Ironically, the recognised healthiness of vegetarians in terms of reduced mortality and morbidity⁴ may have biased the results in the direction of a spurious health risk. If, for instance, out of the 400 original vegetarian and non-vegetarian tuberculosis cases between 1982 and 1993 the vegetarians amongst them survived in greater numbers and were more represented in the 56 cases in the study, then we are left with a false impression that vegetarian diet is more common amongst cases of tuberculosis.

In the clinic control group there could have been an abnormally low proportion of vegetarians deriving from their better health and lower clinic attendance.⁴ Then, even with a normal proportion of vegetarians in the cases of tuberculosis, this figure would have appeared higher than the proportion in the control group when a spuriously elevated risk. The same selection mechanisms may have produced a spurious correlation between the level of vegetarianism and risk of tuberculosis.


AUTHORS’ REPLY

We recognise that British vegetarians have somewhat lower mortality rates than non-vegetarians, but this difference is not large enough to introduce substantial bias as suggested by Dr Davis. In the study by Thorogood et al adjusted mortality rates from ischaemic heart disease and cancer among vegetarians were, respectively, 72% and 61% of the corresponding mortality rates for non-vegetarians. If all-cause mortality was reduced by about one third among vegetarians, who accounted for about half of our case group, then, on the most extreme assumption that 15% of non-vegetarians died during the follow up period, we would expect 10% of vegetarian cases to die also. This difference in survival would increase the proportion of vegetarians among survivors by no more than 1-2%, generating a spurious elevation in odds ratio of about 6%. This is far too small to account for the observed odds ratios of 2-5 or greater.

Our suggestion of an increased risk of tuberculosis among vegetarian Asians is not a recommendation against adherence to a vegetarian diet. Dietary advice needs to take account of the balance of risks and benefits across a wide range of major disease outcomes. The importance of our findings is that they may be pointing to a hitherto unrecognized risk associated with vegetarianism which, if our hypothesis is correct, may be remediable by vitamin supplementation without the need for major dietary change. Indeed, prevention of vitamin D deficiency may be particularly important for the stricter Hindu vegetarians with reduced sunlight exposure who are already recognised as a group at risk of osteomalacia.⁴

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Control and prevention of tuberculosis in the UK

Recent guidelines on the control and prevention of tuberculosis (December 1994;40:1193-200) recommend chemoprophylaxis for children (<16 years) with grade 2-4 HIV reactions who are close contacts of cases of pulmonary tuberculosis or newly arrived immigrants from high prevalence countries. Chemoprophylaxis, they advise, should also be considered for grade 3-4 HIV positive young adult immigrants.

The evidence from randomised controlled trials of prophylactic isoniazid underpins the use of this policy was summarised by Ferebee in 1970⁶ and data abstracted from this review for populations comparable to those for whom chemoprophylaxis is recommended are shown in table 1.

Data in the third column show the likely benefit per 1000 people treated; it may be substantially less than expected. US children in the first trial are comparable to non-immunised UK children undergoing testing before BCG vaccination. The end point of this trial was symptomatic disease: two of the five children in the placebo arm developed tuberculosis meningitis compared with none of those given chemoprophylaxis, although the difference is not statistically significant. The benefit (five symptomatic cases prevented per 1000 children treated) is small and raises questions about a policy of routine chemoprophylaxis for low risk/low benefit groups.

The end point of the second trial was new cases of tuberculosis in a population of mixed exposure risk (37 US centres, 19 Puerto Rican, and one Mexican). Extrapolation from these data to the UK suggests that nationwide compliance with the guidelines might result in about 980 people per 1000 receiving treatment without expectation of benefit. In view of this evidence, the most direct benefit of chemoprophylaxis be measured in the UK subgroups at highest risk to justify future policy recommendations?


The evidence of the difference in tuberculosis morbidity for children infected with tuberculosis but not currently receiving isoniazid may be the result of reduced chemotherapy or too far between contacts. Indeed, prevention of vitamin D deficiency may be particularly important for the stricter Hindu vegetarians with reduced sunlight exposure who are already recognised as a group at risk of osteomalacia.⁴

HARDING

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AUTHOR’S REPLY

A UK study to establish the benefits of chemoprophylaxis would be very difficult in view of the number of subjects needed, coordination required, and ethical difficulties. However, such a study is unnecessary because the effectiveness of chemoprophylaxis as known. It depends on two factors: firstly, the efficacy of chemoprophylaxis and, secondly, the risk of tuberculosis in the population treated. Efficacy is known to be around 80% from the studies Dr Harding quotes, and others. If we assume 60% efficacy and include a “knock out” factor (1-33) for secondary cases prevented as a result of cases prevented by chemoprophylaxis, we arrive at estimates of effectiveness for a range of at-risk populations as shown in table 2.

The 10 year risk of disease in infected children (most of which is in the first two years) is 9 1%, giving an NNT of 15. The two year risk of disease in contacts of smear

Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tuberculosis morbidity</th>
<th>Difference in number/1000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Isoniazid (95% CI)</td>
</tr>
<tr>
<td>Trial 1: US children (1955-7) with &quot;asymptomatic primary TB&quot; and normal chest radiograph</td>
<td>5/495</td>
<td>3/556</td>
</tr>
<tr>
<td>Trial 2: Household contacts of new &quot;active cases&quot; (1958-79) in the USA, Puerto Rico, and Mexico</td>
<td>147/4992</td>
<td>57/4852</td>
</tr>
<tr>
<td>All ages</td>
<td>31/1616</td>
<td>18/1716</td>
</tr>
<tr>
<td>All ages</td>
<td>32/867</td>
<td>10/694</td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>52/3132</td>
<td>17/3022</td>
</tr>
</tbody>
</table>

Table 1: Tuberculosis morbidity, difference in number (95% CI)
Table 2

<table>
<thead>
<tr>
<th>Tuberculosis risk (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>125</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

*NNT = number needing treatment to prevent one case.

positive tuberculosis in the UK National Contact Study was 2.5%, giving an NNT of 50. Interestingly, 4 of the 5 subjects with positive test results in this study were black, but none of the 5 subjects with negative test results were black. A higher rate of positive test results in black subjects is the figure that Dr Harding arrives at via extrapolation from her quoted US data ("980 out of 1000 receive no benefit").

Similar considerations apply to other high risk groups such as new, young, tuberculin positive immigrants.

Risk-benefit analysis favours chemoprophylaxis because it is a low risk intervention. A decision in the individual is best taken after discussion and agreement between physician and patient or parent on the basis of information available.

With regard to cost effectiveness, this depends on other competing demands for resources. If the competition is won through a tuberculosis control programme, chemoprophylaxis comes a long way behind case detection and treatment in terms of cost effectiveness, so that it is inappropriate in a country where resources are severely limited, but in the UK where case detection and treatment are not limited by resources other elements of a control programme, such as chemoprophylaxis and selective BCG vaccination, are appropriate. Prevention of a single case of tuberculous meningitis with permanent neurological deficit in itself represents an enormous cost saving.

The incidence of tuberculosis in unvaccinated children who are tuberculin positive before BCG vaccination in the schools programme are too slight to justify a policy of routine chemoprophylaxis and the guidelines do not recommend it.

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Air pollution and COPD

A number of factors in the panel study reported by Higgins and colleagues (February 1995;50:149-55) need to be addressed before any conclusions can be made as a result of this study.

The most important concern is the method of analysis. Whitemore and Korn1 have shown that the most appropriate method for panel study analysis is individual regression calculation with summary analysis of individual regression coefficients being used to determine whether or not an effect of an environmental factor has occurred. They found that the greatest predictor of a change in symptoms was whether or not an individual had an attack or was symptomatic on the previous day, and recommended that this needed to be addressed in further studies. They also showed a clear cut effect of season and included in their model temperature and relative humidity.

Higgins and colleagues have not addressed seasonal influences and have only looked at mean temperature rather than mean and minimum or dew point temperatures.

In addition, no allowance has been made for the effect of autocorrelation (the tendency for adjacent observations within subjects to be more similar than those between subjects), a very important factor in air pollution epidemiology. Failure to allow for this can result in spurious results.

There is no measurement of particular matter, either as PM10, TSP or black smoke. Although the authors acknowledge this in their discussion, it is well recognised that levels of sulphur dioxide and particulates can co-vary, particularly in areas near power stations. Consequently, even if the missing confounding variables are addressed, any association which might remain with sulphur dioxide may in fact be attributable to particulates.

The OPSIS system gives values recorded many metres above street level and will thus report higher levels of ozone than at street level. Without measurements of particles or street level ozone levels, causal attribution to ozone would be unwarranted.

We have published an effect of sulphur dioxide and British smoke on hospital admissions that were well correlated which we clearly can point to was an association without necessarily implying causality. Subsequent correspondence2 reinforced this cautious approach.

We have shown3 that maximum hourly sulphur dioxide levels correlate with the following morning's peak flow in patients with severe asthma, but we have had difficulty in deciding how to interpret these data without hourly values available, and consequently this has not been published in full; again a more cautious approach.

The first Birmingham panel study, published in abstract form,4 shows a very limited effect of pollen on asthmatic subjects in the summer, but a more significant effect of aerosol strong acid (which Higgins and colleagues did not measure) in the summer although less so in the winter.

The authors also state that nitrogen dioxide has been shown to cause respiratory effects in challenge studies. If the authors read the full literature on nitrogen dioxide challenge they would see that effects are only seen with extremely high levels of exposure, considerably above those normally seen in ambient air.

We would encourage the authors to reanalyse their data using the Whitemore and Korn analysis, accounting for autocorrelation and adequately controlling for confounders to see if there is any residual association. Until then these data are very difficult to interpret and the conclusions drawn by Higgins and colleagues will remain untenable.

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AUTHORS' REPLY: Dr Ayres and Professor Harrison raise a number of points concerning our study and, in particular, question our method of analysis. We agree that this type of data presents its own particular analytical difficulties, but do not agree that there is only one way of dealing with this.

Whitemore and Korn describe their method of analysing panel data in a study in which records were kept for over two years. From this prolonged record of symptoms episodes were made available for each individual subject, and in some cases for more than one subject. They use an analysis which effectively combines the two steps of the Whitemore and Korn procedure using pooled data from all subjects to estimate the effect of pollution in the group. This seems more appropriate for our data as we have a relatively large number of subjects followed for a relatively short period of time, and should give a reasonably unbiased estimate of the co-efficient. It is important to emphasise that differences between subjects are allowed for in this method, which is effectively that recently described by Bland and Altman.1 Yet, relative short period of observation is also relevant to the question of autocorrelation. The statistical methods for time series analysis are at their best when the number of repeated observations is large and the number of subjects is small. Furthermore, these methods do not overcome the problem of having to make assumptions about the error structure in the data. A series of simulations2 suggests that there is little to choose between the various statistical methods proposed for this experimental design. We have therefore deliberately used the simplest model available. However, we agree that in studies in which more prolonged measurements are made, tests for autocorrelation should be applied.

Regarding the possibility that the relationships demonstrated in our study are the product of confounding by covarying unmeasured pollutants, we acknowledge this possibility in our paper, particularly with regard to particulates. At the time we performed our study the means to measure the whole range of potentially relevant pollutants was not available and, indeed, other work from that time, including that of Dr Ayres' group,3 considered only a limited number of agents. Happily the monitoring of an increased number of a wide range of pollutants is becoming more widely available and interesting data should emerge.

The validity of measurements from the OPIS system is also questioned. We have available the traditional measurement methods for sulphur dioxide and these
Control and prevention of tuberculosis in the UK.

M Harding

Thorax 1995 50: 916-917
doi: 10.1136/thx.50.8.916-a

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