Screening children for TB in Europe

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Presentation overview

Childhood TB in Europe

Screening and diagnostics

IGRA: contribution to the diagnosis of active or latent TB in children

Results from the ptbnet IGRA study

Remaining research questions

Conclusions

Acknowledgement & Thanks
Children still suffer from TB in the EU/EEA

- **Almost 40 000 cases were notified in the past decade.**
- A total of 39 695 childhood TB cases (0–14 years of age) were notified between 2000 and 2009 by 27 EU-Member States and three EEA countries.

Age-specific notification rates of childhood TB in EU

- Overall TB rates dropped from 5.5 per 100 000 in 2000 to 4.2 per 100 000 in 2009. Mean annual decline in this period is 2.8% (p<0.001)

• Sandgren, ECDC, Euro Surveill. 2011 Mar 24
Where do the childhood cases come from?

- More than 3,300 cases were notified in 2009.
- Childhood TB cases accounted for 4.2% of all notified TB cases in the EU/EEA in 2009.

Country-specific childhood TB notification rates 2009

> 10 per 100,000 child population

4.1 to 10.0 per 100,000 child population

2.1 to 4.0 per 100,000 child population

< 2 per 100,000 child population

Not included or not reporting

Sandgren, ECDC, Euro Surveill. 2011 Mar 24
Childhood TB is a marker of transmission in the community

- In certain EU settings, childhood TB is on the rise.
- Preventing TB infection in children is the foundation to achieving a TB-free generation in the EU/EEA.
- As children have a higher rate of primary progression to TB upon infection, TB in this vulnerable group is a sign of recent transmission.
- Trends in notification of childhood TB indicate that transmission to children is still occurring within the borders of the EU, particularly in low-incidence countries.

Figure 2a: High- and low-incidence countries for TB (in total population, including adults)

Sandgren, ECDC, Euro Surveill. 2011 Mar 24
What can we do about it?

• Make an accurate diagnosis of active TB in adults and children and treat them promptly and with the appropriate drugs

• Contact-tracing in households and communities

• Screening of TB exposed individuals and treatment of LTBI in children

  • ? With what tests??

  • What is the role of IGRA?
How can the contacts at greatest risk of tuberculosis be identified?

- TB initial yield by contact factors
- In all contacts, by age and HIV status

<table>
<thead>
<tr>
<th></th>
<th>Included studies</th>
<th>Contacts investigated</th>
<th>Cases found</th>
<th>Prevalence (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All contacts</td>
<td>78</td>
<td>898,619</td>
<td>38,209</td>
<td>3.5% (2.3-5.4)</td>
</tr>
<tr>
<td>Child contacts &lt;5y</td>
<td>21</td>
<td>6,617</td>
<td>856</td>
<td>9.6% (5.5-16.0)</td>
</tr>
<tr>
<td>Contacts 5-14y</td>
<td>11</td>
<td>5,366</td>
<td>300</td>
<td>4.5% (1.6-12.3)</td>
</tr>
<tr>
<td>HIV+ contacts</td>
<td>5</td>
<td>282</td>
<td>79</td>
<td>28.4% (9.8-59.2)</td>
</tr>
</tbody>
</table>
Q1.2
How can the contacts at greatest risk of tuberculosis be identified?

- LTBI initial yield by contact factors
- In all contacts, by age and HIV status

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<th>Cases found</th>
<th>Prevalence (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All contacts</td>
<td>82</td>
<td>74,358</td>
<td>40,521</td>
<td>45.9% (41.3-50.6)</td>
</tr>
<tr>
<td>Child contacts &lt;5y</td>
<td>35</td>
<td>13,784</td>
<td>5,256</td>
<td>30.0% (23.4-37.5)</td>
</tr>
<tr>
<td>Contacts 5-14y</td>
<td>23</td>
<td>12,673</td>
<td>6,595</td>
<td>44.0% (30.8-58.0)</td>
</tr>
<tr>
<td>HIV+ contacts</td>
<td>4</td>
<td>108</td>
<td>41</td>
<td>41.2% (23.9-61.1)</td>
</tr>
</tbody>
</table>
Challenges

Diagnostics

Active versus latent TB

Age-dependent performance of some tests?
Paediatric TB: Diagnostic challenges due to low bacillary load

- children less infectious
- lack of "gold standard": microbiological confirmation exceptional
- difficulty in detecting resistance
IGRA and the diagnosis of active or latent TB

- Signs and symptoms
- Microbiology
- Radiology
- Travel
- Contact history
- TST

IGRA
**Diagnostic approaches**

**Microbiological**
- Organism
  - smear
  - culture
  - DNA

**Immunological**
- Host response
  - skin test
  - antigen-specific production of IFNγ
Tuberculin skin test (TST)

- technically difficult in children
- UK: 2 units of SSI tuberculin (PPD)
  - > 200 antigens, incl. BCG Ag
- Read-out: degree of hypersensitivity

**Problem:**

lacks specificity and sensitivity
Gene deletions and the origin of BCG

**M. tuberculosis**
- 10 deletions
- 64 genes

**M. bovis**
- 4/5 deletions
- 30/40 genes

**RD1 region**

**major antigens**
- ESAT6
- CFP10

**T cell tests (interferon-γ)** that distinguish *M. tuberculosis* infection from BCG vaccination

**BCG substrains**
Antigens used:
ESAT-6
CFP10 +/- TB7.7
mitogen
negative control

In principal: can both distinguish between BCG vaccination and *M. tuberculosis* infection

but:
Paucity of data in children
Confusion about use of IGRA

2 commercially available assays
IGRA and National TB guidelines

UK: NICE Guidelines 2006
http://guidance.nice.org.uk/CG33
Spot the Difference

Interferon-γ release assays (IGRA) in paediatric active and latent tuberculosis in London - a side-by-side comparison with TST


Interferon-γ release assays do not identify more children with active TB than TST.

Eur Respir J. 2009 Jun;33(6):1374-8
# IGRA and the diagnosis of active TB

## Results (%) of all three test in the different sub-groups of Active TB

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>QFG-IT</th>
<th>Tspot.TB</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&gt;15</td>
<td>6-15</td>
<td>&lt;6</td>
</tr>
<tr>
<td>All active TB</td>
<td>43</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>(N=91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>83</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>(N=25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>45</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>(N=38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite &amp; Probable</td>
<td>60</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>(N=63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>7</td>
<td>14</td>
<td>79</td>
</tr>
<tr>
<td>(N=28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IGRA missed between 20-40% of definite active TB**
A combination of TST and IGRA increases sensitivity to above 93%
A negative IGRA does not exclude active TB

IGRA is not a rule-out test, but can add value to additional investigations
LTBI: BCG, TST and IGRA

More +ve TST than IGRA
Good agreement between 2 IGRAS (92%, k=0.82)
Conclusion 2: Latent TB

- Good agreement between 2 IGRAS (92%, k=0.82)
- “over-treatment” by Paediatricians, compared to NICE recommendations

- How many children will develop TB if Mantoux > 15, but untreated with chemopro as IGRA negative?
- How many children have neg TST but would have pos IGRA at screening
- Longitudinal survey required
Aims of the project

1. To determine if it is safe to withhold chemoprophylaxis from children exposed to TB with negative IGRA but positive TST

   *Prospective cohort study*

2. To link TB exposure, infection and outcome in children by adapting the existing data collection tool

   *Contact module*
Design

TB exposed children (n=600)

TST and IGRA at screening/3 months

TST+ve/IGRA-ve followed for 2 years

Primary endpoint: Development of active TB
   (Nice: how safe are the guidelines?)

Secondary endpoint: how concordant are TST and IGRA
   (Nice: is the step-wise screening approach justified?)
IGRA and the diagnosis of latent TB

• No “gold standard” for LTBI

• Acknowledged discrepancy of TST and IGRA results
  - due to poor specificity of TST

• Which IGRA is better?
  - Good agreement between 2 IGRAS (92%, k=0.82)
    (similar to Connell et al, PLoS One. 2008 Jul:
     agreement between QFT-IT and T-SPOT.TB 93%, k=0.83).

• Currently: ? “over-treatment” by paediatricians
  - but: to date no studies of negative predictive value of IGRA in children

• Performance in very young children- conflicting messages

• Increased sensitivity in immuno-compromised hosts
Active TB

**Detection of tuberculosis in HIV-infected children using an Elispot**

*Davies et al, AIDS. 2009 May 15;23(8):961-9.*

ELISPOT was positive in 14/21 (66%) with definite TB
ELISPOT was more sensitive than TST for the detection of active TB in HIV-infected children: positive ELISPOT compared with a positive TST [25/39 (64%) vs. 10/34 (29%), P = 0.005]

“However, the sensitivity of current ELISPOT assays is not sufficiently high to be used as a rule out test for TB.”

Latent TB

**High level of discordant IGRA results in HIV-infected adults and children**


HIV+ve children (n=23): tests yielded discordant results
61% of individuals testing positive with T-SPOT.TB, 41% with TST and 28% with QuantiFERON TB Gold (QTF)- older version
Algorithm for use of TB screening in HIV+ve patients

Newly diagnosed HIV or new immigrant with HIV

IGRA at baseline

- positive
  - Investigate for active TB
    - Latent TB: chemoprophylaxis
    - Active TB: TB Tx
  - TB Tx

- negative
  - ? Immune system: check PHA
  - ? Lack of exposure / no infection

Repeat IGRA when “immune reconstituted”

Use as baseline result if concerns of active TB arise later
Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?


- surveyed the literature and contacted experts to identify 33 guidelines and position papers from 25 countries and two supranational organizations.

- considerable diversity in the recommendations on IGRAs, with four approaches commonly proposed:
  - (i) two-step approach of tuberculin skin test (TST) first, followed by IGRA either when the TST is negative (to increase sensitivity, mainly in immunocompromised individuals), or when the TST is positive (to increase specificity, mainly in bacillus Calmette-Guérin-vaccinated individuals);
  - (ii) Either TST or IGRA, but not both;
  - (iii) IGRA and TST together (to increase sensitivity); and
  - (iv) IGRA only, replacing the TST.

Conclusion:
Overall, the use of IGRAs is increasingly recommended, but most of the current guidelines do not use objective, transparent methods to grade evidence and recommendations, and do not disclose conflicts of interests. Future IGRA guidelines must aim to be transparent, evidence-based, periodically updated, and free of financial conflicts and industry involvement.
Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis

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SUMMARY

BACKGROUND: Children infected with Mycobacterium tuberculosis have significant risk of developing tuberculosis (TB) and can therefore benefit from preventive therapy.

OBJECTIVE: To assess the value of interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST) in the diagnosis of TB infection and disease in children.

METHODS: Thirty-three studies were included, assessing commercial IGRAs (QuantiFERON®-TB [QFT] and T-SPOT.®TB) and TST. Reference standards for infection were incident TB or TB exposure. Test performance for disease diagnosis was evaluated in studies assessing children with confirmed and/or clinically diagnosed TB, compared to children where TB was excluded.

RESULTS: Two small studies measured incident TB in children tested with QFT and found weak positive predictive value. Association of test response with exposure —categorized dichotomously or as a gradient—was similar for all tests. The sensitivity and specificity of all tests were similar in diagnosing the disease. Stratified analysis suggested lower sensitivity for all tests in young or human immunodeficiency virus infected children.

CONCLUSIONS: Available data suggest that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children. Heterogeneous methodology limited the comparability of studies and the interpretation of results. A rigorous, standardized approach to evaluate TB diagnostic tests in children is needed.

KEY WORDS: tuberculosis; pediatrics; TB infection; IGRAs; tuberculin skin test
Performance of IGRA in larger cohorts of children in Europe

- Low endemicity
- Low HIV-prevalence
Aims

• enhance the understanding of the pediatric aspects of tuberculosis

• facilitate collaborative research studies for childhood TB in Europe

• provide expert opinion through excellence in science and teaching

• establish a better evidence base for diagnosis and treatment of TB in children
Aim: To investigate factors influencing results of interferon gamma release assays in children using a large European dataset

- Methods: Retrospective analysis of data from children referred for TB screening by TST + IGRA (cases of active TB excluded):
  - household contacts of an active case of tuberculosis or positive TST result reported in national universal childhood TB screening, or originating from a high tuberculosis prevalence area
- Multi-variate logistic analyses examined age, Bacille Calmette-Guérin (BCG) vaccination status, and gender as predictor variables of results
Should we abandon the TST in screening for LTBI?

- Reliability of performance of IGRA in very young children
- How do we interpret indeterminate results
- Negative predictive value, i.e.
  How many children will develop active TB if TST > 15 mm, but untreated with chemoprophylaxis as IGRA negative, according to current guidelines
- Is the step-wise approach of TST first, IGRA second justified?
  How many children with negative TST would have a positive IGRA at screening
- Does the TST boost the IGRA responses
  Current evidence suggests that boosting occurs, but not within first 72 hours
- (Short-term) reproducibility of the commercial IGRA
  Can IGRA be used to monitor therapy or to predict development of active TB

Remaining questions and further research
What are we currently missing?

No data that link exposure/infection to disease
• IGRA detect immune memory but do not confirm the presence or absence of *M. tuberculosis*—active or latent

• higher specificity than the TST

• designed to test for evidence of TB infection, not TB disease

• can be used as a rule-in test for active TB in children, but not as a rule-out test

• higher sensitivity in immunocompromised patients compared to TST

• IGRA should not currently replace the **TST in children**

• **we should not forget the many additional challenging question in childhood TB**

  better microbiological diagnostics

  better biomarkers than IFN-γ

  better vaccines

  **improved understanding of primary TB**

Conclusions
Thank you