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 pre-marketing 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

the requirements of journals. The first would obviously be "adverse drug reaction," followed by the nature of the reaction (and if necessary the organ affected when this is not obvious from the wording of the nature of the reaction) and by the generic name of the suspected drug. Optional key words could be the chemical or therapeutic class and the mechanism. An example is "adverse drug reaction, skin, urticaria, ampicillin, β -lactamines, hypersensitivity." Standardised coding would greatly facilitate the retrieval of information on drug reactions by prescribers, pharmaceutical companies, and anyone else with an interest in the subject.

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Endogenous sex hormones and cardiovascular disease in postmenopausal women

Other sources of variability should have been taken into account

EDITOR,—Elizabeth Barret-Connor and Deborah Goodman-Gruen did not find any association between endogenous sex hormones and the risk of death from cardiovascular and ischaemic heart disease in a cohort study of 651 postmenopausal women living in Rancho Bernardo, California.¹ To study this association the authors measured serum concentrations of androstenedione, total and bioavailable testosterone, oestrone, and total and bioavailable oestradiol in specimens collected at the baseline and stored at -70°C for 10 years. They took into consideration two methodological issues (long term stability of hormones in stored serum at very low temperatures and hormone variability within and among subjects). They did not, however, consider two other important methodological issues.

The first issue relates to the effect of long term storage on the bioavailable fraction of oestradiol. While there is a general consensus on the long term stability of sex hormones stored at very low temperatures, evidence suggests that the bioavailable fraction of hormones in stored specimens increases with time. For example, we have shown that bioavailable testosterone increased up to 30% of the initial concentration over three years' storage at -70°C ; this increase was interpreted as being due to progressive dissociation of the steroid-protein complex in frozen serum.² Other evidence for such dissociation is provided by Langley *et al.*, who reported that the cleavage of oestradiol from sex hormone binding globulin increases with time in frozen serum samples.³

The second issue concerns controlling for another form of hormone variability: the circadian rhythm. In the authors' study blood samples were collected between 730 and 11 am. Production of hormones is characterised by strong circadian fluctuation, and important differences have been detected between early and late morning.⁴ Adjustment for the exact time at which blood was drawn (not mentioned in the authors' paper) could help in controlling for this possible source of error.

In conclusion, study of the relation between hormones and chronic disease is made particularly

difficult by numerous sources of variability. Careful attention should be paid to these before conclusive statements can be made regarding the possible lack of an aetiological role for hormones in chronic disease.

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Authors' reply

EDITOR,—Paola Muti and Maurizio Trevisan are concerned that the absence of any association between oestrogen concentration and the risk of fatal cardiovascular disease in our study may have been due to dissociation of bioavailable oestrogen in the frozen samples over time. The papers they cite raise the possibility of dissociation but do not prove it.

Bolelli *et al.* studied frozen plasma (-80°C) from eight postmenopausal women.¹ Over three years the women maintained the same rank for all hormone concentrations: this rather than the absolute value would be all that is necessary for showing an association in epidemiological studies. Although free testosterone (non-sex hormone binding globulin or albumin bound measured with a commercial coated tube radioimmunoassay kit) showed a 30% increase between the baseline and one year, this increase (within the coefficient of variation) did not change thereafter, suggesting that longer freezing would not have changed the results of the assay further.

Langley *et al.* indirectly measured the rate of dissociation of dihydrotestosterone from sex hormone binding globulin in 15 women, whose menopausal status was not given.² In these serum samples, stored at -20°C , the dissociation rate seemed to increase over 180 days, which is compatible with the early change reported by Bolelli *et al.*

Even if concentrations of bioavailable oestradiol do change over time in frozen samples, in our study, with plasma frozen at -80°C , the correlation of total oestradiol with bioavailable oestradiol was 0.97 ($P=0.001$). We still think that our study makes an association between endogenous oestrogen and coronary heart disease most unlikely in postmenopausal women.

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Hepatitis B vaccination

Information for patients is vital

EDITOR,—P Mantagni and colleagues highlight the need to improve access to hepatitis B vaccination within services for intravenous drug users.¹ Experience of vaccination in genitourinary medicine clinics, which offer an established access point for target groups, has shown that access is only one part of the process of effective vaccination.² It is vital that services offering the vaccine provide effective information for patients and monitor participants from initial to final vaccination. We present audit data showing the importance of identifying drop out rates, gaps in the delivery of information, and patients' knowledge of the vaccine schedule.

A preliminary audit at the genitourinary medicine clinics of University College and the Middlesex Hospitals showed that, despite good access, two thirds of patients who started the six month vaccine course did not complete it. This means that, at a cost of £11.93 per dose, over £600 worth of vaccine may be ineffectively used for every 100 clients starting the course.

A second audit of patients attending University College Hospital's clinic for vaccination explored patients' knowledge of the vaccine schedule and the delivery of information. A questionnaire completed by 66 consecutive patients showed that 49 did not know when their second and third doses were due, 40 did not know that a blood test was needed after vaccination, and 32 did not know that a booster was needed at a later date. Only six knew all of these facts, and 18 knew none of them.

Most patients reported that the vaccine schedule had been discussed in the clinic, but many different staff groups were involved (doctor, 26; doctor and nurse, 13; nurse, 11; doctor, nurse, and health adviser, 7; health adviser, 5; doctor and health adviser, 2; nurse and health adviser, 2). Most patients (40) had received an information leaflet about hepatitis B. This, however, had come from a variety of sources: doctors, nurses, health advisers, and the waiting room. None of the three leaflets available detailed the vaccination schedule. A complementary leaflet was developed during the audit and is available on request.

High drop out rates for the hepatitis B vaccination schedule are expensive, not only financially but also for individual and public health. Educating patients effectively is one factor that can and should be optimised; staff need the time and skills to do this. This requires training and resources.

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All GPs in Brent and Harrow offer hepatitis B vaccination to drug users

EDITOR,—In their survey of the hepatitis B vaccination policies of treatment services for injecting drug users P Mantagni and colleagues do not mention general practice.¹ Colleagues and I have just audited the treatment of drug users in general practice in Brent and Harrow before starting a training programme and an incentive scheme for general practitioners willing to prescribe substi-