## Author's reply

The commentary by Connell *et al*[1] on the data presented in our paper[2] 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.

**Table 1** Re-analysis of IGRA results by age categories

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

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## Indices of bronchial reactivity and sensitivity

Cisneros *et al*[1] 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 $PD_{20}FEV_1$. 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 ($FEV_1$) 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 $PD_{20}$ is not qualitatively different from that provided by DRS. $PD_{20}$ 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 $PD_{20}$, there is a close correlation between DRS and $PD_{20}$.[2] Figure 1 shows the relationship between $\log PD_{20}$ 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.[3] Cisneros *et al*[1] do not state the correlation between $PD_{20}$ and their indices of 'reactivity', but a close correlation would argue against any meaningful differences in the interpretation of $PD_{20}$ and 'reactivity'.

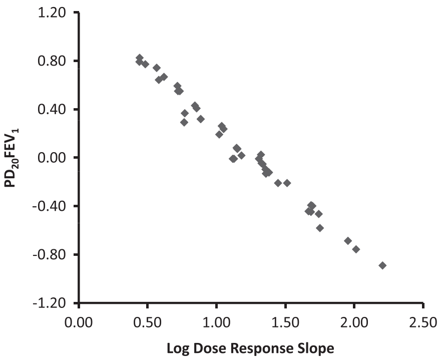


**Figure 1** Log dose–response slope and $logPD_{20}FEV_1$ in 41 subjects with asthma after histamine challenge ($r=-0.97$, $p<0.0001$). Data from these subjects have been reported previously.[2]

Thirdly, there are inconsistencies in the data in their figure 2.[1] Seven subjects have $PD_{20}$ values close to zero (possibly 0.1 μmol?), and therefore should have DRS values of ∼200 (ie, 20% fall/0.1 μmol) and CIR values of ∼2.3 (ie, log 200). These subjects do not appear in figure 2B,C. Furthermore, the distribution of AQLQ differs between figure 2A and B.

The advantage of a continuous measure of airway responsiveness such as DRS, rather than $PD_{20}$, is not that DRS provides qualitatively different information but rather that it yields an estimate of airway responsiveness in all subjects, not just the subset with AHR. Airway responsiveness is a continuum, with the cut-off point for AHR defined arbitrarily. However, AHR can be normalised with inhaled corticosteroid therapy,[3] and subjects with asthma can move in and out of the abnormal range. A more appropriate interpretation of the difference between $PD_{20}$ and 'reactivity' in their relationships with AQLQ reported by Cisneros *et al*[1] would be that quality of life is worse in subjects with AHR, but does not worsen with increasing severity of AHR.

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# 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-rated 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 ($FEV_1$) ($PD_{20}$) and dose–response slope (DRS). Both parameters seem to be qualitatively different since the dose–response curves plotted in their determination are also different. $PD_{20}$ is obtained from curves plotted on a semilogarithmic scale whereas DRS is obtained from a linear dose axis. Moreover, the calculation of $PD_{20}$ uses the fall in $FEV_1$ between the last and penultimate doses while, for DRS determination, the fall in $FEV_1$ 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 $PD_{20}$ and DRS is slight ($r=0.416$, $r=0.042$).

We therefore believe that DRS and $PD_{20}$ are not completely equivalent. DRS allows for airway responsiveness to be assessed in all individuals, including those who do not reach the threshold $PD_{20}$. 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 $PD_{20}$.[3] 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 $PD_{20}$.

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# 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,[1] in line with an asthma prevalence of 9.5% in Swedish young adults.[2] The risk of adulthood asthma after