Author’s reply

The commentary by Connell et al1 on the data presented in our paper2 is a welcome contribution to the debate on the most appropriate method for demonstrating latent tuberculosis (TB) infection in refugee children. Although a comparison of the performance of interferon-γ release assays (IGRAs) with tuberculin skin tests (TSTs) was not the primary aim of our study, the data do allow us to make observations on this topic. We have reassessed our data on the effect of previous BCG immunisation on IGRA and TST positivity (see table 3) and suggest that the very similar ORs for IGRAs and TST might reflect the adjustment of the cut-off point for a positive TST where we had added 5 mm for children under the age of 5 years with a history of previous BCG immunisation (see Methods section). It has been shown that BCG immunisation affects TST reactivity predominantly in children of this age.3 When our data analysis was restricted to include only children aged <5 years, the OR for a positive TST in BCG-immunised children was 3.2 (p=0.1) when the adjusted cut-off was used and 5.1 (p=0.04) when a cut-off of 10 mm was used. We are grateful to Connell et al for emphasising that the antigens used in both types of IGRA are also expressed by a small number of non-tuberculous mycobacteria and therefore can only be regarded as predominantly Mycobacterium tuberculosis-specific, as indicated in the Introduction to our paper.

We do not agree that our data ‘suggest TST may have had superior sensitivity to either of the two IGRAs in household TB contacts (ie, those at highest risk of latent tuberculosis infection)’. By reference to the data in figure 3 of our paper, it can be seen that five of six children (83%) with household TB contact who had a positive TST in association with neither IGRA being positive had received BCG immunisation. Furthermore, we had adjusted the cut-off point for TST positivity by subtracting 5 mm for children with household contact; re-analysis of the data using a cut-off point of 10 mm for all children decreased the OR for a positive result to 2.1 (p=0.1). It is therefore not unlikely that the higher rate of TST positivity in this subgroup reflected previous BCG immunisation rather than false negative IGRA results. With reference to the data in table 1 of Connell et al, we note that the percentage of children without an interpretable result is particularly inflated by the large number of younger children enrolled in the study. This is evident by the breakdown according to age group in table 1 (with the single HIV case omitted). It should also be noted that the failed phlebotomy numbers are further skewed for QuantiFERON-TB gold in tube (QFT-GIT) as, for most of the study, preference was given to attempting the T-SPOT.TB in cases of limited blood volume.

Connell et al did not comment on our finding that an inconclusive test result with one IGRA was usually associated with a valid result for the other IGRA. It is for that reason that we suggested initial testing with an IGRA rather than TST, and testing with the alternative IGRA when the first IGRA gives an inconclusive result. Furthermore, our data suggest that choosing the first-line IGRA according to patient demographic/clinical considerations will minimise the need for repeat testing. This strategy will only be possible when both IGRAs are available, but we believe it has the potential to be more cost-effective and convenient for both children and their families than a primarily TST-based screening approach, particularly in children from refugee families.

Michaela Lucas,1 Pam Nicol,2 Elizabeth McKinnon,3 Rebecca Whidbourne,1 Andrew Lucas,3 Aesen Thambiran,4 David Burgner,5 Justin Waring,6 Martyn French7
1Department of Clinical Immunology, Royal Perth Hospital and Pathwest Laboratory Medicine, Perth, Western Australia; 2School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia; 3Centre for Clinical Immunology and Biomedical Statistics, Murdoch University, Perth, Western Australia; 4Migrant Health Unit, North Metropolitan Area Health Service, Perth, Western Australia; 5Murdock Children’s Research Institute, Royal Children’s Hospital, Parkville, Victoria, Australia; 6TB Control Program, North Metropolitan Area Health Service, Perth, Western Australia; 7School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Western Australia

Correspondence to Michaela Lucas, Royal Perth Hospital and Pathwest Laboratory Med, Wellington Street, Perth, 6000 Australia; michaela.lucas@health.wa.gov.au

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 24 August 2010

Published Online First 21 October 2010


REFERENCES

Indices of bronchial reactivity and sensitivity

Cisneros et al1 report associations between scores on the Asthma Quality of Life Questionnaire (AQLQ) and three indices of bronchial reactivity (dose–response slope (DRS), continuous index of responsiveness (CIR) and bronchial reactivity index (BRI)), which they suggest are qualitatively different from sensitivity, measured by PD20FEV1. This conclusion is questionable.

First, there are no meaningful differences between DRS, CIR and BRI. All are calculated using the final percentage fall in the forced expiratory volume in 1 s (FEV1) and final cumulative dose. The only difference between them is the mathematical transformation applied to the data. Any differences in the associations between AQLQ and DRS, CIR or BRI can only be due to differences in the shape or linearity of the mathematical functions describing their relationships with AQLQ.

Secondly, the information provided by PD20 is not qualitatively different from that provided by DRS. PD20 is calculated by interpolation from standard dose–response curves plotted on a semi-log scale. The same data plotted on a linear dose axis appear as a straight line, the slope of which is the DRS. In subjects with a PD20, there is a close correlation between DRS and PD20.2 Figure 1 shows the relationship between logPD20 and logDRS (r=−0.97, p<0.0001) in 41 subjects with asthma with airway hyper-responsiveness (AHR) to histamine, from a clinical trial in our laboratory.1 Cisneros et al3 do not state the correlation between PD20 and their indices of ‘reactivity’, but a close correlation would argue against any meaningful differences in the interpretation of PD20 and ‘reactivity’.

Table 1

<table>
<thead>
<tr>
<th>IGRA Results</th>
<th>0–2 years (N = 70)</th>
<th>3–4 years (N = 110)</th>
<th>5–16 years (N = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-SPOT.TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient blood volume</td>
<td>21</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Test failed</td>
<td>9</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Indeterminate results</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total N (%) without interpretable result</td>
<td>31 (44%)</td>
<td>32 (29%)</td>
<td>48 (14%)</td>
</tr>
<tr>
<td>QFT-GIT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient blood volume</td>
<td>26</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Test failed</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate results</td>
<td>7</td>
<td>16</td>
<td>47</td>
</tr>
<tr>
<td>Total N (%) without interpretable result</td>
<td>33 (47%)</td>
<td>39 (35%)</td>
<td>61 (18%)</td>
</tr>
</tbody>
</table>


Authors’ response

We read with great interest the comment by Salome and coworkers on our recently published article.¹ We are grateful for their interest in our work, although they attribute to us a conclusion that does not appear in our paper. We conclude that bronchial reactivity indices are independent predictors for the health-related quality of life of patients with asthma and we propose that they might be of use in clinical practice. In our conclusion, however, no comparison is established between bronchial reactivity and sensitivity.

We agree that the analysed indices of bronchial reactivity represent different expressions of the slope of the dose–response curve. Certainly, the differences in their relationship with the Asthma Quality of Life Questionnaire are attributable to changes in shape or linearity due to the mathematical transformation applied in their calculation.

Nevertheless, we do not agree with the assimilation between the provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV₁) (PD20) and dose–response slope (DRS). Both parameters seem to be qualitatively different since the dose–response curves plotted in their determination are also different. PD20 is obtained from curves plotted on a semilogarithmic scale whereas DRS is obtained from a linear dose axis. Moreover, the calculation of PD20 uses the fall in FEV₁ between the last and penultimate doses while, for DRS determination, the fall in FEV₁ is considered that between the last dose and the post-diluent baseline value. These different approaches provide necessarily different values. In fact, and in contrast to Salome and coworkers, in our patients with asthma the relationship between PD20 and DRS is slight (r=−0.416, r=0.042).

We therefore believe that DRS and PD20 are not completely equivalent. DRS allows for airway responsiveness to be assessed in all individuals, including those who do not reach the threshold PD20. Several studies, including some of their own group,² have already shown that DRS to methacholine or histamine is associated with asthma diagnosis and symptoms. Moreover, DRS allows for a better separation of patients with and without asthma than PD20.¹ It has recently been shown that adolescents with asthma remission had a significant decrease in speed of bronchial constriction (bronchial reactivity) whereas the threshold of methacholine (bronchial sensitivity) was not altered.⁴

Finally, and in agreement with Porsbjerg et al.,⁵ we consider that the differences in the estimation procedure and the non-censored character of the DRS, continuous index of responsiveness and bronchial reactivity index should justify their stronger relationship with health-related quality of life than PD20.

Carolina Cisneros,¹ Francisco García-Rio,² Julio Ancochea³

¹Servicio de Neumología, Hospital Universitario La Princesa, P, Madrid, Spain; ²Servicio de Neumología, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain

Correspondence to Carolina Cisneros, Servicio de Neumología, Hospital Universitario La Princesa, C/Diego de León 62, Madrid 28006, Spain; carol9199@yahoo.es

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Hospital Universitario La Princesa y La Paz.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 1 October 2010

Published Online First 27 October 2010

Thorax 2011;66:266. doi:10.1136/thx.2010.152470

REFERENCES


Outcome after bronchiolitis depends on disease definition

Sigurs et al recently published their 18-year prospective controlled follow-up study of 47 subjects hospitalised for respiratory syncytial virus (RSV) bronchiolitis at age <12 months.¹ In the cohort the prevalence of wheezing and asthma was higher than in population-based controls at 3, 7 and 13 years of age.

Asthma was present, depending on definition, in 33–39% of 46 study subjects and in 7–9% of 92 controls,² in line with an asthma prevalence of 9.5% in Swedish young adults.³ The risk of adulthood asthma after...
Indices of bronchial reactivity and sensitivity

Cheryl M Salome, Nathan J Brown, Helen K Reddel, Wei Xuan and Guy B Marks

Thorax 2011 66: 265-266 originally published online October 27, 2010
doi: 10.1136/thx.2010.151639

References
This article cites 3 articles, 3 of which you can access for free at:
http://thorax.bmj.com/content/66/3/265.2#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/