Monitoring tuberculosis treatment outcome: analysis of national surveillance data from a clinical perspective

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ABSTRACT

Background: In 1998, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) published recommendations standardising the evaluation of tuberculosis treatment outcome in Europe. These guidelines fail to account for clinically appropriate alterations in the management of patients.

Objectives: To evaluate tuberculosis treatment outcome in England, Wales and Northern Ireland by redefining the outcome criteria and investigate factors associated with unsuccessful treatment outcome 12 months after notification.

Methods: This was a prospective analysis of a cohort of patients diagnosed in England, Wales and Northern Ireland and reported to the Enhanced Tuberculosis Surveillance system in 2001 and 2002. Proportions of success and failure were calculated based on a new set of criteria following discussion with clinicians treating tuberculosis cases. Logistic regression was used to study risk factors for unsuccessful treatment outcome.

Results: 13 048 cases were notified in the study period. Of the 2676 that were identified as new sputum smear positive pulmonary cases, 2209 (82.5%) had treatment outcome data reported. Using the WHO/IUATLD criteria, 76.8% were classified as successful. In contrast, applying the new criteria, the success rate was 87.5%. This rate exceeds the 85% success target set by the WHO. Risk factors for unsuccessful treatment outcome included male sex (OR 1.27; 95% CI 1.08 to 1.49), being elderly (p trend <0.001), having pulmonary tuberculosis (OR 1.28; 95% CI 1.08 to 1.53) and having resistance to any antituberculosis drug (OR 1.90; 95% CI 1.44 to 2.52).

Conclusion: The proportion of tuberculosis cases with a successful treatment outcome exceeded the target of 85% success rate based on the modified outcome categories. Although the tuberculosis treatment outcome criteria set by WHO/IUATLD appear to be clear, they mix success and failure are not exhaustive and do not reflect decisions taken to account for individual case diagnostic results and therapeutic response. This is particularly relevant for low incidence industrialised countries with readily available resources, expertise and monitoring tools. For example, the outcome of a patient who has his or her treatment changed, suspended or prolonged by a physician for reasons such as adverse drug reactions or initial drug resistance are not considered satisfactory by the current recommendations. Therefore, the outcome definitions mix measures of process and outcome of patient care, for instance, by categorising treatment interruption, a process measure, as a final outcome. Such patients may eventually have a favourable outcome. Furthermore, the outcome category “death” has been the main reason for non-attainment of the 85% success target set by the WHO in many high income countries. In some of these deaths, tuberculosis is only incidental (other comorbidities present) and not causal. It is unreasonable to consider such cases as “failure”. The analysis of death is further complicated by the inclusion of post mortem diagnosed cases in a system where autopsies are not undertaken in a systematic manner. The aim of this study was to evaluate tuberculosis treatment outcome in England, Wales and Northern Ireland in 2001 and 2002 by redefining the criteria for “success” and “failure”, from a clinical perspective. We have also investigated factors associated with an unfavourable tuberculosis treatment outcome.
This was a prospective follow-up of a cohort of tuberculosis patients diagnosed in England, Wales and Northern Ireland and reported to the ETS system in the calendar years 2001 and 2002. At diagnosis, a standard form which permits the collection of clinical and demographic data on age, sex, residence, ethnicity, place of birth, date of diagnosis, disease site, sputum smear and culture status (where available) is completed by the clinician. Typically, tuberculosis treatment lasts 6 months. Less commonly, it may last up to 12 months for tuberculosis meningitis or longer among patients with rifampicin or multi-drug resistant disease. The treatment outcome form reports on the status of the patient 12 months after notification, regardless of whether treatment has been completed. When treatment outcome monitoring forms were not returned, local coordinators contacted clinicians to improve the completeness of data.

**Methods**

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Information on *Mycobacterium tuberculosis* complex isolates and drug sensitivity profile is collated through the UK Mycobacterial Surveillance Network (MycobNet). At the national level, both databases are checked in a multistep process. Firstly, the data are checked for duplicates. The information is then fed back to local ETS coordinators for verification before returning the confirmed data to the national level. The two databases are subsequently linked using an inhose matching software to produce pairs of possible matches based on name, sex, residential address and date of birth. Pairs with a very high degree of similarity are automatically matched. Further pairs with a high matching score are reviewed individually.

**Definition of terms**
In England, Wales and Northern Ireland, all (pulmonary and extrapulmonary) cases of tuberculosis are notifiable. A case can either be culture confirmed (definite) or other than culture confirmed (a clinician’s judgment based on clinical features with or without radiological, histological or tuberculin skin test evidence of tuberculosis, and the decision to treat a patient with a full course of antituberculosis medication). Pulmonary tuberculosis refers to tuberculosis disease involving the lung parenchyma with or without extrapulmonary disease, while extrapulmonary tuberculosis can involve any organ other than the lungs. A cohort is considered as the group of patients notified within one calendar year and whose treatment outcome is to be reported. For this work, analysis included all cases notified in 2001 and 2002. “Any drug resistance” refers to resistance to any firstline antituberculosis drug, while “multi-drug resistance” is resistance to at least isoniazid and rifampicin. Table 2 summarises the treatment outcome definitions used in England, Wales and Northern Ireland.

**Analysis of tuberculosis treatment outcome**
The outcome of the treatment of each case was reclassified as either “success” or “failure”. The criteria used are outlined in table 3. Cases diagnosed post mortem were dropped from the analytic cohort.

The current UK criteria were used to describe the outcome of all cases in a flow chart (fig 1).

To calculate the proportion of cases with a successful outcome, three scenarios were used. Firstly, the proportions of treatment outcome were calculated based on the WHO/IUATLD recommendations (table 1) (ie, including only cases with sputum smear positive pulmonary disease). Secondly, the new criteria (table 3) were applied to this same group of patients. Finally, the new criteria were used to determine the proportion with a successful outcome among all patients with tuberculosis (pulmonary and extrapolmonary).
an outcome reported differed significantly by ethnicity (p<0.001), disease site (p = 0.05) and age (p<0.001).

**Tuberculosis treatment outcome**

Of the 13,048 subjects included, treatment outcome data were reported on 10,684 cases. Figure 1 summarises the treatment outcome results according to the outcome categories used by the UK national surveillance programme: 18.1% did not have outcome data reported. Regional variation in the number of cases notified and the proportion with outcome data reported are shown in table 4.

According to the WHO/IUATLD recommendations, 2676 cases were eligible for inclusion (ie, new sputum smear positive cases). Of these, 2209 (82.5%) had outcome data on treatment reported. Among the 1696 (76.8%) cases who completed treatment, 500 (29.5%) were declared cured. Table 5 summarises the treatment success and failure proportions according to the WHO/IUATLD and new (modified) criteria.

**Determinants of tuberculosis treatment outcome in England, Wales and Northern Ireland in 2001 and 2002**

Table 6 shows the univariable (unadjusted) and multivariable (adjusted) OR, 95% CI and p values for the association between patient characteristics and the outcome of tuberculosis treatment (failure or success) in England, Wales and Northern Ireland. In the unadjusted analysis, factors that were significantly associated with unsuccessful treatment outcome included male sex (OR 1.37; 95% CI 1.22 to 1.54), aged 15 years and over (OR 1.48, 95% CI 1.34 to 1.65; p value for trend <0.001), being reported in London (OR 1.47; 95% CI 1.31 to 1.64), having pulmonary tuberculosis (OR 1.48; 95% CI 1.31 to 1.66) and having disease resistant to any drug (OR 1.69; 95% CI 1.31 to 2.18). MDR tuberculosis had a borderline statistical association (OR 2.09; 95% CI 1.02 to 4.28) with unsuccessful treatment outcome, although with a relatively wide confidence interval. The ethnic groups black Caribbean (OR 0.66; 95% CI 0.56 to 0.77), India/Pakistani/Bangladeshi (OR 0.77; 95% CI 0.65 to 0.92) and any other (OR 0.52; 95% CI 0.45 to 0.60) compared with the white ethnic group were significantly associated with a favourable treatment outcome.

Adjusting for age, sex, place of birth, ethnic group, disease site, region and resistance to at least one first-line drug, factors that were still statistically associated with unfavourable outcome included: male sex (OR 1.27; 95% CI 1.08 to 1.49), age...
DISCUSSION

This study shows that the treatment outcome of sputum smear positive pulmonary tuberculosis cases was successful in 87.5% using the new criteria in England, Wales and Northern Ireland in 2001 and 2002. This success rate exceeds the WHO target rate of 85%, in contrast with the 76.8% rate obtained using the WHO treatment outcome surveillance criteria. The study also suggests that the main factors associated with unfavourable tuberculosis treatment outcome include male sex, higher age, people with unknown place of birth, having pulmonary tuberculosis or resistance to any antituberculosis medication (OR 1.90; 95% CI 1.44 to 2.52).

Tuberculosis outcome surveillance is important for two reasons. Firstly, it allows the measurement and comparison of the performance of tuberculosis services locally, regionally, nationally and internationally. The collection of information on outcomes depends heavily on the collaboration of local tuberculosis departments. The departments will do this better if the exercise is beneficial to them. This is the second important reason for tuberculosis treatment outcome surveillance. It allows local tuberculosis departments to list all cases where the tuberculosis service failed, and perform a review of such cases. Even a large department in the UK will have no more than about 20 such cases in a year. There may be much to be learned from discussion of the details of these cases in regular meetings by tuberculosis case managers and other responsible partners.

The main difficulty in converting the WHO treatment outcome definitions into categories of success and failure in a high income low incidence context such as the UK is what to do...
with those patients who are still on treatment after 12 months, those transferred out and patients who have either died or whose treatment is interrupted for clinical reasons. To clinicians managing tuberculosis, treatment for longer than 12 months is much less of a problem. Most have had their initial treatment plan appropriately adjusted in the face of toxicity or drug resistance and can be predicted after 12 months to do well. They should then be classed as successes. A few remain a cause for concern as they may still be culture positive at this stage. These should be classed as failures. Patients with rifampicin or multi-drug resistant disease, in addition, should have their final outcome monitored at 24 and 36 months. Perhaps a modification to the treatment outcome reporting form would allow these distinctions to be made.

It was not possible to classify the majority of patients who completed treatment as cured by virtue of a negative follow-up culture. Ideally, it would be useful to assess outcome based on a cohort of culture positive and culture converted cases. However, only a small proportion of cases (29.5%) had culture conversion documented. This is probably one of the reasons why the WHO recommends that cases declared cured or who complete treatment be considered a “success” and analysed as one group. Nevertheless, it should be standard practice to obtain follow-up cultures after 2 months and at completion of treatment in tuberculosis patients wherever possible. Usually difficulties in obtaining samples from patients who are no longer symptomatic hamper the bacteriological confirmation of cure. Invasive methods such as induced sputum, gastric aspiration and bronchoscopy may not be appropriate for monitoring in all such cases. However, such investigations may have high public health significance in pulmonary cases, as this would not only ascertain infectiousness but also permit the identification of cases who require close clinical and therapeutic monitoring.

As suggested by previous authors, we excluded post mortem diagnosed cases. Including these cases leads to an overestimation of the number of tuberculosis cases because of the difficulty in distinguishing inactive from active tuberculosis disease on necropsy specimens. In addition, most of the elderly who account for a large proportion of the deaths may die with and not from tuberculosis. Moreover, post mortem examinations are not consistently carried out in the UK. This inconsistency makes within and between country comparisons inappropriate. This study also used treatment cohorts for 2 years, contrary to the WHO recommended yearly cohort analysis. This increased our statistical resolution in studying risk factors for unsuccessful treatment outcome. Over the 2 year period, there was no major change in the case definition, management and surveillance guidelines for tuberculosis in the UK. The cohorts were therefore comparable.

These results should be interpreted bearing in mind the following weaknesses. The information used for the analysis was derived from routine data with potential for errors in coding, and between observer variability that are inherent in the collection and entry. Incomplete or inaccurate matching between the different surveillance databases (MycobNet and ETS) is possible. This could lead to the observation of spurious and/or null associations. However, the routine application of rigorous checks, including automated and manual checks in the ETS system, reduce the probability of these errors. Differences in the extent to which clinicians ascertain outcome in pulmonary and extrapulmonary cases may be another limiting factor contributing to differences in outcome.

Failure to report outcome data in about one-fifth of the sputum smear positive pulmonary tuberculosis cases is disappointing given its public health implications. The main shortcoming of the first 2 years following the introduction of tuberculosis treatment outcome monitoring as a component of the ETS was implementation and logistic difficulties in some regions. Two UK regions had particularly low outcome report results. However, there is evidence of improvement in case outcome reports from initial analysis of subsequent national tuberculosis outcome surveillance data from these regions. Perhaps timely dissemination of outcome reports to the different partners involved in the data collection process could serve as a motivation to trigger more rigorous case finding and complete reporting. A pilot system for active follow-up of missing cases has been set up and should inform future data.

In addition, the group without outcome data were more likely to be white Caucasians, have pulmonary disease and be older, all factors associated with unfavourable treatment outcome in this study. This implies that the outcome of the entire cohort is likely to be less than the observed success rate.

The denotification rate in this study appeared small. This may be explained by the delay between statutory notification and completion of ETS forms. In many parts of the country, cases initially reported to the ETS and later found not to have tuberculosis are denotified early in the process before the data are forwarded to the national level.

In our risk factor analysis, those with an unknown place of birth were found to have a higher risk of unsuccessful treatment outcome, which may be a proxy for other unmeasured indicators of poor outcome. Statistical adjustment was limited only to the variables routinely collected by the tuberculosis surveillance system. Comorbidity and risk factors such as alcohol dependence, homelessness, imprisonment, injecting drug use, immigration status, unemployment and HIV infection (as demonstrated by some other studies) could explain at least in part some of the association observed in our regression model. The findings of this study, however, agree with previous reports that adjusted for some of these factors.

The above findings have both public health and clinical implications. Our results strengthen and build upon earlier criticisms that the WHO tuberculosis treatment outcome criteria appear to be clear and comprehensive, criticisms that the WHO tuberculosis treatment outcome criteria are primarily suitable for high burden and low income countries. It has also been argued that they mix measures of process and outcome in a way that makes the results of tuberculosis treatment outcome difficult to interpret from a clinical perspective. The targets for treatment currently suggested by the WHO are not attainable in settings with very high mortality rates among elderly patients who may die with, rather than of, tuberculosis. In addition, variation in clinical management and the use of modified standardised courses of therapy that result in eventual cure are more likely in a resource rich setting. The modified criteria used in this study give a better insight into the effectiveness of tuberculosis treatment services in case holding and ability to complete treatment. These evaluation criteria could be considered by the WHO for low incidence and resource rich countries.

In conclusion, although the tuberculosis treatment outcome criteria set by the WHO appear to be clear and comprehensive, they have limitations and require further refinement in well resourced countries to permit an objective evaluation of tuberculosis treatment programmes. Tuberculosis management should integrate risk assessment for unsuccessful treatment outcome. There is a need for the collection of information on comorbid states and detailed cause of death associated with...
tuberculosis by surveillance systems in order to give a better understanding of treatment outcome. Future research should focus on identifying causes of treatment failure, including default from treatment and mortality (a common reason for unsuccessful treatment outcome) in tuberculosis patients, especially among the elderly.

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Competing interests: None.

Ethics approval: This study was carried out with national surveillance data. The Health Protection Agency has PIAG approval to hold and analyse national surveillance data for public health purposes.

REFERENCES

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