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Author's reply

We thank Dr Leung and colleagues for their interest in our data[1] and their insights into the management of individuals with HIV and tuberculosis (TB) co-infection. We agree that, as with any retrospective study, it is possible that some events may have been misclassified despite our best efforts. However, we would be surprised if this were the case for hepatotoxicity, which is measured by objective blood test results, or treatment interruption.

Highly active anti-retroviral therapy (HAART) has radically altered the management of HIV and TB co-infection. Our overall aim was to describe the occurrence of adverse events and treatment interruption in this era. Data drawn from before this may not serve as a valid comparator. We looked carefully for differences according to anti-retroviral usage but none were observed. As highlighted in our discussion, there do exist a number of other factors that are difficult to control and may account for differing results between studies. Our data suggest a role for ethnicity, which might explain the divergent results seen between populations. As Dr Leung mentions, differences in event rates according to HIV infection with rifampicin and pyrazinamide combination are intriguing. It has been postulated that this reflects immune function.[2] We found no evidence for this when we analysed our event rates according to either baseline blood CD4 count or changes in this value at 2 months.

We agree that maintaining patient cooperation and adherence with appropriate drug regimens is vital to outcome for both TB and HIV, especially when the management of both conditions may be complicated by the development of drug resistance. However, in our cohort we observed reassuringly high levels of TB treatment completion and low rates of TB recurrence (regardless of HIV infection), as well as excellent virological responses to HAART.[3]

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Diagnosis of COPD

Shahab *et al* recently reported significant under-diagnosis of chronic obstructive pulmonary disease (COPD) in England.[1] Adults over 35 years were regarded as having airway obstruction (COPD) if the forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio was <0.70. This conforms with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[2] adopted by various organisations, albeit that no data were obtained after bronchodilation. Even the GOLD group acknowledges that there is no evidence that this cut-off point signifies clinically validated airway obstruction and that "the use of this fixed ratio may result in over-diagnosis of COPD in the elderly, especially of mild disease. Using the lower limit of normal (LLN) values for FEV_1/FVC that are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal is one way to minimize the potential misclassification."[2] This statement does justice to science and to authors of predicted values for spirometric indices who carefully defined the LLN for various indices, none of them advocating the use of a fixed cut-off point. In fact, in 45 publications, an overwhelming majority found that the LLN for FEV_1/FVC fell below 0.70 with age.[3]

In the 1995/6 study of a representative sample of the English population, valid spirometric data were obtained in 11 854 men and 13 554 women.[4] Measurements in 6053 non-smoking white people with no reported diagnosis of asthma or respiratory symptoms were used to derive prediction equations for the FEV_1/FVC ratio and its LLN. For an adult woman of 160 cm and a man of 174 cm, the LLN for FEV_1/FVC fell below 0.70 at ages 61 and 48 years, respectively. Using a fixed ratio, airway obstruction will hence be under-diagnosed below those ages and over-diagnosed above those ages.

Using data on 25 408 subjects,[4] we established how often FEV_1/FVC was <0.70 (method A) or below the LLN (method B). Figure 1 illustrates the misclassification rate. We expressed the difference between A and B as a percentage of B. Thus, 0% means equal prevalence, 100% means that the fixed ratio for FEV_1/FVC identified twice as many subjects with airway obstruction as the LLN method (50% false positives), and −80% means that the fixed ratio method failed to identify 8 out of 10 subjects with airway obstruction (80% false negatives). Using the NHANES III database and data from a Dutch population, sample findings were comparable with those in fig 1; the 2001 Health Survey for England data used by Shahab *et al* produced results nearly identical to those in fig 1. The trend in non-smoking men and women with no reported diagnosis of asthma or respiratory symptoms (a healthy reference group) is the same as that in the whole population.

The findings in a healthy reference group illustrate the inappropriateness of using a fixed FEV_1/FVC ratio for establishing airway obstruction. Applying that criterion to the whole population leads to substantial over-diagnosis of airway obstruction in middle-aged and elderly subjects, particularly in men, and unacceptably large under-diagnosis in younger adults. We recommend that organisations like GOLD, the American Thoracic Society, European Respiratory Society, British Thoracic Society and the National Institute for Clinical Excellence—who all recommend an FEV_1/FVC ratio of <0.70 as evidence of airway obstruction—return to evidence-based medicine and revise their guidelines.

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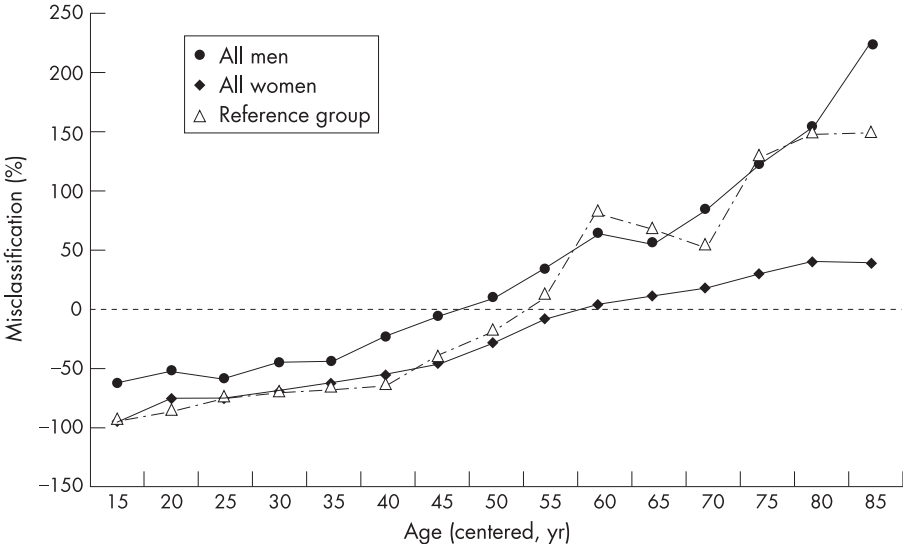

Figure 1 Percentage of subjects with airway obstruction (FEV_1/FVC <lower limit of normal) misclassified using GOLD guidelines (FEV_1/FVC <0.07), as a function of age. Misclassification: negative value = under-diagnosis; positive value = over-diagnosis. Data from 1995/6 Health Survey for England.[4]

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Authors' reply

We are grateful for the comments by Falaschetti *et al* on the usefulness and suitability of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard for the diagnosis of COPD. We appreciate that there are other approaches to defining abnormal airflow—indeed, one co-author (JB) was involved as a consultant to the study cited in their letter[1]—but our objective was to assess the extent of under-diagnosis according to current conventional criteria. We agree (and have acknowledged in the paper) that the lack of post-bronchodilator values will lead to overestimation of the prevalence of COPD, but do not believe that this effect would be of sufficient magnitude to account for more than a small minority of the under-diagnosis apparent, especially when considering the inclusive definition of COPD diagnosis used in our study. We have reanalysed the data using the lower limit of normal (LLN) method based on reference values from Falaschetti *et al*[1] and find that estimates of COPD prevalence (11.2%; 95% CI 10.5% to 11.9%) and under-diagnosis (78.8%; 95% CI 76.1% to 81.5%) are very modestly reduced compared with GOLD standard figures for prevalence (13.3%, 95% CI 12.6% to 14.0%) and under-diagnosis (81.2%; 95% CI 78.9% to 83.6%). Equally, smoking prevalence figures are somewhat higher among LLN-defined cases of COPD (39.5%; 95% CI 36.3% to 42.7%) than among GOLD-defined cases (34.9%; 95% CI 32.1% to 37.8%). However, irrespective of the criterion used, under-diagnosis of COPD remains a major problem, particularly among smokers (figs 1 and 2).

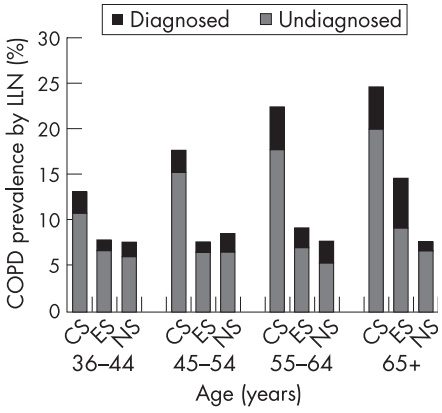

Figure 1 Prevalence and diagnosis of chronic obstructive pulmonary disease (COPD) stratified by age and smoking status using the lower limit of normal (LLN) method. CS, current smokers; ES, ex-smokers; NS, never smokers.

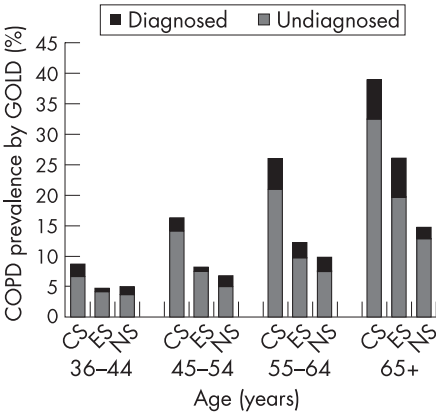

Figure 2 Prevalence and diagnosis of chronic obstructive pulmonary disease (COPD) stratified by age and smoking status using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) method. CS, current smokers; ES, ex-smokers; NS, never smokers.

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Reducing door-to-antibiotic time in community acquired pneumonia

We were interested to read the study by Barlow *et al*.[1] We also audited door-to-antibiotic time in community acquired pneumonia. An initial audit in January 2005 (n = 83) showed a door-to-antibiotic time of 7 hours 37 minutes with a delay from seeing the doctor to receiving antibiotics of 5 hours 45 minutes. 36% of patients had a delay of >8 hours. The main reason identified was that, if patients arrived on the ward after a drug round, they would not receive any drugs until the next scheduled drug round. For patients admitted at night this could mean a delay of up to 8 hours. The data were shared with doctors in the Accident and Emergency department who were asked to prescribe the first dose of antibiotic as a "stat" once-only dose on the front of the drug chart, and then to give the chart to the nurse in charge of the patient. We re-audited in October 2006 (n = 34). The delay in doctor-to-antibiotic time had fallen to 3 hours 15 minutes, with the delay for intravenous antibiotics being 2 hours 11 minutes—a reduction of 2 hours 30 minutes. 3% of patients waited >8 hours for their antibiotic and 74% received their antibiotic within 4 hours.

This simple intervention, at no cost, greatly reduced the delay in patients receiving antibiotic therapy. It is likely that this is also an issue in other infections and we believe that there is no reason why this should not be standard practice in Accident and Emergency departments and on admission wards.

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Is childhood immunisation associated with atopic disease from age 7 to 32 years?

We read with interest the study by Nakajima *et al*[1] which concluded that, in Tasmanian children, there are small age-dependent associations between childhood immunisation and asthma, eczema and food allergy, but that these effects should not deter parents from immunising their children. However, it could be that the small (but significant) effects that were found are due to residual confounding since the authors made no adjustment for socioeconomic status, a factor found to be associated with allergy.[2–4]

On the other hand, the effects may have been underestimated since the authors included diseases preventable by childhood vaccinations (diphtheria, pertussis, measles, mumps and rubella) in the model, but these (what they call) "confounders" are in fact intermediate variables which possibly "take away" the association between vaccinations and allergy.

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