Tuberculosis case finding in South Africa
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General Discussion
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The studies in this thesis showed that the prevalence of culture positive TB was higher than expected in two communities in the Western Cape province of South Africa and the rate of diagnosing patients by the health services lower than expected. In the same province, a survey showed that a group of symptomatic individuals exiting two primary healthcare facilities had a 5% prevalence of culture positive TB and that these individuals had not been tested for TB within the health facilities they attended. In five other provinces of South Africa, the initial rate of loss to follow-up after diagnosis was on average 25%. Facilities with longer sputum smear turnaround times tended to have a higher initial loss to follow-up.

When interpreting the thesis findings with the onion model, a framework to assess the fraction of TB cases accounted for in notification data illustrated in Figure 1 (1), it can be estimated that of all prevalent TB cases in the study populations, at a given point in time, approximately 22% are asymptomatic, 44% symptomatic without having attended the health services, 4% symptomatic and having attended the health service but not yet diagnosed, 9% having been diagnosed, but not yet started on treatment, and 22% having started on treatment. These estimates are crude approximations, depending in part on HIV prevalence which is known with uncertainty and in part on variation in space and time which was captured insufficiently by the relatively small studies.

Figure 1: Onion Model - a framework to assess the fraction of TB cases accounted for in notification data
The thesis showed that case finding in the communities in South Africa where these studies were done, was inadequate, although the national proportion of cases detected has been estimated at 69% by the WHO (2). A national prevalence survey to determine the level of case finding overall, and to identify target groups and areas for improved case finding is recommended by the WHO (3) and underscored by the findings.

Facilities with a longer sputum turn around time tended to have higher rates of initial loss to follow-up. The TB incidence among healthcare workers at primary healthcare facilities in five provinces was about 2.5 times higher than the general population. The incidence of TB among healthcare workers was not associated with the infection control measures instituted at facilities. In communities in the Western Cape province, a higher burden of TB was demonstrated amongst community based health research fieldworkers than in the population where they worked.

These findings mirror discussions in a current series on TB case finding in the International Journal of Tuberculosis and Lung Disease (4–8), showing that although the global case finding and treatment success rates are almost reaching the set WHO targets of 70% and 85% respectively, many cases are still not detected within communities and healthcare facilities. Poor case finding is probably one of the most important determinants of the slow decline in the global TB incidence (9). With the current decline estimated at only 2% per annum, the elimination target of an incidence of <1 case /million population in 2050 will not be reached, since that requires a decline of 20% per annum (2). Additional efforts to identify and treat cases are therefore paramount, especially in a country like South Africa where the additional burden of HIV increases TB incidence (10,11) and complicates the clinical presentation of TB disease (12–14).

The very high culture positive TB prevalence rate and the limited case detection in the Western Cape is concerning, although these findings might have been expected taking into account previous smaller prevalence surveys (15,16) in the same province. The high initial loss to follow up rate (25%) in the five other provinces was unexpected, especially since a previous study showed an initial loss to follow-up rate of 17% (17,18) in 2007, albeit only in the Western Cape. These results were disseminated and the expectation was that service providers would have addressed the issue. A novel finding was the number of TB cases exiting primary healthcare facilities without being tested in the Western Cape. This has not been described before and should be acted upon, after confirming the findings with a bigger sample including other facilities. Infection control measures and TB in primary healthcare workers have not been described in the South African context. The high standardised incidence ratio amongst healthcare workers is concerning and an occupational TB programme should be a priority.
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The thesis findings were limited mainly by the fact that studies were done in specific geographical areas and not necessarily representative of the whole country. The prevalence survey and exit studies were limited to the Western Cape province of South Africa, while the initial loss to follow up and infection control studies were limited to five other provinces of South Africa and sampled from a list of facilities supported by the Technical Assistance and Support project/Tuberculosis (TASC II TB) of University Research Corporation, LLC (19) which may have introduced selection bias. The exit study was limited by its geographical area and the poor response rate which might have led to selection bias. The studies were all cross sectional in nature, which might have led to the possibility of reverse causality. Because individual healthcare workers were not enrolled in the infection control study and the unit of investigation was healthcare facilities, the burden of disease may have been underestimated and HIV status was not ascertained.

IMPLICATIONS FOR THE TB PROGRAMME

The study findings lead to the following recommendations for the TB programme in South Africa:

- improve TB case finding, elaborated under recommendations for further research
- reduce initial loss to follow up
- improve sputum smear turn around time
- monitor TB among health care workers
- evaluate TB infection control audit tools

These recommendations are justified below.

Reduce initial loss to follow-up

Currently initial loss to follow-up is not an indicator routinely monitored in the South African National TB programme. It is however possible to monitor the number of individuals who do not start treatment by comparing the case finding and treatment registers at healthcare facilities. All cases with a positive TB result in the case finding register should be initiated on treatment and entered into the treatment register. Healthcare workers at facilities should be trained to check this regularly and to follow-up individuals who are not started on treatment at their facilities. Correct contact details for all individuals entered into the case finding register are therefore crucial. Resources should be made available to ensure that health workers are not overburdened by the additional task of tracing TB patients. For instance, tracer teams or community healthcare workers employed by non-governmental organisations could assist in finding cases within the community (20). These teams could assist healthcare workers with patient education...
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(21,22), especially when individuals first access care to get sputum investigations. Similar to the achievements of HIV treatment programmes (23,24), patients should at that point in time be empowered to understand the implications of a positive TB result and the importance of initiating and completing treatment, for them as individuals and for the community where they live (25). Additional interventions addressing the health systems gap, for instance an electronic ‘flagging’ system linking the laboratory database and the electronic TB register (ETR.net) (26), indicating which patients have not been initiated on treatment, could be introduced and operational research done to ensure the interventions are effective and efficient.

**Improve sputum smear turnaround time**

We found that many primary healthcare facilities do not receive sputum smear results within 48 hours of requesting it from centralised laboratories, as is advised by the WHO (27) and the National TB programme (28). Facilities with a prolonged sputum smear turnaround time tended to have a higher proportion of initial loss to follow up. A study investigating the accuracy of the Xpert MTB/RIF assay (Cepheid, USA) used at a study laboratory within five kilometres of the enrollment facility indicated 98.2% of smear positive and 72.5% of smear negative cases in comparison to MGIT culture are identified on the first sample (29). The median time to detection is 0 (IQR 0-1) days with Xpert, 1 (IQR 0-1) day with smear and 16 (IQR 13-21) days with liquid culture and the median time to treatment for smear negative patients when using Xpert 5 (IQR 2-8) days in comparison to 56 (IQR 39-81) days when not using Xpert (30).

Although South Africa is currently implementing Xpert at centralised laboratories as a first line test for TB (31) to address turnaround time amongst other issues (32,33), sputum smear is still used to monitor the disease cohort to comply with WHO guidelines (34). When test results are not available within the specified time range, patients may become despondent and not return to facilities to start (18,35–37) or continue (38–40) TB treatment. Therefore it is imperative to ensure that sputum results reach facilities when indicated and to monitor the turnaround times of the tests currently in use. Although short message system (SMS) printers have been installed at some facilities to improve turnaround times (41), the maintenance of these printers should be a priority. Additional mobile health technologies (42–45) could be used to ensure healthcare workers and patients are informed about test results and patients started on treatment soon after the diagnosis has been confirmed.

**Monitor TB among health workers**

The studies included in the thesis have shown that healthcare workers at primary healthcare facilities and community healthcare researchers have a higher burden of TB than the general population. Currently occupational TB amongst healthcare
workers is not monitored routinely (46) although many studies have indicated that TB in healthcare workers is an issue that needs to be addressed (47–51). Resources should be made available for healthcare workers to easily access TB diagnostic and treatment facilities when they develop respiratory symptoms, without being subjected to stigmatisation (52–55). An occupational TB register could be implemented to monitor cohorts of healthcare workers as was done in Russia (56) and is advised by the WHO (57). Community healthcare workers should be included in this cohort (49). An organisation employing healthcare workers (58,59) and community healthcare researchers working in the field of TB should have and implement an occupational TB policy, as was done at the Desmond Tutu TB Centre, Stellenbosch University.

Evaluate TB infection control audit tools

The thesis shows that there was no significant association between a TB infection control audit tool score and whether healthcare workers developed TB at primary healthcare facilities during a specific time period. TB infection control audit tools are used to monitor the risk of transmission of TB within facilities on at least an annual basis (60). As a proxy measure, TB amongst healthcare workers gives an indication of transmission (61). Healthcare workers may be considered a sentinel population for this purpose. However, if infection control audits are performed without the concomitant measurement of TB in healthcare workers, it remains uncertain whether it measures transmission risk and which components of the tool do this best. These tools should also be validated within the context where they are used (62). Different infection control audit tools used in the South African TB programme should therefore be re-evaluated and validated in the presence of an occupational TB register for healthcare workers. If possible, tools should be simplified to indicate key findings. Other methods of measuring airborne transmission could be investigated as well (63,64).

IMPLICATIONS FOR FURTHER RESEARCH

The study findings support the following research priorities:

- conduct a national TB prevalence survey
- investigate effective ways of case finding

These priorities are justified below.

Conduct a national TB prevalence survey

The WHO advised the South African National TB programme in 2010 (3) to do a national TB prevalence survey because national TB prevalence data are lacking and South Africa is one of the countries with the highest TB burden in the world (2). This
advice is underscored by the findings in this thesis, indicating that current estimates of case detection in South Africa may be too optimistic. A national prevalence survey will inform the programme about the level of case detection and give a more accurate estimate of the TB burden in South Africa. A similar scenario existed in Viet Nam in the early 2000s where the case detection rate was estimated as ≥70% and the treatment success rate ≥85%, but there was no evidence of a decrease in disease burden (3). A national prevalence survey in 2006-7 indicated the TB prevalence was 1.6 times higher than previously estimated and the true case detection rate was only 56% (3,65). Subsequent efforts have led to the expansion of active case detection and contact tracing. A similar approach could be followed in South Africa and diagnostic tools such as Xpert could be tested in the context of a national prevalence survey as was previously done on a smaller scale (66).

The data could also be used to identify risk factors for poor case detection in South Africa in addition to informing the TB programme about the level of case detection. Previous analyses using data from the 1996 South African census and 1998 District Health Information System (DHIS) survey (67) have shown self-reported TB diagnosis to be independently associated with cigarette smoking, alcohol consumption and a low body mass index, as well as a lower level of education, unemployment and lower household wealth. If there were high levels of community income inequality, there was an increased TB prevalence as well. However, these analyses did not include HIV status of individuals and bacteriological confirmation of TB diagnosis was not done. A national prevalence survey could confirm these findings while taking into account the effect of HIV but would not indicate where interventions should be focused. Smaller studies could be used to populate the ‘onion model’, as was done in this thesis, to indicate the focus areas for interventions.

**Investigate effective ways of case finding**

Apart from passive case finding, as is currently recommended by the WHO, provider-initiated case finding, including screening for cases within facilities and active case finding within the community (7), should be investigated in the South African context. As was shown in the thesis, individuals attend facilities but may not be diagnosed with TB although they have respiratory symptoms. Case finding studies from the early 70s in Kenya (68–72) indicated a good yield when screening for cases within facilities, interviewing elders in villages to identify possible cases, and revisiting individuals who previously had TB. These strategies could be adapted for the South Africa context. Interventions to screen individuals within facilities, for instance the use of cough officers (73), should be tested. Studies have tested active case finding strategies in communities by using mobile services (74,75), by doing contact tracing in the households of TB cases (76–78) or through door-to-door surveys (79–81). It seems from current literature on active case finding (74,82–84) that more smear
negative cases are found. This means that more sensitive methods for smear negative diagnosis, such as Xpert (29,85) or chest x-ray (84,86), should be used when testing such strategies in the community.

It is however imperative to ensure that additional cases found with these strategies are started timely on effective treatment (87) as it is unethical not to treat such individuals and pointless to identify additional cases if not treated. Although TB treatment in South Africa compared to other high burden countries is expensive (>US$1000 per patient), South Africa is a middle-income country able to fund most of its own TB programme (2). Economic constraints should not prevent treating all cases. However, the cost-effectiveness of case finding strategies should be determined (88–90) to ensure the equitable distribution of funding within the TB programme and the Department of Health, especially in the context of the concomitant HIV epidemic (91).

CONCLUSION

This thesis has shown that TB case finding in South Africa is not currently sufficient according to the set targets of the WHO. As a consequence, TB transmission continues within facilities and in communities. TB programme strategies to improve case detection and research studies to investigate effective ways of case finding should be implemented in order to address this issue.
REFERENCES

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