Summary
The studies presented in this thesis were focused on the quality of diagnostic care provided to suspected tuberculosis (TB) patients and centre on four principle investigations. The central aim of the studies presented in Chapters 2 and 3 was to gain understanding of the current quality of TB care and reasons for not following the guidelines. The overarching aim of the study presented in Chapter 4 is to develop strategies to diagnose TB in patients whose initial tests are negative for smears. A prospective study to determine the predictors of culture-negative TB among smear negative TB cases is described. Finally, in Chapter 5 we explore the level of salivary NO and its metabolites as a potential biomarker to detect the earliest and most difficult to diagnose TB cases. In the final chapter of this thesis, Chapter 6, we presented the overall major findings, methodological considerations, and general conclusion of the studies.

In Chapter 1 of this thesis, we summarize the result of a literature review related to research questions regarding the quality of diagnostic care provided to suspected TB patients. In its Global TB Report 2013, the WHO highlighted detection of missed cases as a priority action to reach 2015 global targets. The estimated TB case detection rate (percentage of detected cases among the estimated number of incident cases) in Ethiopia has been consistently low; the WHO estimate is 64% for all forms. In a recent Ethiopian national population based survey in 2011, the prevalence of bacteriologically-confirmed TB (smear and/or culture positive) for persons aged 15 years and above was 277 per 100 000. Besides, reports from previous studies, showing a high proportion of TB among young persons, suggests that TB is circulating in the community and that there is a need for more efforts to limit the spread of TB disease.

Current TB control strategies in many countries depend on care that is provided to persons who have symptoms of TB and/or those who have the disease. In most high-burden countries, TB is still diagnosed using tools such as direct sputum microscopy and chest radiographs. When applied to resource-limited settings, these methods suffer from significant limitations; accuracy is suboptimal and fails to diagnose one-third to half of all TB patients. To improve the accuracy of diagnostic work-up several new diagnostic tests have been suggested. However, no single parameter has gained undisputed acceptance. Predictive models for the diagnosis of TB provide a useful framework for systematization of the diagnostic approach and are able to standardize data collection from clinicians. These models could be used to identify patients at very high risk of TB that may require further diagnostic tests after the results of a negative smear test. Besides, further research is necessary to determine the usefulness of these prediction models to establish the exact causes of false smear negative TB (patients that have TB, but have a negative smear test). Furthermore, substantial effort has been devoted to improving physician compliance with evidence-based guidelines. Studies of the quality of TB evaluation (i.e. diagnostic workup of patients with symptoms suggestive of TB) in high burden countries have generally shown poor adherence to international or national guidelines. While previous research has assessed barriers patients face in accessing primary care centers that provide TB diagnostic services, less is known about barriers
providers in these settings face in adhering to guidelines for evaluating patients for TB. We identified diagnostic guideline adherence and professional practice, as relevant elements of the under-emphasized theme in quality of TB care.

The aim of the study reported in Chapter 2 was to determine quality of diagnosis and monitoring of treatment response of patients with smear-negative TB compared with smear-positive cases. A retrospective review of medical records of newly diagnosed TB cases was performed and we descriptively analysed the proportion of TB cases managed according to ISTC protocol. Our findings show poor standardized clinical care offered to smear-negative TB cases compared to smear-positive TB cases. This could be due to the assumption that the prognosis for smear-negative cases is better than for smear-positive cases. However, this assumption can only be valid if microscopy procedures are followed completely and reliably. Therefore, there is a need to explore the reasons behind poor standardized clinical work-up in smear-negative compared to smear-positive TB cases.

The research aim of the second study, described in Chapter 3, was to explore TB service providers’ reasons for not complying with TB treatment guidelines at health facilities in Ethiopia. A descriptive qualitative design was used. Focus group discussions (FGD) were held with 39 service providers involved in TB care. A questioning route for the FGDs was prepared, with open-ended questions, probes and prompts. The questions were based on information from the current literature (sensitizing concepts), and had been reviewed by stakeholders and adapted accordingly. The topics were quality deficits, compliance with TB guidelines and information transfer. For the data analysis we used the qualitative content analysis approach based on the constant comparison method. Codes and categories emerged inductively from the data through careful examination by the researcher. The main reasons for non-compliance with TB treatment guidelines were (1) insufficient diagnostic modalities, limiting the capacity to correctly diagnose TB and provide the right regimen; (2) ambiguity in guideline recommendations especially for specific sub-groups of patients, making it difficult to prioritize them to the right regimen; and (3) poor documentation concerning referred patients, with no appropriate examination and difficulty obtaining information from previously treated patients. Our findings offer real-life examples of what is needed to customize TB guidelines to local contexts of healthcare in order to improve compliance. We recommend developing intervention strategies that are not only tailored to average patients. Consideration should be given to specific sub-groups as an important influence on guideline compliance.

Despite the considerable incidence of culture-negative TB, little is known about this specific group’s clinical manifestations compared to culture-positive TB among smear negative cases. In Chapter 4, we hypothesize that culture-negative TB cases may present with no significant differences in clinical and radiographic abnormalities when compared to those cases with a culture-positive and smear-negative result. A prospective evaluation study was designed to determine the predictive ability of routine diagnostic tests and clinical symptoms. While application of predictive modelling in patients
with clinical suspicion of TB has been described before, previous studies based their analysis on combining only independent significant predictive variables into a decision model. Therefore, in this study, we evaluated the performance of predictive models when all and only significant variables were considered for estimating the probability of TB; (1) among all clinical suspects and (2) among smear negative cases. Employing all variables and only independent significant ones into a regression model, failed to discriminate between culture-negative and culture-positive among smear-negative TB cases, thereby supporting our hypothesis that among smear-negative cases, culture-negative TB may present with no differences in clinical and radiographic abnormalities compared to those with culture-positive TB. This finding emphasizes that medical providers should neither rely on culture as the gold standard tests for TB, nor expect a clinical presentation with the symptoms characteristic of advanced TB in order to diagnose and initiate treatment in culture-negative TB. Furthermore, our findings suggest that independent significant variables (positive sputum smear and chest radiography compatible with TB) remain critical elements in prediction of culture-positive TB among patients with clinical suspicion.

In the Global TB Report 2014, the WHO declared that “one of the most urgently needed tests is a rapid biomarker-based test that can diagnose TB”. Ideally, such TB biomarker should be able to detect the earliest and most difficult to diagnose TB cases, and should be suitable for use in resource-limited settings. A series of reviews has shown that biomarkers such as NO have the potential for screening TB suspects. Human mouth represents the environment with a constant supply of NO metabolites from L-arginine. The production of stable salivary NO metabolites, may be affected during nutritional deficiencies, a common condition in TB suspects. Several studies reported that patients with active TB are more likely to experience wasting, and have a lower body mass index (BMI) than healthy individuals. Therefore, it is hypothesized that patients unable to respond with an effective production of salivary NO metabolites in response to \textit{Mtb} infection, are more likely to have severe (commonly seen as wasting in TB suspects) and more infectious forms of TB. In Chapter 5, an exploratory study to compare the salivary NO levels in confirmed and unconfirmed suspected TB patients by sputum smear microscopy, chest radiography and molecular GeneXpert tests, is summarized. The objective of the study was to examine the diagnostic value of the level of salivary NO metabolites, in order to assess microbiological outcome (infectiousness), and its association with the severity of the disease (commonly seen as wasting) in TB suspects. The results of our findings support our hypothesis that patients unable to respond with an effective production of salivary NO metabolites in response to \textit{Mtb} infection, are more likely to be associated with increased risk of acquiring TB. Interestingly, the results could not support our second hypothesis that levels of salivary NO could be associated with the severity of the TB. This finding is also in line with the study of Idh et al., in which they neither found an association between BMI and NO levels at
treatment initiation. However, larger clinical studies, including long term clinical follow up will be essential to test this hypothesis thoroughly.

The findings in this study presented in this thesis suggest a number of avenues for further research and specific public policy implications for professional practice. Our findings indicate that the degree of trust that TB service providers had in the diagnostic test results had a great impact on clinician’s compliance with the guidelines. Thus, addressing their negative perception of sputum smear microscopy may be just as important as scaling up the diagnostic test. Consideration should be given to specific sub-groups (smear and culture negative TB suspects) as an important influence on guideline compliance. However, in our study a critical question was whether smear and culture negative patients can be detected early by predictive modelling. Our finding is in agreement with a previous study that reported that predictive models based on clinical variables may not be useful to discriminate culture-negative TB, because of the variable presentations of symptoms. These symptoms are somewhat ubiquitous in a clinical setting, thereby non-specific, and could possibly indicate a multitude of other illnesses. Although the coexistence of illness in smear and culture negative TB is problematic in itself, a fundamental challenge arises when clinical responses to this uncertainty are guided by the single disease paradigm that dominates the existing health care system. This paradigm leads to ‘incomplete assessment of diagnostic outcome and failure to modify the clinical approach accordingly’. One possible direction for further research is the use of a diagnostic panel, i.e. a group of experts who assesses the results from all available relevant patient data to reach a final diagnosis in each patient. However, few studies have systematically examined the accuracy of TB diagnosis by such a panel and the type of diagnostic evidence available. Besides, approaches that combine clinical judgment based on all available information with additional value of new diagnostic tests have been proposed, but rarely addressed. Furthermore, we suggest that future quality improvement initiatives should focus on the role for real-time, clinic-level monitoring of smear negative TB suspect evaluation practices, in order to capture individual data on clinical measures related to care of smear-negative TB from every patient evaluated.