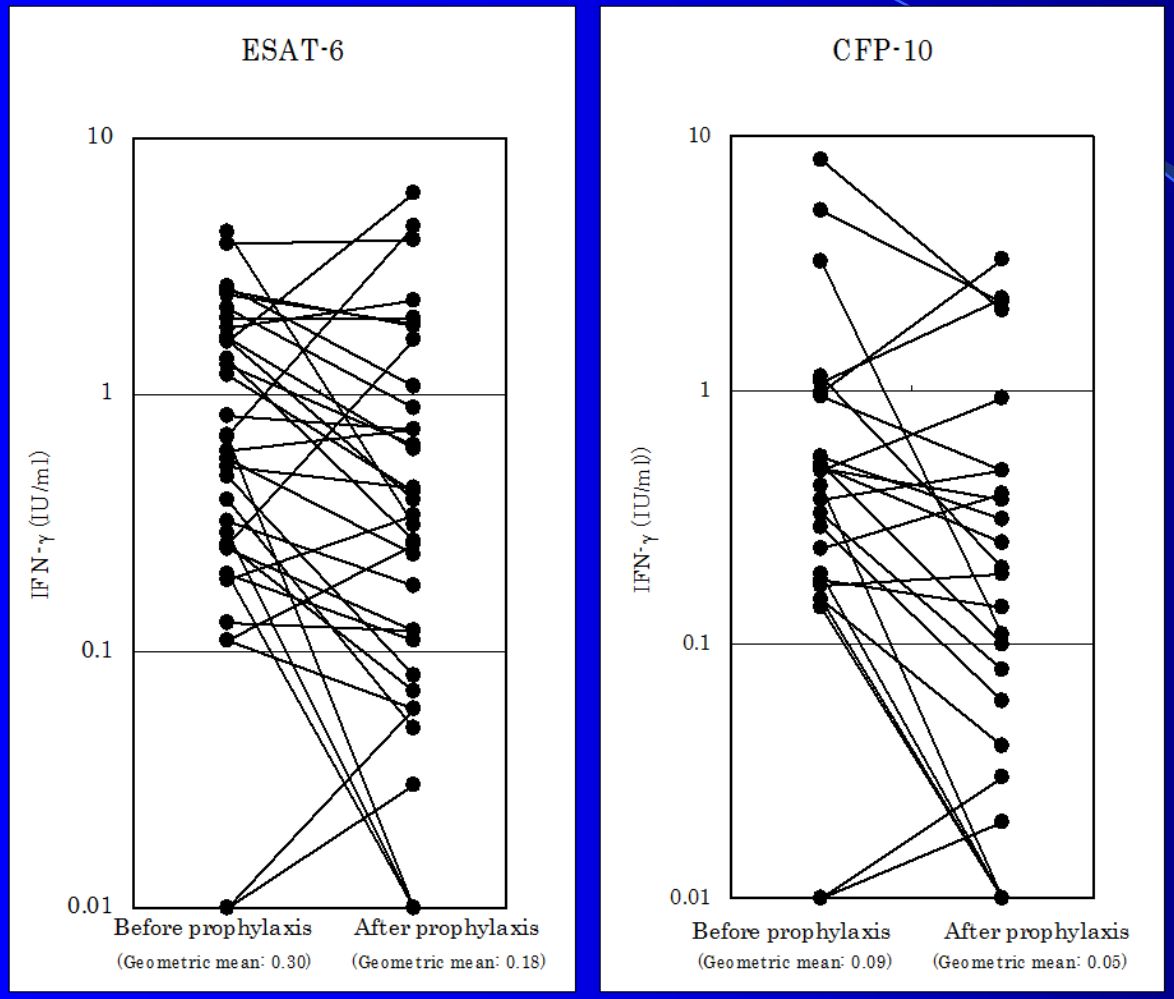


Geometric mean	0.381	0.442	0.087	0.192

p = 0.332 (Wilcoxon's rank test)

p = 0.344 (Wilcoxon's rank test)

QFT responses before and immediately after chemoprophylaxis-case 2

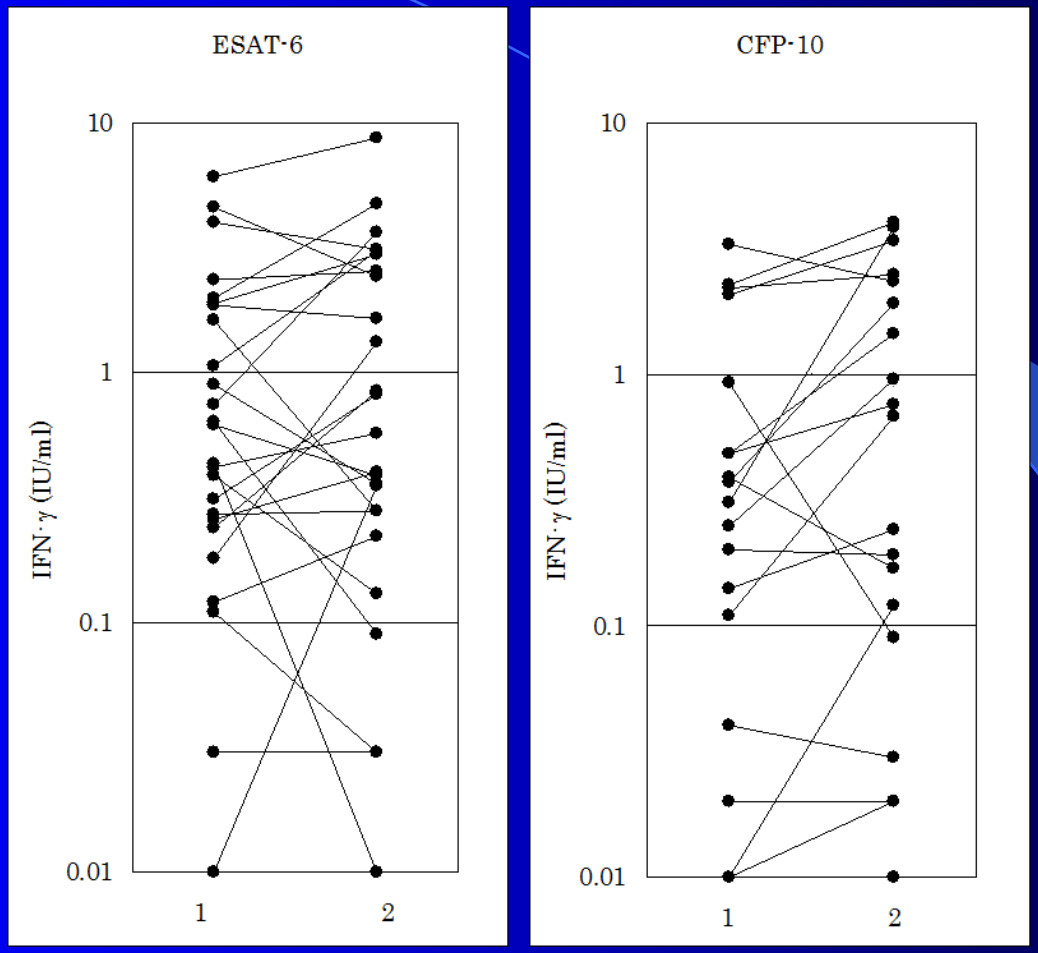


Rate of reversion (pos to neg) 32%

(dependent *t*-test; ESAT-6: p=0.020, CFP-10: p=0.005)

Higuchi K, Effects of prophylaxis on QuantiFERON TB-2G responses among children. Kekkaku 2008;83:603-609.

QFT responses at 9 months after chemoprophylaxis-case 2



Geometric mean	0.28	0.29	0.08	0.09

(dependent *t*-test; ESAT-6: p=0.86, CFP-10: p=0.033)

Conclusion

QFT responses significantly declined after the treatment of LTBI, despite the rate of reversion in QFT being low. These results suggest that TB control needs more effective ways to treat LTBI. New drugs (perhaps RIF for 3 or 4 mo) or better regimens (i.e. 9 or 12 mo INH instead of 6mo) would have a large impact on TB control.

These low reversion rates also suggest that QFT would not be useful as a marker to evaluate the success of treatment for LTBI if the success of chemotherapy is defined as reversion in the QFT test.

However, the finding that QFT responses significantly decline after the treatment of LTBI suggests the possibility that this decline could be used as a marker of the susceptibility of the infective *M. tuberculosis* strain to the prophylactic drug used.

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