DISCUSSION
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5.1. Origin of the problem

This doctoral study originated from historical data reported from developed nations at the turn of the century. A number of isolated reports identified a phenomenon of age and gender based difference in peak tuberculosis mortality in the late 19th and mid 20th centuries. In 1939, Frost estimated the trend in the age specific mortality caused by tuberculosis based on data obtained from the US Registration system for the state of Massachusetts for the period 1880 – 1930. Frost noted that in successive decades, the peak in mortality was invariably associated with a lower age group among women, as compared to men. In other words, younger women were at a higher risk of mortality as compared to men in the same age group. A similar finding had been reported by Daw. The purpose of Daw’s analysis was to compare different statistical methods and their effect on trend estimation. Daw based his data on the Registrar-General’s Decennial Supplement of 1921, and the Registrar – General’s Statistical Review for the period 1851 – 1940. The tables reported in the publication of Daw are revealing in terms of the unique age-sex difference in tuberculosis mortality. The data identified an identical observation to that reported by Frost, that peak mortality was higher in younger women than men in identical age groups. Frost noted that “…the only other data which I have been able to study so far are for England and Wales, 1850 – 1930 ….. They show substantially the same relations as the Massachusetts data; also, the records for females show much the same thing but with a more pronounced peak at the earlier age.” A comparison of tuberculosis mortality rates between three European nation (England, France and Sweden) for the period 1931 – 1936, reported by Dahlberg too revealed a peak in mortality in the younger age groups amongst women than that of men. Similar data were reported by Yerushalmy and Moriayama, who noted a higher mortality in the younger age groups among women than men. Peak mortality among the socio-economically vulnerable non white women were reported to be at even younger ages than white women. In 1952, Sigurdsson and Edwards reported mortality data based on ‘old medical records’ from Iceland. These data also reflected the age-sex difference in peak mortality. Nearly all these studies showed another phenomenon. With the progression of time, the age difference of peak mortality between the genders become inapparent, with the peak mortality shifting from lower age groups to higher age in later decades in women. For instance the data from Iceland showed that between 1926 – 30, peak mortality amongst women was between 15 – 19 years, which
shifted to 20 – 29 years during 1936 – 45 and further shifted to 30 – 39 years during 1946 – 1950s. An identical observation can be extracted from the data reported by Daw. Between 1851 - 60, peak mortality amongst women was between 25 – 34 years which shifted to 35-44 years during 1891 – 1900s. Other studies reflected similar findings. For instance, data reported by Yerushalmy and Moriyama showed that during 1939 - 41, the peak mortality in white women was between 25 – 29 years and shifted to 30-34 years during 1943. Data from Serbia conducted during 1992 – 2000 showed the peak mortality amongst women was between 45 – 54 years. This observation possibly reflect the shifting epidemiology of tuberculosis. Although there was no further investigation of this phenomenon in developed nations, the American Journal of Epidemiology reprinted Frost’s observations of 1939 in an issue of the journal in the year 1995.

The search for tuberculosis studies reporting age-sex disaggregated data in developing countries including India yielded few studies. The possible reason for this bias could be due to the overwhelming tuberculosis mortality among men, so that publications, even those that reported gender distributed data, did not report the data by age group. Age and sex segregated prevalence data from India were however available, with the first post-independence data available from the ICMR nationwide survey to determine the tuberculosis burden. Review of these data indicated that the peak prevalence of tuberculosis was in the younger age groups in women than men. Several independent studies reported from different parts of the country till the 1980s, continued to report a higher peak prevalence in the younger age groups amongst women than men. In data from prevalence surveys conducted post 1980s however, the age difference became inapparent between the genders, thus mimicking the phenomenon reported in the developed countries. Public sector treatment utilization data, representing tuberculosis in lower socio-economic strata, however still identify more young women than men patients. Prevalence surveys conducted in the vulnerable tribal populations too revealed a peak prevalence in women in the younger ages than that of men. These observations were the basis for analysis of age-gender based mortality data in a current cohort of tuberculosis patients.

The review of literature also identified risk factors for mortality that are specific to males or are easily available from the RNTCP records viz., older age, previous history of tuberculosis, treatment default, alcoholism and tobacco consumption / heavy smoking. Few studies have attempted to investigate some
significant gender-related variables identified through qualitative studies which identified the determinants predisposing women from low income countries to the risk of tuberculosis mortality. 17,20,48,86,94

5.2. Tuberculosis and gender: qualitative to quantitative design

Gender based studies investigating tuberculosis risk factors have primarily used a qualitative approach. 17,20,47,48,94 Weiss et al., in a multi-centric study conducted in India, Bangladesh, Columbia and Malawi, identified a higher stigma index amongst Indian and Bangladeshi women with tuberculosis than men. 47,48 Reports indicative of stigma specific to women patients with tuberculosis included factors such as inhibitions while discussing their illness with family or friends, perception of unwelcome presence at the social events, fear of termination of marriage were identified in Indian as well as other developing countries. 48,94 Whether these complex socio-behavioural factors could increase the risk of tuberculosis mortality in women have not been investigated using quantitative study designs. As such, the second focus of the study was to investigate these risk factors primarily using a quantitative approach.

5.3 Study methodology in context to published Indian studies

A snapshot of all published studies investigating survival and risk factors associated with tuberculosis mortality, revealed an aggregation of studies in the southern parts of the India, from authors associated with the two premier tuberculosis research institutes in these parts of the country. 22–24 The exception to this was the study reported by Pardeshi in 2009. 26

This study was however, based wholly on secondary data obtained from the RNTCP records. Mortality estimates were based on treatment outcome records of the programme. 26

Based on these findings, the current study adopted a retrospective cohort design, with the cohort comprising of 3802 pulmonary tuberculosis patients registered at the six TUs in Pune city between January 2009 and December 2010. The methodology was comparable to that reported by Kolappan et al in 2006 and 2008, 23,24 but differed in two key aspects. Firstly, instead of majorly basing the analysis on RNTCP data, the study contacted each and everyone of the 3802 patients of the cohort at the given addresses, and ensured collection of primary data from the sample. Secondly, risk factors investigated in the current study were more extensive, and incorporated gender-related variables from
previously reported qualitative studies and investigated their association to risk of tuberculosis mortality among women through quantitative measures.

5.4. Characteristics of the cohort in context to published literature
The profile of the study cohort was similar to that reported from other Indian studies. Identical to data from other Indian studies, \(^{22-24}\) 66% of the patients in the current cohort were male as compared to 34% women patients with tuberculosis. Similar to data based on anti tuberculosis treatment utilization in India, \(^{40}\) over 50% of women patients with tuberculosis were under or equal to 30 years as compared to 33% of male patients. The clinical characteristics of the cohort was similar to those earlier reported with majority of the registered patients being sputum positive (74%) and accessing anti tuberculosis treatment for the first time (81%). \(^{22,23,25}\) The proportion of patients with tuberculosis who were also infected with HIV was 10.7%, higher than national estimate which report a prevalence of 5%. \(^{1}\) This observation could be ascribed to the study being set in Pune, designated as ‘category A district’ by the National AIDS Control Organization (NACO) (that is more than 1% ANC prevalence in district in any of the sites in the last three years). \(^{109}\) The HIV status in the current cohort was unknown among 34% of the patients, similar to national estimates (37%). \(^{1}\) The proportion of patients with known diabetes mellitus was 7.8% which was lower than that reported in studies conducted amongst patients registered for DOTS in Puducherry \(^{110}\) and Kerala \(^{111}\) (20.7% and 23.2% respectively).

5.5. Provision of incorrect contact information at the time of registration
Provision of incorrect contact information by the patient at the time of registration for treatment is a deterrent to treatment compliance. It is also an impediment for conducting cohort studies like the current study where patients need to be followed up till study outcome. Correct contact information is also of critical importance in the background of the epidemic of drug resistant tuberculosis. As each patient was contacted at the given address, it was possible to determine from this study, a profile of patients who provide incorrect information at the time of registration for treatment. During follow up, it was observed that 10% of the cohort could not be contacted due to incorrect contact information at the time of registration for DOTS. Upon comparison of characteristics of these patients with those providing correct addresses, registration at TUs located in the peripheral areas of the city was significantly associated with the characteristics of patients who had provided incorrect
contact information. Association between engagement in migration prone occupations and registering at the TUs located in the newly developing areas in the city was also observed, indicating that patients who are migrants may be unwilling to provide correct addresses. Earlier studies have identified migration as a major variable affecting treatment compliance, outcome, re-infection and mortality risk.\textsuperscript{27,61,112–121} These data therefore suggested the need for programme managers at TUs where patients are likely to be in migration prone occupations to be vigilant and ensure validation of addresses at the time of patient registration. An observation worth noting was that there was no difference between untraceable patients and those who could be contacted in terms of treatment outcome, suggesting that even though patients were willing to complete treatment, they were unwilling to divulge contact details. The reasons for divulging incorrect addresses not apparent from our study which could be investigated further through qualitative studies.

5.6. Mortality estimates in context to the existing literature

Indian studies reporting tuberculosis mortality data have used two measures, the CFR and the SMR.\textsuperscript{23,24} CFR represents the number of deaths among patients with tuberculosis, while SMR is the number of observed deaths, as compared to the expected number of deaths in the population.\textsuperscript{23,24} Data from India and other low income countries have consistently indicated a higher burden in absolute numbers among males,\textsuperscript{22–24,55,56,72} which is supported through a higher CFR in males in all age groups in this cohort. Conversely survival was higher among women patients. Despite a consistently higher CFR, analysis of SMR data by age group and sex from this study identified a higher mortality in younger women than men in the equivalent age groups. This indicated an excess mortality in lower age groups amongst women than expected mortality in the population. This key finding from this study indicated that when traditional measures of mortality burden are used, the aggregated burden in the younger age groups in women is usually overshadowed by an overwhelming burden in absolute terms in men with tuberculosis.

The overall SMR (26.2) and CFR (15.2\%) at eighteen months after initiation of DOTS observed in this cohort were however higher than that reported by Kolappan et al., (6.1 and 9.4\% at 20 months respectively) in a study conducted in urban Chennai.\textsuperscript{24} The SMR observed in the current cohort was also higher than that reported from a study conducted in the rural areas in Velliyyur, South India (26.2 versus 4.2),\textsuperscript{23} although the CFR was comparable in both studies (15.2\% at 18 months versus 13.8\% at 24 months).\textsuperscript{23}
The difference in SMR between studies could arise due to differences in timing of studies, and the data source used for estimating SMR. SMR in the current study was calculated using data on mortality from the National Family Welfare Statistics in India 2011 as compared to SMR in studies conducted by Kolappan et al was calculated using data from the Sample Registration System India 1998. Although Indian studies have reported SMR, this measure has not been reported disaggregated by age groups and sex. As such none of the previous studies were able to identify the excess mortality in women aged between 30 and 39 years compared to men, that was detected by this study.

5.7. Profile of expired patients

The profile of patients expired due to tuberculosis in this cohort was similar to those reported in other Indian studies. Risk of mortality as measured by CFR was higher among male patients with tuberculosis similar to reported in Indian studies. The risk of mortality was associated with patients aged more than 30 years. This was younger than 45+ years previously reported by Vasantha et al., and Kolappan et al., in independent studies conducted in the rural areas of Tiruvallur district in southern India. The socio-economic characteristics of expired patients included families below poverty line, monthly income less than ₹2040 per month and with minimal education indicating a traditional profile of tuberculosis reflecting the ‘social barometer’. Similar to observations reported from earlier studies, the current study revealed an association between low BMI, contact with another person with tuberculosis, longer delay (patient, as well as diagnosis), treatment default, treatment failure and alcohol consumption. Patients using over-the-counter medication without a prescription/self medication were also likely to be at an increased risk of mortality. Although a few qualitative studies have identified self medication and diagnosis delay among women, paucity of quantitative data was observed in Indian studies. These risk factors were validated in the current study. Indirect data revealed the extent of illness of expired patients. The proportion of usage of hired vehicle was higher among expired patients, probably reflecting the extent of illness, so that they were unable to use the public transport system or walk to the nearest treatment centre. Another interesting observation revealed in this data and not in published literature were the association between complaints related to the side effects of DOTS drugs followed by interruption/irregularity in the course of treatment and risk of mortality. Psycho - social determinants not discussed in the quantitative studies otherwise, revealed association between single marital status and absence of spouse during treatment as significant risk factors.
factors associated with mortality. The current study identified an association between perception of unwelcome presence at social events and problems while negotiation of marital alliances in the family due to disease, and mortality risk in women.

Multivariate analysis however revealed association between risk of tuberculosis mortality with only five of these determinants (that is, monthly income less than ₹2040 per month, BMI less than 18.5 kg/m², interruption of treatment due to DOTS drugs related side effects, alcohol consumption and single marital status). With this background of expired patients with tuberculosis, further analysis was undertaken to identify profile of women patients at risk.

5.8. Profile of expired women in context to existing literature
Investigation of the profile of women patients confirmed that young age increased the risk of mortality in women. The mean age at registration with the DOTS centres was also significantly lower among women than men with a higher proportion of women tuberculosis patients belonging to younger age groups than men. It is interesting to note that as compared to men, amongst women patients with tuberculosis, risk of mortality was associated with dependent status or being engaged in daily wage related occupations, having minimal education, with history of contact with another person with tuberculosis, having BMI less than 18 kg/m², using over-the-counter drugs for initial management of symptoms, being either single or without spousal support. These women were more likely to perceive social stigma and domestic abuse due to disease, indicative her social vulnerability. Complaints of DOTS drugs related side effects followed by missing treatment doses was also significantly associated with deceased women. Several of these factors including self medication, longer diagnosis delay and reported perception of social stigma, indicate a complex interplay factors that come into play before the woman accesses DOTS treatment. This compares with standard clinical parameters increasing risk of mortality after initiation of treatment, which include earlier report of tuberculosis, sputum status, treatment compliance and presence of co-morbidities. Thus a major finding of this thesis was the role of social vulnerabilities enhancing a woman’s risk of mortality.

It is significant to mention the association of increased mortality risk with diabetes, although it was not observed in the multivariate analysis. Considering that the diabetes prevalence in the population may be as high as 19% compared to 1% prevalence of HIV, the study suggests that diabetes should not be ignored while formulating gender
inclusive guidelines for tuberculosis. The current study investigated tobacco and alcohol related behavioural risk factors among women patients, which is unlike previously published studies. An association between smokeless tobacco consumption and risk of mortality in women as compared to men was observed in this study. As compared to surviving women, a significant proportion of expired women were reported to have consumed alcohol in this cohort. It should also be noted that, amongst expired women reportedly consuming alcohol, only nine were female sex workers (FSW).

5.9. Utility of the study and future research scope
This analysis identified women specific factors associated with risk of mortality, which highlighted factors associated with the social vulnerability of women. These included no or five years of education, single marital status, perception of social stigma owing to disease status, suffering DOTS drugs related side effects and irregularity during the course of treatment. Three of these risk factors (age, residence and dependent status) are routinely collected and is a part of the DOTS treatment card, which is used for registration of patients prior to initiation of treatment. Three additional risk factors identified through this study (marital status, education and history of self medication prior to registration for DOTS treatment), were incorporated and the predictive and negative value of this tool was determined. It was possible to achieve a positive predictive value of over 55% using a combination of five risk factors. As data on all these risk factors can be collected by non-medical staff at tuberculosis clinics in low resource settings, this predictive scale can alert the treatment provider on those women who may be at a higher risk of mortality. As staff at the tuberculosis clinics are in regular communication with patients during the course of treatment, women with higher risk scores can be especially counselled in order to address her social vulnerabilities. Thus, this study leaves scope for further research to validate this tool. If found valid, this tool may contribute to saving young women who may be at an increased risk of mortality due to social circumstances.

5.6. Limitations
Two limitations of the current study need to be noted. At the end of eighteen months after initiation of DOTS, 10.7% of the cohort could not be contacted for their survival status. In order to address this limitation, these patients were excluded from the subsequent analysis. The second identified limitation of the study was unknown HIV status amongst 34% of the
cohort. This data is unlikely to distort the key observations of the study, as there were a higher proportion of males with unknown HIV status than females patients.

5.7. Conclusion

In conclusion, the study identifies the need to conduct further studies in other low resource settings to determine if the increased risk of mortality among young women tuberculosis patients may be occurring in similar settings. As the risk factors appear to be related to social factors, an increased focus on young women tuberculosis patients at DOTS clinics may alleviate the increased risk of mortality.