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System for screening new immigrants is inadequate

EDITOR,—Meirion R Evans rightly points out the lack of a national policy for control of tuberculosis in the United Kingdom.[1] The impact that this has had on the allocation of resources for control is unknown, but the lack of evidence of the effectiveness of some elements of current control measures does not help.

Evans states that "active measures to detect clinical disease are necessary in tuberculosis contacts, immigrants, and other high risk groups." The epidemiological basis for including immigrants as a high risk group is the relatively high rate of notifications in this group, especially within five years of their arrival in the United Kingdom. There is conflicting evidence, however, on the contribution made by ethnic minority groups to the recent increase in notifications of tuberculosis in the United Kingdom. More importantly, the justification for screening immigrants should be based not on the potential but on the actual detection of previously undiagnosed cases of disease. A published audit of screening of immigrants in Blackburn showed that only 0·1% of those screened were found to have active disease,[2] which is the same as the detection rate resulting from examinations at the port of arrival.[3] In Birmingham no active cases were detected from screening 226 immigrants in one year.[4] There is little evidence that improvements in the system for screening immigrants will have any impact on the control of tuberculosis.

The present system for identifying and following up new immigrants for screening is inadequate, and a critical review of its value as a control measure is long overdue.

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Tuberculosis as a predictor of survival in AIDS

Study had several flaws

EDITOR,—Several problems with Thomas V Perneger and colleagues' paper on whether the onset of tuberculosis in AIDS predicts shorter survival challenge their findings.[1] Firstly, the title is misleading. The study evaluated people diagnosed as having AIDS during a 13 year period, whereas the title implies a 13 year follow up. This potential misinformation should be clarified by the reporting of median follow up in the text. Mean follow up, which the authors report, can be heavily skewed by a few subjects with lengthy follow up.

Studies of the prognosis of disease require that subjects be identified at a uniform point in the course of the disease. Given the history of the AIDS epidemic and the fact that the study began in 1979, this requirement was not met. Most AIDS defining illnesses were not identified or used as criteria until the mid-1980s, so many people with AIDS during the early years of the epidemic would not have been diagnosed as having the disease (and therefore not included in this cohort). A later start point should have been chosen. Additionally, inception cohorts are affected by referral patterns, which are not described for the 52 centres that participated in the study.

Accurate ascertainment of primary cohort subgroups is also imperative in studies of prognosis. The paper notes that some cases of tuberculosis were diagnosed at necropsy. The authors do not state, however, whether all subjects in the cohort who died underwent necropsy. If they did not then underestimation of the rate of tuberculosis is likely.

Studies that use survival analysis should ensure that censoring is random (non-informative). This is partially accomplished by including in the hazards model all covariates that may show an association between the likelihood of follow up and either the predictor or the outcome under study. For example, socioeconomic status is probably associated with the likelihood of contracting tuberculosis, the likelihood of long term follow up being maintained, and the duration of survival. Yet it was not included in the model in the study.

Finally, many potentially confounding variables were not included in the model. These include the site of tuberculosis, presence or absence of infection with *Mycobacterium avium complex* (long term antituberculosis treatment may have prevented the development of this infection), AIDS defining illness, CD4 cell count, and frequency of follow up visits (patients with tuberculosis are likely to have been followed up more closely, which may have improved their care).

The identification of predictors of survival in people with HIV infection or AIDS is important. Future investigators may benefit from following guidelines for such studies.[2]

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Authors' reply

EDITOR,—Anyone who works with patients with AIDS is unlikely to believe that the phrase "over 13 years" in the subtitle of our paper referred to survival rather than to the study's duration. Similarly, only casual readers will have missed our reporting of median survival in both the results section and the abstract.

The Centers for Disease Control's 1987 definition of AIDS was used for all participants in the study. Because participants were identified a posteriori, from the medical records of all HIV positive patients, this definition was also applied to those who developed AIDS before 1987. We know little about referral patterns and agree that the cohort may not be representative of all European patients with AIDS. While this may bias estimates of the incidence of tuberculosis, we fail to see a plausible mechanism by which baseline referral patterns would have affected the observed association between tuberculosis and mortality later during follow up.

Necropsies were performed according to clinical need and local habits, not systematically. Thus we agree that the incidence of tuberculosis might have been underestimated in our study. Again, we are not sure whether this would have affected the association between tuberculosis and mortality, especially as only 5% of cases of tuberculosis were diagnosed at necropsy.

No survival analysis can ensure that censoring was random, for if we knew what happened to patients after censoring we would not have censored them. In our analysis most patients died during follow up; among the 26% who did not, most censoring occurred as a result of termination of the study. We are therefore confident that no major bias occurred. We wish that we had had indicators of socioeconomic status (we did not), but if poor patients with tuberculosis are more likely both to die and to be lost to follow up then the association of tuberculosis with mortality would have been even stronger had we obtained perfect follow up.

The spectre of hidden confounders looms behind every study. But raising the issue is not enough; one should also make a strong case that the putative confounder is a better explanation than that proposed for the observed association. Two of the authors' hypotheses regarding confounders (that *Mycobacterium avium complex* infections are prevented and care improved in patients with tuberculosis) suggest that differences in mortality between patients with AIDS with and without tuberculosis might have been even greater had we taken these variables into account. Nevertheless, as we stated in the paper, because of possible confounding (notably by immunodeficiency) we do not think that our study established a causal relation between tuberculosis and mortality.

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Standardised coding is needed for reports of adverse drug reactions

EDITOR,—Reports of adverse drug reactions make up a considerable proportion of the medical literature. Adverse reactions to recently marketed drugs may not have been detected during premarketing studies, and information about such reactions must be transmitted rapidly to all prescribers. This is usually achieved for serious reactions, but knowledge of milder reactions is often restricted to specialists.

Data on adverse drug reactions published in books and medical journals have to be taken into account when the role of drugs is assessed. It may, however, be difficult to retrieve and compile all the available published information since articles do not use standardised key words. For example, Medline (to which most journals refer for key words) lists only "drug hypersensitivity," "drug tolerance," and "drug interactions," although these represent only a small proportion of observed adverse drug reactions and restrict reported reactions to those due to particular mechanisms.

So that data can be compiled rapidly it is important to create and standardise coding for all adverse events attributed to drugs. Such coding should not be too precise since the knowledge of the mechanism of the reaction is often missing. Three to six key words could be given according to