



**Agreement**  
**between classic diagnostic procedures**  
**and the new**  
**Interferon-gamma release assay**  
**for detection of**  
**TB disease in Children**



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*Rethinking the Epidemiology of Tuberculosis Infection - February 21,22 Vancouver 2007*



# The Bambino Gesù' Children Hospital

## *The past*

*In 1869 the Bambino Gesù was founded as a small 12-bed hospital in the historical centre of Rome and was **the first children's hospital in Italy***

*In 1924 the hospital was donated to the Pope*



## **The present**

138 years later, the hospital is still property of the Holy See and the size is **800 beds**.

It is a **Research Hospital** and provides a complete range of pediatric healthcare services



The Mission of our Hospital  
**"Cure the sick, serve the ill"**



# Purpose

Talking about IGRA's?

Not as broad term

To evaluate the agreement between  
QFT-G and  
the classic TB Diagnostic procedures  
in Children

especially in children under 5 years



# IGRA's State of the Art

Which is the performance in ACTIVE TB in adults in various setting?

EDITORIAL COMMENTARY

Interferon- $\gamma$  Release Assays: What Is Their Role in the Diagnosis of Active Tuberculosis?

**Madhukar Pai and Dick Menzies**

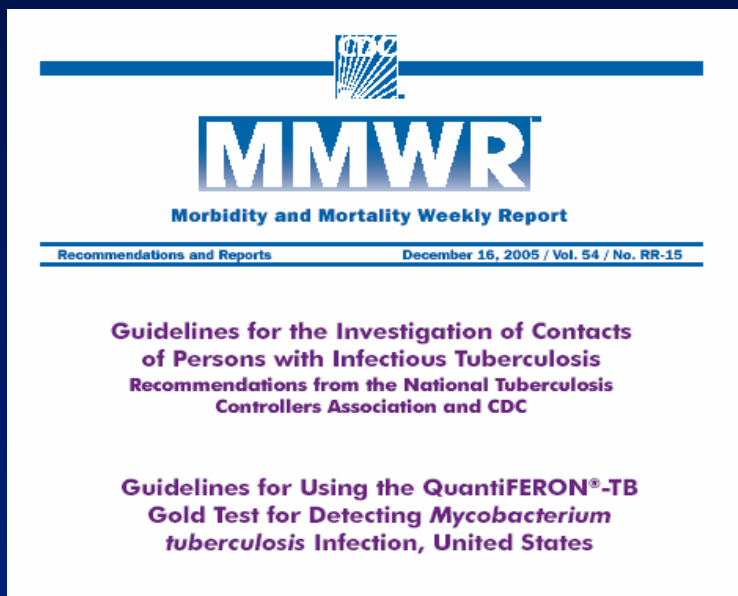
Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, and Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

*the sensitivity (conservatively estimated without excluding indeterminate results) of QFT-G varied from 55% to 88%, with a weighted, pooled mean of 75% (95% CI, 71%–78%).*



# State of the Art

## What about IGRA's in children?



### 1. CDC Guidelines

*.....No published data document the performance of QFT-G in children aged <17 years.*

### 2. NO experimental evidence in children under 5 years



# Work-out plan

This work was prompted during **daily** clinical practice in our children hospital

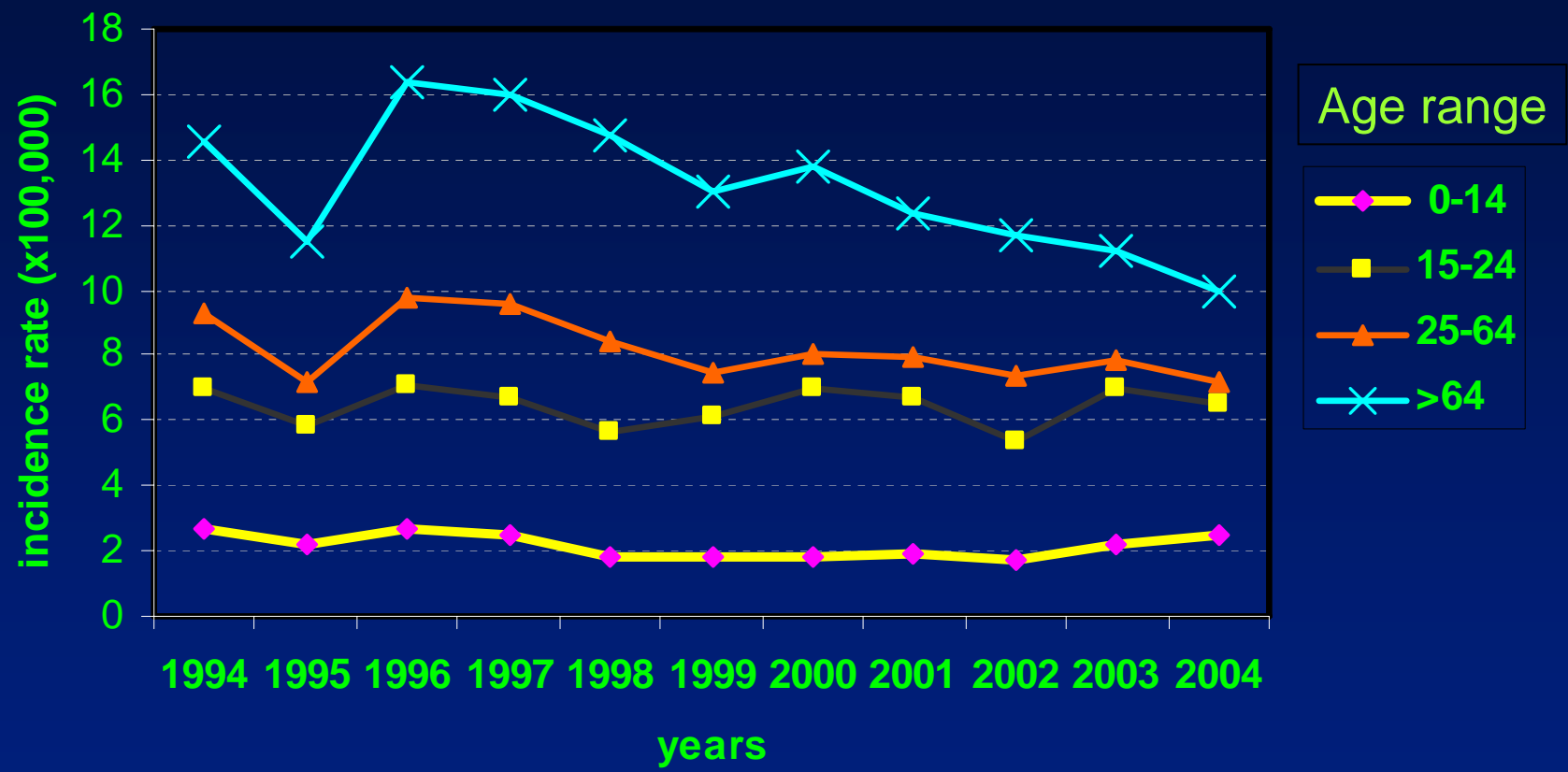
We enrolled a cohort of consecutive patients

- ✓ To understand **if** and **how** QFT-G works in children evaluated for TB
- ✓ To consider QFT- G becoming part of our **TB diagnostic flow-chart**
- ✓ To use QFT as a diagnostic TB test in pediatric settings also for children

**under 5 years**



# TB Incidence in Italy 1994 - 2004



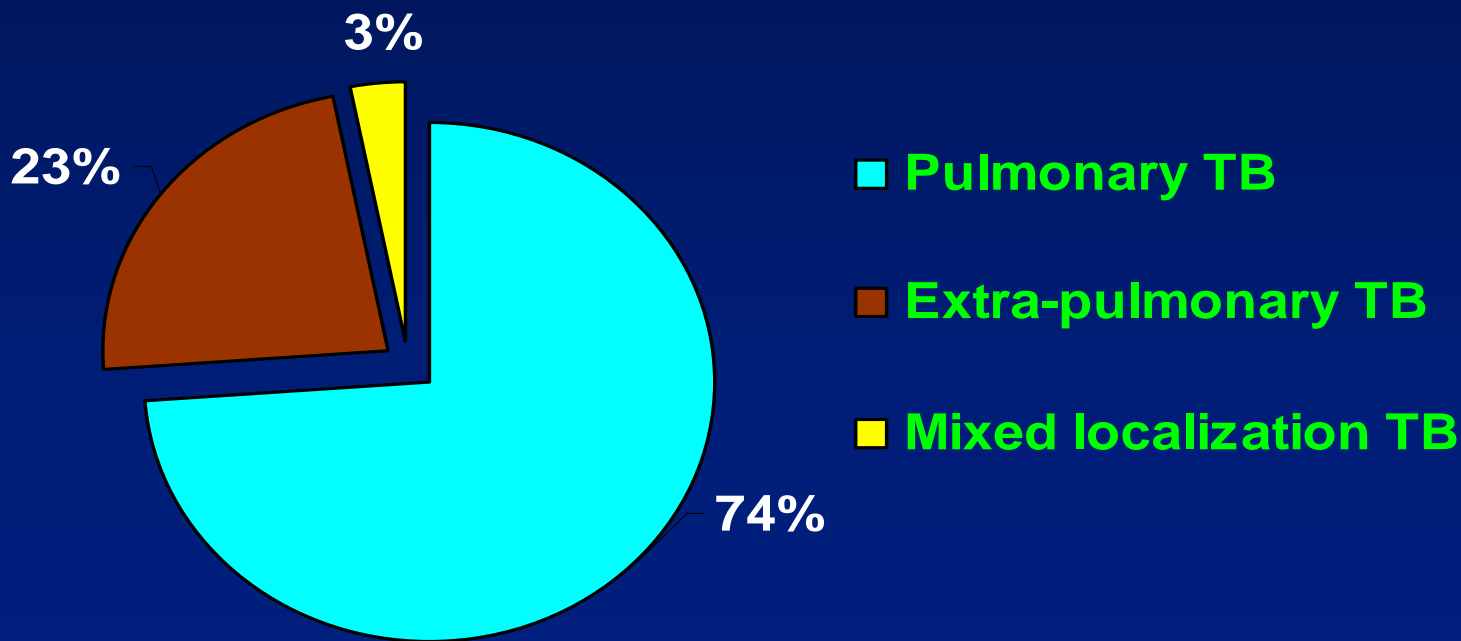
Italy is a low incidence country: 2-2.5 cases per 100.000 children  
*data according to Italian routine surveillance systems*



# TB localization in Italian Pediatric Patients

## 0-14 years

### 1994 – 2004 (No. of cases 1936)



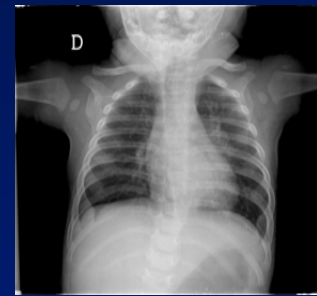


# Classic Diagnostic Procedures

✓ Clinical findings



✓ Radiological finding



✓ TST



After 48-72 hours



✓ Microbiological procedures



# Microbiological procedures Pediatric Hospital Bambino Gesù

3 respiratory samples collected in early morning,  
or other appropriated specimen

- ✓ AFB fluorescence Stain,
  - ✓ solid and liquid media cultures\*,
  - ✓ NAAT (Cobas Amplicore<sup>®</sup> - Roche)

\* Any mycobacteria culture positive was identified using gene sequencing analysis of 16S rDNA 500 bp (Microseq<sup>®</sup> - Applied Biosystem)

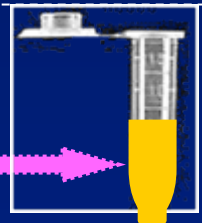


# Additional Procedures since May 2004

## The new Interferon - gamma assay

**QuantiFERON-TB GOLD<sup>®</sup> liquid antigen**  
*(Cellestis Limited, Carnegie, Victoria, Australia)*

5 ml of whole blood were collected in a heparinized syringe



All samples were tested in duplicate

All results were maintained blinded



# Inclusion Criteria

## Eligible criteria

- Symptoms in TB close contacts
- Fever not responding to drug therapy
- Radiological findings
- TST positive

## Exclusion criteria

HIV / AIDS  
Past history of TB  
active disease

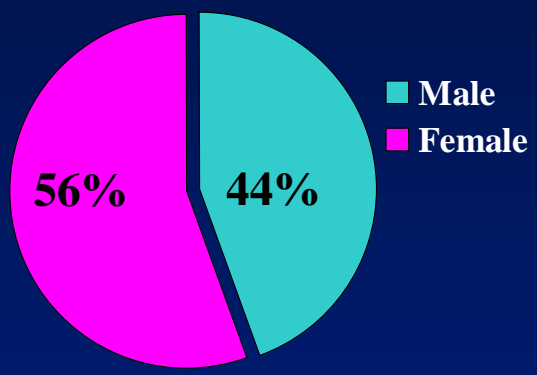


# Patients' characteristic

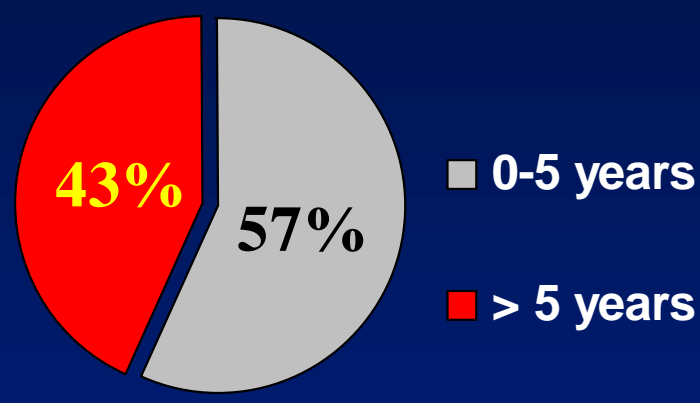
## 106 children



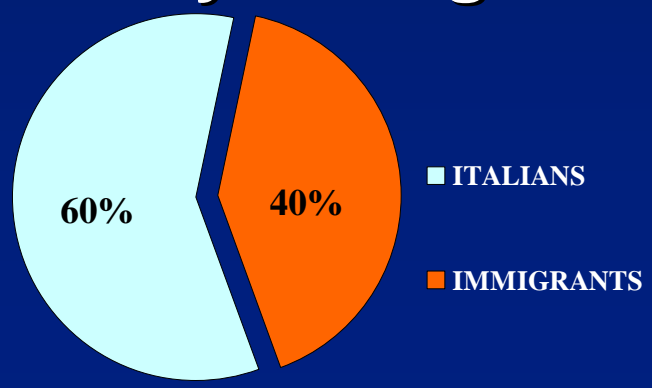
### Gender



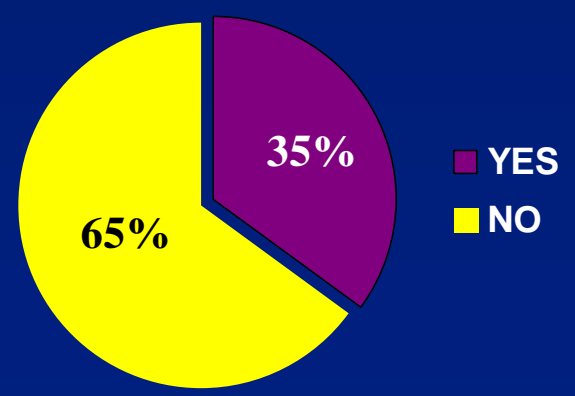
### Age



### Country of origin



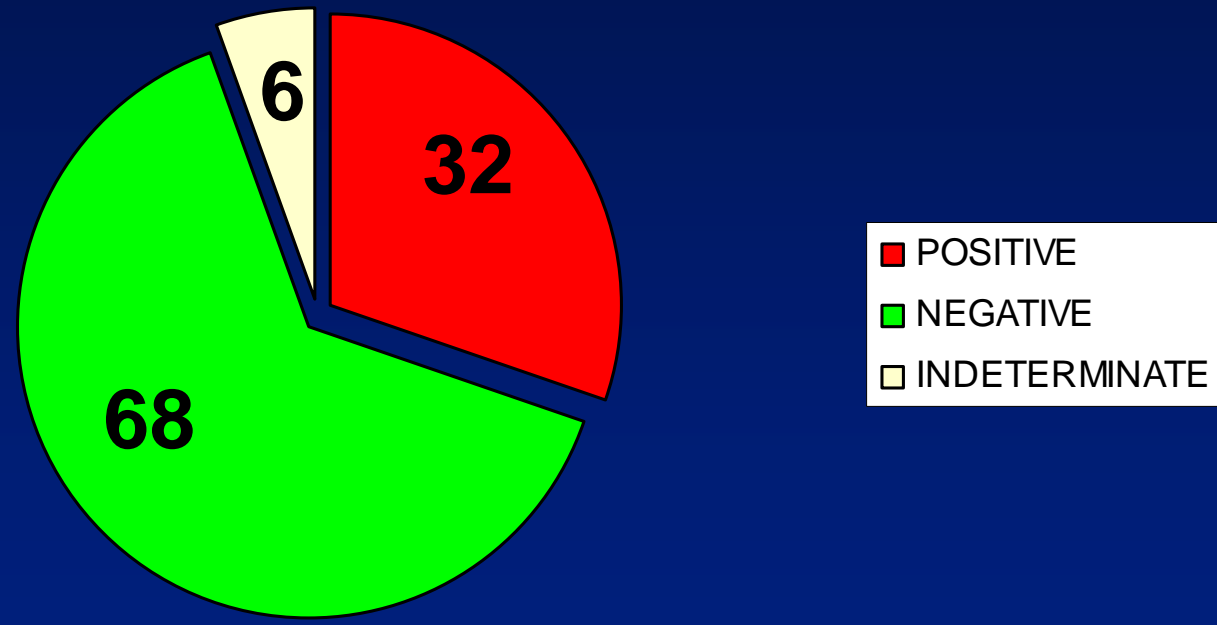
### BCG vaccination





# QuantiFERON-TB Gold

## Results N=106





# About Children with QFT-G Indeterminate Results N=6

5 children were not TB affected

Patient characteristics

- 2 Males and 3 Females
- 4 under 5 ys and 1 over 5 years
- 3 from Italy and 2 from endemic countries
- 1 BCG vaccinated and 4 Not vaccinated

TST was **NEGATIVE** in all five patients

**1 child was TB affected**

Male, over 5 ys coming from Perù, not vaccinated

TST and Culture were **POSITIVE**



# 1 . Agreement TST vs QFT-G

99 Children (106 – 7) \*

|                               |    |
|-------------------------------|----|
| TST Positive / QFT-G Positive | 29 |
| TST Negative / QFT-G Negative | 35 |
| TST Positive / QFT-G Negative | 32 |
| TST Negative / QFT-G Positive | 3  |

Agreement 64.6%; K (95% CI) = 0.347 (0.173-0.521)

- \* 6 QFT-G results Indeterminate
- 1 patients died before reading TST



# 2 . Agreement Culture vs QFT-G

95 Children (106 – 11) \*

|                                   |    |
|-----------------------------------|----|
| Culture Positive / QFT-G Positive | 17 |
| Culture Negative / QFT-G Negative | 64 |
| Culture Positive / QFT-G Negative | 4  |
| Culture Negative / QFT-G Positive | 10 |

Agreement 85.3 %; K (95% CI) = 0,612 (0.412-0.636)

\* 6 QFT-G results Indeterminate  
 5 patients no sample collected for culture



# QFT-G performance Overall

## Final TB diagnosis N= 41

Sensitivity 78 %

Specificity 100 %

Positive Predictive Value 100 %

Negative Predictive Value 86.8 %

Positive Likelihood Ratio infinity

Negative Likelihood Ratio 21.9 %

**Accuracy 91 %**



# QFT-G performance Overall

## Pulmonary TB diagnosis N=35/41

Sensitivity 88.6%

Specificity 100 %

Positive Predictive Value 100 %

Negative Predictive Value 93.6 %

Positive Likelihood Ratio infinity

Negative Likelihood Ratio 11.4 %

**Accuracy 95.7%**



# Potential bias?

Let's check with:

**QUADAS** and

**STARD**

Although...

- ✓ The low number of cases may affect precision
- ✓ We did not evaluate children HIV + or immunosuppressed

But at present...



# Remarks

- ✓ This is one of the **first experiences** using QuantiFERON-TB GOLD in a pediatric population in a TB **low incidence country**

## About children under 5 years

- ✓ The Accuracy of QFT-G was high 0,946 -0,881
- ✓ Sensitivity of QFT-G was between 88-95.6%
- ✓ Specificity and Positive Predictive Value were 100%.
- ✓ In Our experience QFT-G is **reliable in childhood**

# Conclusion



## Agreement

**between classic diagnostic procedures  
and the new Interferon-gamma  
release assay QFT-G  
for detection of TB disease in Children  
is as Equivalent as in Adults**



Thank you for your attention



## Acknowledgments

**Donato Menichella, MD** Chief of Microbiology Laboratory Staff  
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**Luana Coltella PhD** Microbiology Laboratory - Division of Mycobacteria  
**Silvia & Eugenia** Microbiology Laboratory - Division of Mycobacteria

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