

The projects from Tasmania, Poland and the UK provide great examples of a better alternative: provide GPs with high quality spirometry services for high risk patients. These can be scheduled at convenient times every 1–6 weeks in each GP office, or at locations in each community with easy access.

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# The evidence based treatment of tuberculosis: where and why are we failing?

Lawrence Peter Ormerod

## THE SCALE OF THE PROBLEM

Tuberculosis is increasing both globally and nationally, so its management is becoming even more important. Globally, it is estimated that there are at least 7.96 million (95% confidence interval 6.3–11.1) clinical cases, with 3.52 million (2.8–4.1) sputum microscopy positive cases, and 1.87 million (1.4–2.8) deaths.<sup>1</sup> This gives a case fatality rate of 23%. In addition, 32% of the world's population (1.86 billion) are infected, as judged by a positive tuberculin skin test.<sup>1</sup> In England and Wales after a nadir of 5000 cases per year, numbers have reached over 8000.<sup>2</sup>

## THE SCIENTIFIC BASIS FOR SHORT COURSE CHEMOTHERAPY

Each of the antituberculosis drugs vary in their abilities to kill organisms, to sterilise lesions and to prevent the emergence of drug resistance.<sup>3</sup> Isoniazid is the best drug for killing rapidly dividing organisms, followed by rifampicin and then streptomycin and ethambutol. Rifampicin is best for dormant organisms with occasional spurts of metabolism, and pyrazinamide is best for organisms in an intracellular (acid) environment. Multiple controlled clinical trials have been carried out in a number of countries.<sup>3</sup> These show that a 6 month regimen comprising a 2 month phase of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E), followed by a 4 month continuation phase of rifampicin and isoniazid,

designated 2RHZE/4HR, gives a greater than 95% cure rate, and a relapse rate of less than 5%. This applies whether the drugs are given daily throughout treatment, daily in the initial phase with an intermittent (thrice weekly) continuation phase or fully intermittent throughout.<sup>3</sup> If the regimen is shortened to 4 months by a shortened continuation phase, relapse rates rise to over 10%.<sup>4</sup> The 6 month short course regimen also performs well in the presence of a proportion of isoniazid and/or streptomycin resistance, but much less well if there is initial rifampicin resistance.<sup>5</sup> The fourth drug in the initial phase, ethambutol, is included to cover the possibility of drug resistance. Six month short course regimens have performed well in England and Wales in both clinical trial conditions, with relapse rates of 1–3%,<sup>6</sup> and in routine clinical practice with relapse rates of 0–4%.<sup>7,8</sup> Monitoring of the treatment used in patients with pulmonary disease in the 1983 and 1988 national surveys showed a big change towards pyrazinamide containing regimens, but this was not accompanied in many cases by the appropriate reduction of treatment duration to 6 months that this change allowed.<sup>9</sup>

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## EVIDENCE BASED GUIDELINES AND ASSESSING THEIR IMPACT

The first national guidelines on treatment of tuberculosis were produced in 1990. These were evidence based and peer reviewed, but were "pre-SIGN" and so did not have evidence categories given to recommendations.<sup>10</sup> They allowed the fourth drug in the initial phase, ethambutol (E), to be included for those at higher risk of isoniazid resistance. The recommendations for non-respiratory disease had to be based largely on general principles. However, the results of national studies on lymph node tuberculosis, which accounts for 50% of all non-respiratory tuberculosis, published shortly afterwards, confirmed that a 6 month short course of chemotherapy gave as good results for this form of disease as 9 month regimens.<sup>11 12</sup> The publication of national treatment recommendations did allow the first national criterion based audit of tuberculosis treatment to be carried out on those cases treated in the 1993 notification survey.<sup>13</sup> This showed, among other things, that although there had been a substantial move to pyrazinamide containing regimens, treatment durations remained too long in a significant minority of patients. The publication of this audit "completed the loop", with guidelines, then criterion based audit and then feedback.

During the 1990s, the SIGN group had produced their recommendations<sup>14</sup> for levels of evidence in guidelines. This development, together with the data from audit<sup>13</sup> and treatment studies,<sup>11 12</sup> allowed the production of further evidence based treatment guidelines in 1998, with the treatment of both pulmonary and lymph node tuberculosis carrying "A" category support.<sup>15</sup> The treatment recommendation for all forms of tuberculosis, with the exception of central nervous system disease, was 2RHZE/4HR, with ethambutol (E) now only omitted for those at defined low risk of isoniazid resistance. This latter recommendation was supported at that time by continuous data from the mycobacterial resistance network (Mycobnet) showing isoniazid resistance at 6% overall, but under 2% in previously untreated white cases and 5–10% in all other ethnic groups.<sup>16</sup>

In 1998, the final quinquennial national survey was carried out, over a 12 month period, which was also the pilot for continuous enhanced surveillance. This allowed, in 1999, the re-audit of the treatment of pulmonary and lymph node tuberculosis, again using a criterion based audit. At the same time, European outcome criteria had been agreed which allowed for

the first time comparison at the national level with other countries management and outcome for tuberculosis.<sup>17</sup>

The 1999 audit of treatment,<sup>18</sup> using the same duration criteria as in earlier studies, showed some improvement in the proportion of patients having treatment unreasonably prolonged. The overall outcome of patients with pulmonary disease cured/completed treatment at 80% also compared favourably with those reported from other European countries. A number of deficiencies however were highlighted. Less than half of persons advised to have a four drug initial regimen on isoniazid resistance risk grounds actually did so, which may increase the risk of further drug resistance developing. Eleven per cent of patients did not receive combination tablets which are an aid to adherence, and only 41% could be shown to have had the minimum monthly urine/tablet checks on adherence recommended. The relationship between adherence (formerly compliance) and relapse has been well demonstrated with good adherence being associated with a relapse rate of 1%, moderate adherence with a relapse rate of 6% and poor adherence with a relapse rate of 50%.<sup>19</sup>

## RELEARNING "OLD" LESSONS

Lessons about the compliance (or adherence) of patients to medication and of physicians with recommended treatment are not new. The previous generation of respiratory physicians and scientists were only too well aware of these areas. Wallace Fox, the leader of the MRC Tuberculosis Unit, summarised these in 1983.<sup>20 21</sup> Identified patient factors were those who defaulted from treatment, the regularity of collecting treatment, the regularity of taking treatment, and pill counts and urine tests. Economic and psychological factors were recognised, as were some factors related to age and sex.<sup>21</sup>

Physician elements identified were the use of fixed drug combinations, the use of pill counts and urine tests, the use of short course regimens, the use of intermittent regimens and the use of fully supervised treatment or what would now be called Directly Observed Therapy.<sup>21</sup> It was also recognised that there were wider medical elements, such as the dissemination of information, government policies, formal statements from, for example, the World Health Organisation (WHO) or British Thoracic Society, national surveillance, research and education.<sup>21</sup> To these may now be added what I would term "system factors" which are to do with resource availability. From 1990<sup>22</sup> onwards to 2000,<sup>23</sup> the Joint Tuberculosis

Committee of the British Thoracic Society had recommended a *minimum* of 1 whole-time equivalent for every 50 notified cases in a district *plus full* clerical support in order to effectively run a district tuberculosis service. Audit of provision against this standard has shown major shortcomings in provision, which will then impact on such areas as the ability to carry out effective adherence monitoring.<sup>24</sup>

## WHERE WE CURRENTLY STAND

The National Institute for Health and Clinical Excellence (NICE) produced updated evidence based recommendations for Tuberculosis Control and Prevention in 2006,<sup>25</sup> which in terms of recommended treatment differ little from those of the Joint Tuberculosis Committee,<sup>15</sup> other than now recommending a four drug initial phase for all patients. Monitoring of the outcome of treatment 12 months after notification is by the Enhanced Surveillance System reporting to the HPA. Ditah and colleagues,<sup>26</sup> in this issue of *Thorax*, report the outcome of a 2 year cohort under this system and suggest some modifications (*see page 440*). They point out that the UK uses modified WHO/International Union Against Tuberculosis and Lung Disease (IUATLD) criteria for pulmonary tuberculosis applied to all cases,<sup>17</sup> but that these mix both process and outcome. The main reason that the WHO target of 85% for cure and completion is not met is that death from all causes is included as a reason for failure. Post mortem cases are included, even though such examinations are not systematically carried out, and in some cases the tuberculosis is incidental to the death.

Age is strongly associated with an unsuccessful outcome under the WHO criteria. This has been recognised in the UK for many years. Data from the 1978/9 notification study showed that age, x ray extent, sputum smear positivity and cavitation were all independent risk factors.<sup>27</sup> An analysis of deaths from 1983 to 1985 notified cases also showed a 10-fold increase in deaths over age matched controls.<sup>28</sup> Currently, some 25% of tuberculosis cases, mainly pulmonary, are in the white ethnic population, with a median age of 55 years, and many older than that which explains the trend to "unsuccessful" outcome because of a higher death rate. It is reasonable therefore to modify the outcome criteria as suggested, which raises the rate of successful cure or completion of treatment to 87.5% in those with a reported outcome.

Caution however is required on two counts before congratulating ourselves on

such a high cure and completion rate. Firstly, no outcome was reported in 18.1% (2364) of cases, and the demographics of the non-reported cases showed higher age and higher proportions of white ethnicity and pulmonary tuberculosis, all of which are more associated with adverse outcome. These individuals, if they had had reports, are likely to reduce the overall success figures as the authors themselves accept. Secondly, enhanced surveillance reports outcome if properly recorded but may miss important process errors, which would only be apparent as later relapse or drug resistance. The pilot for enhanced surveillance showed less than half were getting an appropriate four drug regimen, 11% were not on combination tablets and only 41% had minimum compliance monitoring,<sup>18</sup> all factors potentially leading to later relapse. Relapse is not recorded under enhanced surveillance but between 5% and 10% of notifications have a history of prior tuberculosis treatment, suggesting their current episode is a relapse. Relapse rates after treatment are seldom reported in the UK,<sup>29</sup> but would be expected to be between 0% and 3% from data from controlled clinical trials.<sup>3</sup>

Modification of the reporting criteria for the UK enhanced tuberculosis surveillance system seems appropriate from the analysis<sup>26</sup> but strenuous efforts need to be made to increase the level of outcome reporting above the current 82%, ideally to 100%. Short cross sectional audits may also be needed to confirm appropriate regimens, combination tablets and adequate adherence monitoring are being used.

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# Short course of antibiotic treatment in acute exacerbations of COPD

Robert Wilson

Antibiotics are commonly prescribed empirically for lower respiratory infections. Infections of the airway mucosa are

much more common than pneumonia and the illness they cause is less severe because the infection is superficial, most of the bacteria being found associated with mucus in the lumen. In many cases the infection will resolve spontaneously without antibiotic treatment. Most adult

patients are experiencing an exacerbation of chronic lung disease, particularly chronic obstructive pulmonary disease (COPD), when neutrophilic inflammation in response to bacterial infection leads to increased sputum volume and viscosity, and breathlessness due to airflow obstruction. In these circumstances, bacteria are cultured from sputum in about half of the cases which means that, in some of the others, accepting that sputum culture is not a sensitive investigation, antibiotics are given unnecessarily. Antibiotics are essential when a patient with severe COPD presents with purulent sputum and systemic symptoms of infection, but they are often given either to speed up recovery from a bacterial infection that

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