Review Article

MORTALITY PATTERN AMONG TUBERCULOSIS PATIENTS ON TREATMENT IN NIGERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Tuberculosis (TB) has continued to be associated with a substantial number of deaths, even in the era of effective antimicrobials. Nigeria is one of the countries with a high tuberculosis burden and has sub-optimal documentation of TB related deaths. Vital statistics/registration is not robust, and mortality surveys are rarely undertaken. In this study, we aimed to determine a precise estimate of TB related deaths on treatment and the trends in death rate while on TB treatment in Nigeria.

Methods: We searched electronic databases for eligible studies from 1st January 2000 to 31st December 2017. We generated pooled death rate estimates using random-effects models and determined trends using meta-regression.

Results: We identified 546 studies, of which 28 fulfilled the criteria for quantitative analysis. Overall, studies reported on 64,999 individuals. The pooled TB death rate during treatment was 6.6% (95% CI; 5.2-8.1%). There was a non-significant rise in TB related deaths on treatment of 0.2% per year (p-value = 0.454).

Conclusion: We found a low TB related deaths on treatment, death rate and slight temporal rise over the study years. There is a need for continuous vital registration, including TB related death, and mortality survey among TB patients.

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INTRODUCTION

In 2016 the World Health Organization (WHO) estimated Tuberculosis (TB) mortality of 17(16-19)/100,000 population among its 194 member states, with 22 high burden countries making a significant contribution.[1] Nigeria is among these high burden countries with a TB incidence and mortality of 307,000/100,000 and 115,000/100,000, respectively.[1] Mortality data for TB had been obtained from vital registrations (VR) and mortality surveys[2]; however, VR is not robust, and mortality surveys are infrequently done in many developing countries, including Nigeria.[3]

Tuberculosis related mortality has been a measure of the efficiency of TB control and, as such, it is a prime focus for policymakers.[4, 5] Although concerted efforts to reduce TB death has been ongoing, it is not without challenges. Curbing death from TB has been limited by low case detection, increasing occurrence of TB drug resistance, economic impediments and limited access to TB care.[6] Furthermore, in spite of attempts at achieving a fairly representative spread of national TB treatment centres across Nigeria, TB is still associated with death and disability in addition to the indirect cost incurred in an effort to seek care.[7]

With concerns about the completeness of VR and TB case reporting in Nigeria, it is likely that TB prevalence and mortality are underestimated.[1,8] To improve the reliability of accessible data on TB mortality, repeated community-based surveys would be required not only to appreciate the burden but also to establish trends. In the interim, a meta-analysis of observational studies in epidemiology (MOOSE) technique could be used to enhance the validity of available data. To address this gap, we conducted a meta-analysis to estimate TB mortality rate and trends in patients initiated on TB treatment in Nigeria.

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METHODS

Search strategy

We searched databases such as (PubMed) EMBASE AJOL, BIOLINE, Google scholar and LILACS for studies reporting death among patients with TB. We searched for literature spanning 1st January 2000 to 31st December 2017. The search strategy combined keywords and medical subject headings (MeSH), using multiple search strategies: We used the search strategy of the free text terms 'death' AND 'tuberculosis' with the 'OR' operator including the evaluated MeSH headings 'tuberculosis' AND 'mortality' and 'Nigeria'. We searched retrieved articles in search of other relevant bibliographies. A manual search was done for pertinent literature in subject-specific speciality journals without online versions. Accessible authors were contacted concerning incomplete data.

Eligibility criteria and study selection

Eligible studies comprised of clinical trials, retrospective and prospective cohort studies, cross-sectional studies, and case-control studies (with a report of mortality data) were assessed. We included studies reporting pulmonary and extrapulmonary TB with no sex or age restriction.

We did not include studies on high-risk populations (those with naturally exaggerated death rate) considering their potential to present exaggerated death frequency. Furthermore, presenting data before the year 2000, those with small sample size (which we defined as sample size less than 100) were excluded. We also excluded studies without primary data, commentaries, literature reviews, studies adjudged to have poor quality based on the NIH criteria,[9] studies with inappropriate data, and studies with inadequate data.

Data Extraction

Two independent reviewers assessed titles and abstracts. We obtained full-text articles of abstracts with information suggestive of fulfilling the inclusion criteria. We abstracted the following information from the eligible studies; name of first author's; year of publication; study design; study setting, age group of the study population, the study setting; anatomical site of TB infection (pulmonary / extra-pulmonary) method of diagnosis, the order of TB treatment (new or retreatment), number of persons with TB, number of deaths while on TB treatment, TB/HIV death and TB death in HIV negative patients. Data was coded based on the author's name, and year of study. We assessed Multiple Coder agreement based on Cohen's kappa.

Operational definitions:

Tuberculosis (TB) death was defined as individual dying during TB treatment (all-cause mortality). The primary outcome measure was the proportion of TB patients on TB treatment that died of TB within the designated period of study.

Quality of Included studies

Study quality was independently assessed by two authors using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[9] We evaluated studies with queries appropriate to their study design. Study qualities were graded as good (G), fair (F) or poor (P) according to the rating of at least 70%, 50%, or lower than 50%, respectively.

Statistical analyses

The primary outcome measure was the proportion of death from TB. We estimated standard error of proportions using a binomial probability distribution. Cumulative and sub-group pooled effect size using a random-effect model with DerSimonian-Laird iteration was determined. A pooled proportion estimate and confidence interval, in accordance with the weighted least square (weighting is given by the reciprocal sum of, between and within-study variances), was generated. Between study and heterogeneity using Cochran's Q test was evaluated. We a priori, defined low, medium and high heterogeneity as a Cochrane Q of 25%, 50%, and 75%, respectively. We explored potential confounders and modelled proportion trends using meta-regression. Publication bias with funnel plot, Begg's rank correlation methods and Egger's weighted regression test were assessed. Analyses using STATA software (version 11) was performed. The significance level for Cochran's test was fixed at 0.05. We did iteration sensitivity analysis to determine the effect of sample size variation on the aggregate proportion of TB death.

RESULTS

Characteristics of included studies

We found 546 citations of which 28 articles satisfied all inclusion criteria and were included in both qualitative and quantitative summary (meta-analysis).[10 - 37] (Figure 1) These comprised of 25 retrospective cohort studies and 3 prospective cohort studies with the characteristics of included studies as shown in Table 1. Compliance with meta-analysis guidelines was assessed using PRISMA and MOOSE checklist.

Quality assessment

Based on the 10 quality domains evaluated, all studies satisfied a minimum of six of the quality

criteria. A number of benchmark failed were: sample size justification, insufficient

sample size, study power description, or variance and effect estimates not properly documented. All included studies had scores of at least 70%; details of the rating process is presented in Table 2.

Overall prevalence

Accordingly, our meta-analysis obtained an overall pooled TB related deaths on treatment prevalence in Nigeria of 6.6% (95% CI; 5.2-8.1%). This was derived from the analysis of cumulative individual data from 64,999 individuals with TB, spanning 17 years (2000-2017). (Figure 2)

Table 1 depicts subgroup analyses for the proportion of TB death based on several characterizations; namely study setting, study design, site of tuberculosis, year of study, age category, site of study, and disease category. Remarkable differences were noted in the proportion of TB related deaths on treatment.

The proportion of death among TB patients was higher in studies within a hospital setting with a prevalence of 4.9 % (95% CI: (4.6-5.2) compared to the proportion in the single large community-based study with a prevalence of 0.8% (95% CI: 0.7-0.9).

TB related deaths on treatment was higher in retrospective studies compared to prospective studies, with proportions of 5.8% (95% CI: 5.5-6.1) and 0.8% (95% CI: 0.7-0.9), respectively.

The proportion of death from pulmonary TB was 0.9% (95% CI: 0.8-0.9) compared to 5.9% (95% CI: 5.6-6.2) from both pulmonary and extra-pulmonary sites. When assessed based on year of study, proportions ranged from 0.8% (95% CI: 0.7-0.9) in studies of 2015 to 8.6% (95% CI: 7.5-9.7) in studies of 2003. The pooled proportion in adult populations yielded a higher proportion of TB related deaths on treatment with a figure of 4.3% (95% CI: 4.0-4.7). Conversely, studies restricted to the single site had a higher proportion with a value of 5.4% (95% CI: 5.0-5.7), compared to 1.0% (95% CI: 0.9-1.1) in studies involving multiple sites. Furthermore, studies reporting on new and re-treatment TB cases had a higher pooled proportion of TB related deaths on treatment, with a figure of 4.9% (95% CI: 4.6-5.2)

The proportion TB related deaths on treatment among HIV negative TB patients was 5.2% (95% CI: 3.1-7.3) [Figure 3];

whereas the proportion was 3.6% (95% CI: 2.5-4.7) in those with TB/HIV co-infection. [Figure 4]

We sought evidence of a trend in the proportion of TB related deaths on treatment over the period 2000-2017 using meta-regression modelling.

We found a non-significant rise in the proportion of TB related deaths on treatment among studied Nigerian populations at a rate of 0.2% per year (p-value = 0.454) [Figure 5]. There was no evidence of confounding using covariates: study setting, study design, site of tuberculosis, age category, site of study, and disease category.

We found no evidence of publication bias using Egger's and Begg's test statistics (p-value =0.101 for both tests). We used augmented data to model data symmetry on the funnel plot. We concluded no graphic evidence of publication bias since augmented plot depicted TB related deaths on treatment in the negative range, which is not biologically plausible. [Figure 6]

DISCUSSION

In this study, we have found a pooled TB death rate of 7% among persons on TB treatment in Nigeria. We have further shown evidence of a non-significant rise in the TB death rate over 17 years. Assuming that Nigeria had a TB incidence of 219/100,000 population in 2016,[1] then we would be estimating an occurrence of TB related deaths on the treatment of 15/100,000 population, with an uncertainty interval of (9-21)/100,000 population. To our knowledge, this study, with an appraisal spanning 2000-2017, is the most robust and extensive review of the burden of TB death in Nigeria so far. Moreover, it is the first study to assess the trend in the TB related deaths on treatment in Nigeria using meta-analysis modelling.

Our finding is consistent with an earlier study by Straetemans et al[38], which reported a TB case fatality rate during treatment of 5.8% (95% CI: 3.1%–8.4%) using pooled data from 17 studies with global distribution. Several other Nigerian studies have found low death rate among patients on TB treatment.[16, 24, 25] Nevertheless, findings from such studies do not consistently depict low TB related deaths on treatment.[15] Our findings suggest a marginal lower TB death rate in HIV positive patients. Although TB could occur at any point along the spectrum of immunoparesis in HIV infection, perhaps our finding could be accounted for by the additive mortality benefit of HIV treatment.[1,39]

Although there is a decline in global TB related mortality, our data suggest a contrasting rising propensity among treated cases. WHO had reported a similar trend as depicted (graphically) in its 2017 Global TB report.[1]

This finding underscores the need for sustained TB surveillance and VR documentation and reportage to serve as a veritable data source for TB control. It equally serves as a mirror of the efficiency of national and global TB control interventions. In the context of global socio-economic dynamics, assessing TB death trend is pertinent because of its critical role in gauging progress towards the "End TB Strategy" milestones of percentage reduction in the absolute number of TB deaths (compared with 2015 baseline) of 35% by 2020, and 75% by 2025.[1]

We found a striking difference in higher rates of TB related deaths on treatment in hospital-based studies compared to report from the community. This could be attributed to the likelihood of patients seen in the hospital being more sick with late presentation.[40] Similarly, the disparity between retrospective and prospective studies could be due to variation in rigour between the two study designs. Retrospective design is more prone to bias on account of differences in coding and storing mortality data and recall bias.[41] Tuberculosis programs by default rely on microscopic examination of sputum for diagnosis, with microscopy skill acquired over several years having a legacy effect, as such patients presenting with pulmonary TB are more likely to be diagnosed and commenced on therapy early.[42] It is thus probable that they would have a lower death rate compared to those with extra-pulmonary manifestation. TB related deaths on treatment is higher in children.[43] Although we found a lower death rate in children, our finding is insufficient to make such a conclusion. Data from isolated reports are likely to have a smaller study population and accordingly less precise.[44] Perhaps it may account for the higher death rate reported in single-site studies. Our data suggest higher death occurring among those on re-treatment. Patients on re-treatment for TB are more likely to be non-compliant and defaults on treatment due to treatment fatigue, with an attendant higher risk of dying.[45] Furthermore, TB/HIV co-infection is associated with an increased risk of death.[46] A meta-analysis by Jenkins et al. had depicted a higher risk of death in children with TB/HIV co-infection.[43.] Similarly, an earlier meta-analysis had found a higher risk of TB death when associated with HIV in adults.[38] In contrast, we have found a lower rate of death among those with TB/HIV co-infection. Perhaps the difference may be related to active TB case finding among those with HIV and their earlier access to care, as well as the time of commencement of TB therapy. It is worthy of note that only a few studies disaggregated their data by HIV status as such as limiting the power of our deduction. However, further studies would be needed to fully substantiate the assumption.

This study has a number of limitations. There are unrepresented year bands within the study time frame because some studies did not meet the inclusion criteria. It was impossible to compute the proportion of TB death in studies without clearly defined measures of TB cases or with lumped death where we could not delineate death due to TB. We also had to exclude studies solely reporting high-risk populations such as re-treatment or multidrug-resistant tuberculosis (MDR-TB). Including such data would have created a false high death rate. Many societies in Nigeria bury their dead without recourse to documentation with relevant authorities. Thus we are aware of the inherent likelihood of under-reported death in TB occurring outside hospitals. Nevertheless, verbal autopsies still represent the next best source of mortality data, pending when the country would have a robust, vital registration register.

In summation, our meta-analysis has depicted a low overall pooled TB death rate in patients on treatment over two decades, and a non-significant rise in the rate. These findings underpin the need for a concerted effort at consolidating earlier gains made in TB control and establishing mechanisms to eliminate death from TB, culminating in achieving the "End TB Strategy". Indeed, TB deaths should be preventable with early diagnosis and appropriate treatment.[1] While we were unable to establish HIV treatment status of those with TB/HIV co-infection and timing of commencement of HIV treatment, future studies should aim to include use of anti-retroviral therapy as a potential confounder. This would allow an appreciation of the role of HIV treatment in modulating TB death.

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