PostScript

LETTERS TO THE EDITOR

If you have a burning desire to respond to a paper published in *Thorax*, why not make use of our ''rapid response'' option?

Log on to our website (www.thoraxjnl.com), find the paper that interests you, and send your response via email by clicking on the ''eLetters'' option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on ''read eletters'' on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Increasing paediatric empyema admissions

Empyema is most often a complication of bacterial pneumonia or, less commonly, thoracic trauma or surgery. There have been reports of increasing numbers of children presenting to regional units in the UK,[1–3] but there are no published national data that may provide evidence of a clear trend. Analysis of national routine admissions data provides information on health service utilisation and may provide a marker for the incidence of this relatively uncommon disease.

Hospital admissions in England were obtained from the hospital episode statistics system (www.dh.gov.uk). This database contains personal, administrative, and medical data on all patients admitted to NHS hospitals in England. It records episodes of care following admission to hospital and assigns a primary diagnosis on discharge using the WHO International Classification of Diseases (ICD). Data are available by financial year (1 April to 31 March). From April 1995 diagnoses were classified using the 10th revision of ICD (ICD 10).

We identified admissions with a primary diagnosis of pyothorax (which includes the diagnoses of empyema, pyopneumothorax (pneumoempyema) and abscess of the pleura or thorax) in ICD 10 (code J86) between April 1995 and March 2003. The numbers of admissions for abscess of the pleura or thorax are likely to be small compared with those for empyema and pyopneumothorax, hence this code provides a good indication of trends in empyema. Age-specific admission rates were calculated using population data from the corresponding period. To investigate changes over time we used rate ratios to describe the increases over the 8 year period and tested for time trend by fitting linear regression equations for each age group. All analyses were undertaken using Stata version 8.

There were a total of 1379 admissions for pyothorax from April 1995 to March 2003 in children aged 0–14 years. The rate of admission increased from 14 per million in 1995/6 to 26 per million in 2002/3 with a significant upward linear trend ($p = 0.003$). The rises were greatest in children aged 1–4 years in whom admissions rose threefold over the 8 year period (fig 1). There were smaller rises in infants under the age of 1 year and in children aged 5–9 years and those aged 10–14 years, but a test for linear trend was not significant in any of these age groups (table 1). Admissions were slightly higher in boys than girls throughout the period, although the rates of increase were similar in both sexes.

We have identified increased admission rates from 1995 to 2003 for pyothorax in children of all ages between 0 and 14 years and across both sexes, most prominent in the 1–4 year olds. Trends in admissions must be interpreted with caution as they can reflect changes in health care, in disease labelling, coding or recording, as well as in the underlying epidemiology of the condition. We were unable to assess the accuracy of clinician diagnoses or recording. However, we consider it likely that any diagnostic transfer would remain within the ICD labels of pyothorax and ''pleural effusion, not elsewhere classified (NEC)'' (J90) which includes pleurisy with effusion but excludes chylous and tuberculous effusions and pleurisy not otherwise specified. Over this period admissions for pleural effusion NEC also rose significantly (not presented). It is also likely that some empyema cases could be coded as a secondary diagnosis under a primary diagnosis of pneumonia, in which case these data would under-represent the incidence of the problem. These rises are unlikely to be explained by major shifts in health seeking behaviour as empyema is a serious condition requiring hospital admission. This increase in pyothorax admissions is therefore likely to be due largely to an increase in the incidence of empyema.

Thoracic surgery and trauma account for less than 2% of empyema, which is most commonly caused by bacterial pneumonia. A rising incidence in childhood empyema associated with *Streptococcus. pneumoniae* serotype 1 infection has been observed in the USA.[4 5] The majority of children in the north east of England presenting with empyema from February 1997 to August 2001 were infected with serotype 1,[3] which is not included in the heptavalent conjugate pneumococcal vaccine. There was also a consistent year-on-year rise in the number of children presenting with empyema in the same region from 1998 to 2001.[3] We recognise that the number of admissions nationally for empyema is small, but these large increases in recent years warrant further investigation.

R Gupta
Lung and Asthma Information Agency, Community Health Sciences Department, St George's Hospital Medical School, London SW17 0RE, UK

S Crowley
Department of Child Health, St George's Healthcare NHS Trust, London SW17 0QT, UK

Correspondence to: Dr S Crowley, Department of Child Health, St George's Healthcare NHS Trust, London SW17 0QT, UK; suzanne.crowley@stgeorges.nhs.uk

doi: 10.1136/thx.2005.049510

RG is funded by Asthma UK, British Lung Foundation, and British Thoracic Society.

Competing interests: none declared.

References

1 **Ress JHM**, Spencer D, Parikh D, Weller P. Increase in incidence of childhood empyema in West Midlands, UK. *Lancet* 1997;**349**:402.
2 **Playfor SD**, Stewart RJ, Smith CM, *et al.* Childhood empyema. *Thorax* 1999;**54**:92.
3 **Eastham KM**, Freeman R, Kearns AM, *et al.* Clinical features, aetiology and outcome of empyema in children in the north-east of England. *Thorax* 2004;**59**:522–5.
4 **Byington CL**, Spencer LY, Johnson TA, *et al.* An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. *Clin Infect Dis* 2002;**34**:434–40.

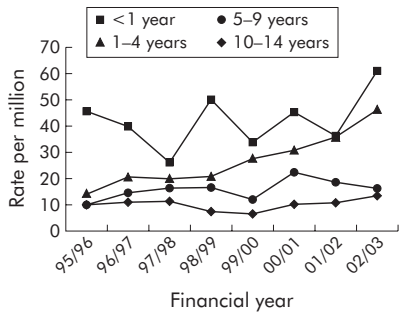

Figure 1 Trends in admission rates for pyothorax by age in England, 1995–2003.

Table 1 Number and rate of admissions for pyothorax in children aged 0–14 years in England in 1995/6 and 2002/3: rate ratios between 2002/3 and 1995/6 with 95% confidence intervals and linear regression p values

Age or sex	Number		Rate per million		Rate ratio	95% CI	p value (trend)
	1995/6	2002/3	1995/6	2002/3			
<1 year	28	34	46	62	1.3	0.8 to 2.3	0.4
1–4 years	37	107	14	46	3.2	2.2 to 4.8	<0.001
5–9 years	33	50	10	16	1.6	1.0 to 2.5	0.1
10–14 years	31	44	10	14	1.3	0.8 to 2.1	0.6
Boys	71	125	15	27	1.8	1.3 to 2.4	0.02
Girls	58	110	13	25	1.9	1.4 to 2.7	0.004

5 **Byington CL**, Samore MH, Stoddard GJ, *et al*. Temporal trends of invasive disease due to Streptococcus pneumoniae among children in the intermountain west: emergence of nonvaccine serogroups. *Clin Infect Dis* 2005;**41**:21–9.

Repeated tuberculin testing does not induce false positive ELISPOT results

The Enzyme Linked ImmunoSpot (ELISPOT) is a new rapid T cell based blood test (otherwise known as an interferon-γ assay) for the diagnosis of latent tuberculosis infection.[1–3] The commercially available form of the assay, T-SPOT® TB (Oxford Immunotec, Abingdon, UK) has European regulatory approval as an in vitro diagnostic test and is increasingly being used in clinical practice. The test is based on the enumeration of interferon-γ producing T cells which are specific for two highly antigenic proteins, early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10).[1] These proteins are expressed by *Mycobacterium tuberculosis* but are absent from *M bovis* BCG vaccine. Hence, the test does not give false positive results in BCG vaccinated individuals.[1–3]

ESAT-6 and CFP-10 are, however, contained within tuberculin purified protein derivative (PPD). Since ELISPOT is a highly sensitive method for measuring even low numbers of antigen specific T cells,[4] concerns have been raised as to whether repeated tuberculin skin tests might induce T cell responses to these specific antigens, resulting in false positive ELISPOT results.

As T-SPOT® TB enters clinical practice, it may initially be used by some people in conjunction with the tuberculin skin test. It is therefore important to know whether false positive ELISPOT results are induced by tuberculin testing. The following results strongly suggest that this is not the case.

The results reported here are from a 2 year follow up of a group of people with potential point source exposure to multidrug resistant tuberculosis on a maternity unit in Modena University Hospital, Italy.[5] Forty four BCG unvaccinated subjects were negative at initial screening by tuberculin skin test and ELISPOT, 3 months after the point source exposure ceased. All participants had negative results on serological testing for HIV infection. Tuberculin skin tests were administered and read by two experienced chest physicians using 5 units of PPD-S injected intradermally about 2 hours after blood was drawn for ELISPOT assays. The ELISPOT assays were performed and scored, as previously described,[5] by two technicians without knowledge of personal identifiers. All these individuals underwent repeated testing by skin test and ELISPOT at 9, 15 and 24 months after the point exposure. At 24 months all 44 individuals remained ELISPOT negative, although three had become positive with the tuberculin skin test (fig 1). Thus, inoculation of three PPD skin tests over a 21 month period in 44 initially ELISPOT negative individuals did not induce any false positive ELISPOT results.

These results show that repeated tuberculin skin testing over time does not induce a T cell response to ESAT-6 or CFP-10 resulting in false positive ELISPOT results. Our findings suggest that this new interferon-γ blood assay could be used in association with the standard PPD skin test without any reduction in its high diagnostic specificity. Given the high sensitivity of the ELISPOT assay for detecting even low numbers of antigen specific T cells, the absence of a detectable response to ESAT-6 and CFP-10 suggests that T cells specific for these antigens were not induced by repeated inoculation of PPD. This is consistent with the observation that ESAT-6 has very poor immunogenicity when administered as a candidate vaccine, unless inoculated with powerful adjuvants.[6] This is in stark contrast to its potent immunogenicity when presented to the immune system during natural *M tuberculosis* infection; indeed, ESAT-6 is the strongest known target of T cell responses during tuberculosis infection.

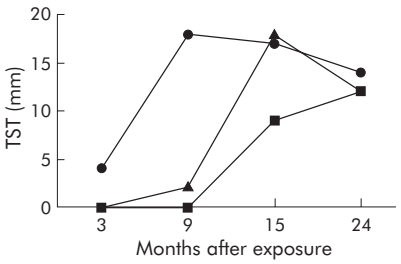

Figure 1 Time course of development of positive Mantoux results in the three participants who became tuberculin skin test (TST) positive as a result of repeated skin testing.

Our results also suggest that T-SPOT® TB could be especially useful in distinguishing true latent tuberculosis infection from false positive tuberculin skin test results that have arisen through ''boosting''. Boosting occurs in people who undergo repeated tuberculin skin tests (such as healthcare workers) and causes false positive skin test results in uninfected people. This phenomenon is a major problem in tuberculosis screening programmes for healthcare workers, prisoners, and other groups at persistent risk of tuberculosis exposure, and was almost certainly the reason why three individuals in our study developed positive skin test results after repeated testing. Our findings suggest that T-SPOT® TB will maintain its high specificity even in individuals with false positive skin test results due to boosting from repeated tuberculin testing. Thus, use of T-SPOT® TB could enhance our ability to screen for latent tuberculosis infection even in populations who have already been repeatedly screened by the skin test.

L Richeldi
Respiratory Disease Clinic, University of Modena and Reggio Emilia, and Azienda Ospedaliera Policlinico di Modena, Modena, Italy

K Ewer
Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

M Losi, P Roversi, L M Fabbri
Respiratory Disease Clinic, University of Modena and Reggio Emilia, and Azienda Ospedaliera Policlinico di Modena, Modena, Italy

A Lalvani
Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence to: Dr A Lalvani, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK; ajit.lalvani@ndm.ox.ac.uk

The study was approved by the Modena research ethics committee and each study participant provided written informed consent.

doi: 10.1136/thx.2005.049759

This work was supported by the Wellcome Trust and Azienda Ospedaliera Policlinico di Modena.

Competing interests: AL is a named inventor on patents relating to T cell based diagnosis filed by the University of Oxford. Regulatory approval and commercialisation of ELISPOT (T-SPOT TB) has been undertaken by a spin out company of the University of Oxford (Oxford Immunotec Ltd), in which AL has a share of equity and to which he acts as scientific advisor in a non-executive capacity. KE is a named inventor on a patent application relating to the application of ELISPOT filed by the University of Oxford. The University of Oxford has a share of equity in Oxford Immunotec Ltd.

References

1 **Lalvani A**, Pathan AA, McShane H, *et al*. Rapid detection of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Am J Respir Crit Care Med* 2001;**163**:824–8.
2 **Lalvani A**, Pathan AA, Durkan H, *et al*. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. *Lancet* 2001;**357**:2017–21.
3 **Ewer K**, Deeks J, Alvarez L, *et al*. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. *Lancet* 2003;**361**:1168–73.
4 **Lalvani A**, Brookes R, Hambleton S, *et al*. Rapid effector function in CD8+ memory T cells. *J Exp Med* 1997;**186**:859–65.
5 **Richeldi L**, Ewer K, Losi M, *et al*. T cell-based tracking of multidrug resistant tuberculosis infection after brief exposure. *Am J Respir Crit Care Med* 2004;**170**:288–95.
6 **Brandt L**, Elhay M, Rosenkrands I, *et al*. ESAT-6 subunit vaccination against Mycobacterium tuberculosis. *Infect Immun* 2000;**68**:791–5.

Clinical importance of the Step 3 choice in asthma

We read with interest the meta-analysis by Masoli *et al*[1] which aimed to further guide clinicians in their choice between addition of long acting β_2 agonists (LABA) or use of higher doses of inhaled corticosteroids (ICS) in patients with symptomatic asthma. The pooled odds of at least one moderate or severe exacerbation was 1.35 times higher in those receiving a higher dose of ICS than in those treated with LABA.

Unfortunately, it is difficult to draw any meaningful conclusion as to the clinical relevance of these findings or to compare at a glance the results with those of the previous MIASMA study[2] because of differences in the summary statistics presented. For clinicians to understand the clinical context of these two studies, it is helpful to calculate the number needed to treat (NNT), as was done in the original MIASMA study.

Of the 2312 patients randomised to LABA treatment included in the newer study, 184 experienced one or more moderate or severe exacerbations (an incidence of 79.6 per 1000 patients) compared with 243 of the 2264 patients randomised to high dose ICS treatment (an incidence of 107.3 per 1000 patients). These incidences give an attributable risk reduction of 27.7 per 1000 patients which represents an NNT of 37, meaning that for every 37 patients receiving LABA in preference to high dose ICS, one less will experience an exacerbation. The corresponding