Active Case Finding for Tuberculosis in Nepal

Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy (PhD) in Global Health

By

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Declaration

I hereby declare that this PhD thesis is a presentation of my original research work. Material contained herein has not been previously published, accepted or presented for the award of any University degree. Wherever contributions of others are involved, every effort has been made to indicate this clearly, with due acknowledgement made through co-authorship of publications and is summarized below.

The field work for the research reported in this thesis was conducted by a team of BNMT staff. The field programme was co-ordinated by Mr Raghu Dhital. District project co-ordinators supervised a team of community health mobilisers and female community volunteers in each district. These teams conducted the active case finding and gathered the data, conducted the patient interviews for the costing studies.
Data management was designed and supervised by the KNCV consortium partners for IMPACT TB, Dr Jens Levy and Mr Puskar Paudel. Ms Kritika Dixit conducted monitoring and evaluation of data under the TB REACH project. Dr Noemia Taxiera de Filha and Mr Bhola Rai trained field staff in TB patient costing and Dr Noemia Taxiera de Filha conducted the health economic analysis. The IMPACT TB steering Committee of Mr Luan Vo, Professor Knut Lonnroth, Professor Bertie Squire, Dr Jens Levy and Dr Maxine Caws (IMPACT TB PI) provided advice and guidance on design, analysis and interpretation of the research.

ABSTRACT

Background: Tuberculosis is one of the leading causes of death in globally and especially in LMICs. Despite being a preventable, curable disease, a person dies of TB every 20 seconds and every 2 minutes child dies because of tuberculosis. The Covid-19 pandemic had a devastating impact on access to TB diagnosis and treatment and the burden of TB disease. 10.6 million people fell ill with TB in 2021. Of these, approximately 6.4 million people with TB were 'missing': i.e. not diagnosed and notified through national TB programmes.

The first national TB Prevalence survey for Nepal revealed that the burden of TB in Nepal is 1.6 times higher than WHO previously estimated. This showed that there are about 40,000 TB cases 'missing' every year in Nepal. This case detection gap reflects the substantial barriers to access TB diagnosis and care, particularly in rural Nepal. It is vital that Nepal closes the case detection gap to achieve the commitments to the END TB strategy and accelerate progress towards TB elimination. Active Case Finding is an essential component, of a comprehensive strategy to find, diagnosis and treat missing cases, but stronger evidence is required for national TB programmes to build evidence informed and cost-effective ACF strategies integrated with, and complementary to, existing passive case finding services.

Aims: The thesis aimed to strengthen evidence to inform policy on effective ACF strategies appropriate to be implemented by the Nepali National TB programme embedded within the Nepali health system.

Two major themes were explored (1) yields and additionality achieved using different ACF models (2) the potential impact of ACF on prevalence and intensity of catastrophic costs for TB patients in Nepal.

Methods: The studies reported in this thesis were conducted within two major Birat Nepal Medical Trust (BNMT) community based TB active case finding implementation projects: the TB REACH wave 5 and IMPACT TB projects. The TB REACH project was implemented in 8 districts in the mid west and far west region. The IMPACT TB project was implemented in 4 districts of the central region of Nepal. Within both projects, the yield and additionality of active case finding using either the advanced molecular diagnostic GeneXpert test or smear microscopy for TB diagnosis was

compared. Three case finding strategies were employed: social contact tracing, TB camps in hard-to-reach areas and screening at hospital OPD visits (TB REACH only). A network of community health workers identified individuals for screening, through interviewing index TB patients or consultation with health service providers. After verbal screening, symptomatic individuals were tested using either smear microscopy or GeneXpert tests. Case notification and additionality (crude and adjusted) was compared with control districts using TB REACH recommended methodology for analysis.

The second theme of the thesis explored patient incurred costs for TB and the potential role of ACF in reducing prevalence and intensity of catastrophic costs. Patient Cost data were collected using an adapted, translated and validated version of the WHO TB patient costing tool. For the TB REACH project, a cross sectional (single interview timepoint) survey wasconducted during the intensive phase of treatment. During the IMPACT TB study, the costing tool was adapted to a longitudinal design and additional interviews conducted during the continuation phase and at treatment completion. Socio-economic impacts were also evaluated throughout the treatment to understand changes in socioeconomic impacts and household recovery during treatment.

Results: The yield study from TB REACH project (chapter 3) showed that the project identified 1,092 TB cases. The highest yield was obtained from OPD screening at hospitals (n=566/1092; 52%). The proportion of positive test using GeneXpert (n=859/15637; 5.5%) was significantly higher than from smear microscopy testing (n=120/6309; 2%). The project achieved 29% additionality in case notifications in the GeneXpert intervention districts.

Similarly, the IMPACT TB yield study (chapter 4) showed that the project identified 1,133 TB positive cases during community-based TB ACF implementation. The positive rate of tested individuals during active case finding using GeneXpert and microscopy was (n=764/17114; 4.5%) and (n=437/13285; 3.3%), respectively. Social contact tracing for TB using GeneXpert testing yielded an additional 22% to district level TB notifications in Nepal.

The TB REACH cross sectional patient costing study (chapter 5) revealed that the prevalence of direct catastrophic costs was lower for ACF patients when compared with PCF patients (13% *vs* 33%, p = 0.029). Furthermore, patients over 60 were

particularly vulnerable to catastrophic costs when diagnosed passively rather than actively.

The IMPACT TB longitudinal costing study (chapter 6) revealed that the socio-economic impact was severe for both groups (ACF and PCF) throughout the whole treatment, with 32% of households incurring catastrophic costs. ACF was associated with significantly lower patient costs during the pre-treatment period (mean total pretreatment costs of 56 USD and 87 USD for ACF and PCF groups, respectively. P<0.001). Three quarters of patients experienced extreme poverty in the intensive phase of treatment. ACF reached more vulnerable patient groups, with those diagnosed more likely to have no formal education, work in the informal sector or be from the lowest socioeconomic groups. Incurment of costs over the catastrophic costs threshold was also associated with 'no education' status, reflecting the severest financial impact of TB on the most vulnerable population groups.

Conclusions: Community based ACF is an important strategy to both close the case detection gap, improve equity of access to TB services and reduce patient incurred direct and catastrophic costs. Substantial additionality in TB case notifications was demonstrated through OPD screening and social-contact tracing strategies. GeneXpert based ACF was a more effective strategy with higher yields than smear microscopy based ACF. Although TB camps had a relatively low yield, this strategy reaches remote populations and is an important component of comprehensive TB case finding strategy in the context of Nepal. Early detection and treatment of TB can subsequently prevent suffering, death and further transmission of TB and substantially contribute to achieve the WHO End TB strategy targets by 2035. The community based ACF approach mitigated costs and reached the most vulnerable patients. Socio-economic consequences are severe and sustained on TB affected households in Nepal and therefore social protection policies have to be implemented to achieve the zero catastrophic costs milestone of the End TB strategy.

This thesis provided significant evidence to inform both national and global TB ACF policy, and translation of policy to effective action.

ACF should be scaled up nationwide, integrated within the existing health services applying comprehensive access to GeneXpert testing. It is vital that Nepal closes the case detection gap for TB to accelerate progress towards the END TB strategy goals.

ACF scale-up has significant potential to contribute to the reduction of TB and to the elimination of catastrophic costs for TB patients in Nepal.

List of Publications

This thesis is based on the following published manuscripts.

I. Gurung SC, Dixit K, Rai B, Dhital R, Paudel PR, Acharya S, Budhathoki G, Malla D, Levy JW, Lönnroth K, Ramsay A, Basnyat B, Thapa A, Mishra G, Subedi B, Shah MK, Shrestha A and Caws M. Comparative Yield of Tuberculosis during Active Case Finding Using GeneXpert or Smear Microscopy for Diagnostic Testing in Nepal: A Cross-Sectional Study. *Tropical Medicine and Infectious disease, MDPI. Trop. Med. Infect. Dis. 2021, 6, 50.* https://doi.org/10.3390/tropicalmed6020050

II. Gurung SC, Rai B, Dixit K, Worrall E, Paudel PR, Dhital R, Sah MK, Pandit RN, Aryal TP, Majhi G, Wingfield T, Squire B, Lönnroth K, Levy JW, Viney K, van Rest J, Ramsay A, Santos da Costa RM, Basnyat B, Thapa A, Mishra G, Moreira Pescarini J, Caws M, Teixeira de Siqueira-Filha N. How to reduce household costs for people with tuberculosis: a longitudinal costing survey in Nepal. *Health Policy and Planning, 2020, 1–12. doi: 10.1093/heapol/czaa156*

III. Gurung SC, Dixit K, Rai B, Caws M, Paudel PR, Dhital R, Acharya S, Budhathoki G, Malla D, Levy JW, van Rest J, Lönnroth K, Viney K, Ramsay A, Wingfield T, Basnyat B, Thapa A, Squire B, Wang D, Mishra G, Shah K, Shrestha A, de Siqueira-Filha NT. The role of active case finding in reducing patient incurred catastrophic costs for tuberculosis in Nepal. *Infect Dis Poverty* 2019; 8(1): 99

IV. Gurung SC, Dixit K, Paudel R, Sah MK, Pandit RN, Aryal TP, Khatiwada SU, Dhital R, Paudel P, Shrestha G, Rai B, Budhathoki G, Khanal M, Mishra G, Levy J, Van de Rest J, Thapa A, Ramsay A, Squire B, Lönnroth K, Basnyat B, Caws M. Additionality of GeneXpert or smear based active TB case finding among social contacts of index cases in Nepal. *Tropical Medicine and Infectious disease, MDPI. Trop. Med. Infect. Dis. 2023, 8, 369. https://doi.org/10.3390/tropicalmed8070369*

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ABBREVIATIONS

ACF	Active Case Finding
AFB	Acid Fast Bacilli
BCG	Bacille Calmette-Guerine
BNMT	Birat Nepal Medical Trust
CBDOT	Community Based DOT
CHVs	Community Health Volunteers
DoHS	Department of Health Services
DOTS	Directly Observed Treatment Short-Course
DST	Drug Susceptibility Testing
ECF	Enhanced Case Finding
EDPs	External Development Partners
EPTB	Extra Pulmonary TB
FAST	Find cases Actively, Separate safely and Treat effectively
IGRAs	Interferon-Gamma Release Assays
LMICs	Low and Middle Income Countries
LTBI	Latent Tuberculosis Infection
MDGs	Millennium Development Goals
MDR-TB	Multi Drug Resistant-Tuberculosis
MoHP	Ministry of Health & Population
NSP	National Strategic Plan
NTCC	National Tuberculosis Care Center
NTP	National TB Programme
PCF	Passive Case Finding
SDGs	Sustainable Development Goals
TB	Tuberculosis
TBST	TB Antigen-Based Skin Tests
TST	Tuberculin Skin Test
TWG	Technical Working Group
UHC	Universal Health Coverage

UNHLM	UN High Level Meeting
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant-TB

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1.1 Research Objectives and Overview

1.1.1 Objectives

The thesis aimed to strengthen evidence to inform policy on effective ACF strategies appropriate to be implemented by the Nepali National TB programme embedded within the Nepali health system.

Two major objectives were explored (1) the yields and additionality achieved using different ACF models (2) the potential impact of ACF on prevalence and intensity of catastrophic costs for TB patients in Nepal.

1.1.2 Thesis Overview

The thesis is structured into 7 chapters.

Chapter 1 gives an overall introduction of tuberculosis (TB) disease including history of TB, causative agent, mode of transmissions, signs and symptoms, diagnosis, treatment, prevention and control. The global TB scenario, including the political landscape with a brief overview of the major declarations and strategies guiding TB actions at a global level, including the sustainable development goals (SDG), End TB strategy, Moscow Declaration to End TB, the political declaration at the UN high level meeting on TB in 2018.

Background to the context of TB in Nepal, the development of active case finding interventions, the links between Tb and poverty and the definition and global scenario around catastrophic costs for TB patients is then discussed.

Chapter 2 describes the setting for the research studies, the research methodology, and data analysis for each chapter. Two large TB active case finding projects implemented by Birat Nepal Medical Trust (BNMT) formed the foundation of this thesis: a TB REACH wave 5 project and the IMPACT TB project (www.impacttbproject.org).

Chapter 3 reports the comparative yield of tuberculosis and additionality to district level case notifications achieved during active case finding using GeneXpert (4 districts) or smear microscopy (4 districts) for diagnostic testing in Nepal. This was a cross

sectional study from the BNMT TB REACH wave 5 project, which has been published in Tropical Medicine and Infectious Diseases.

Chapter 4 reports the yield and additionality achieved from the IMPACT TB project, which compared ACF using smear (2 districts) or GeneXpert (2 districts) among social contacts of TB cases. IMPACT TB installed a four-module GeneXpert machine in three locations of each intervention district to expand coverage and equity of access. This work has been submitted to the journal Tropical Medicine and Infectious Disease - MDPI.

Chapter 5 examines the prevalence and intensity of catastrophic costs incurred by TB patients within two districts of the TB REACH wave 5 project, using a cross-sectional methodology (interview at single timepoint). The analysis compares the costs incurred by patients who were diagnosed by passive or active case finding methods. The chapter examines the potential role of active case finding in reducing patient incurred catastrophic costs for tuberculosis in Nepal. The work has been published in Infectious Diseases of Poverty.

Chapter 6 presents an evaluation of patient incurred costs within four districts of the IMPACT TB project applying a longitudinal methodology (interviews at three timepoints during treatment). The analysis explores the potential contribution of ACF to reducing patient incurred catastrophic costs, as well as socioeconomic impacts of TB disease and household income recovery during treatment in Nepal. This work has been published in Health Policy and Planning journal.

Finally, Chapter 7 summarizes the major findings of the thesis and discusses the implications, further research and policy translation. The thesis concludes with recommendations to strengthen aspects of TB care in Nepal, which arise from the thesis findings.

CHAPTER 1: INTRODUCTION

1.1 Overview of tuberculosis (TB)

Tuberculosis (TB) is one of the leading causes of death globally, with over 80% of cases occurring in low and middle-income countries (LMICs). Despite being a preventable, curable disease, it remains one of the most intractable public health challenges.

WHO estimates that in 2021, 10.6 million people fell ill with TB. Of these only 6.4 million people were diagnosed through government national TB programmes (NTP) globally (1). These figures mean that a person dies of TB every 20 seconds and every 2 minutes a child dies from tuberculosis.

There is to date only one approved vaccine for TB, the Bacille Calmette-Guerine (BCG) vaccine, which is over 100 years old and has limited efficacy. The BCG vaccine is widely used because it can prevent severe disease in infants but it does not adequately protect adults. There is an urgent need to prevent TB disease with vaccines. Although there are 16 TB vaccine candidates at different stages of evaluation in early January 2023, an effective vaccine is likely to be at least a decade from approval (2).

If the current level of investment in TB services and research does not significantly change along with our overall strategy, globally 43 million people will develop TB, 6.6 million will die of this curable disease and the global economy will lose 1 trillion USD between 2023 and 2030. Investment in tuberculosis is one of the cost-effective health interventions, with a return of 40 USD for every dollar invested (3).

Nepal's first ever prevalence survey revealed that the TB burden is almost 1.6 times higher than has been previously estimated by WHO. About one hundred and seventeen thousand (117,000) people are living with TB disease in Nepal and about sixty-nine thousand (69,000) people develop tuberculosis in Nepal every year. Over half of these TB cases were not diagnosed via the national TB Programme. Forty-seven people are dying every day because of TB in Nepal. The prevalence survey also revealed that 70% of TB cases in Nepal are asymptomatic (4). This is consistent with the results of other prevalence surveys in the region, which have all demonstrated that the burden of TB has been substantially underestimated in Asian countries. For

example, evaluation of Indian data from multiple sources resulted in an >80% increase in the estimated incident TB cases, from 1.6 million to 2.9 million in 2014 (5, 6).

The World Health Organization (WHO) and global health community have set ambitious targets for 2035 in the END TB strategy (7). These are to reduce global TB incidence by 90% and deaths from TB by 95% between 2015 and 2035. Even these targets only represent a reduction in TB to the levels seen in developed western nations today, not elimination. However, it is universally acknowledged that tuberculosis targets are not achievable unless there is a dramatic escalation in TB control efforts and significant paradigm shifts in our approach (8, 9).

WHO has strongly recommended high-incidence countries scale up active case finding (ACF) and systematic screening in specific high-risk populations, such as the close contacts of index patients (10). However, integrating ACF into existing health care services is important to optimize resources and achieve sustainability (11).

The covid-19 pandemic had a devastating impact of the provision of TB services, and exacerbated access barriers to TB diagnosis and cure. There was a decrease of 50% or more in TB notifications in many countries (12).

Within the TB community, there is a consensus that to bring the global TB epidemic into the elimination phase, a comprehensive set of activities is needed with a focus on finding all cases, treating them promptly and correctly and preventing people infected with *Mycobacterium tuberculosis* from falling sick, based on the three tenets of **search, treat and prevent** (13).

1.2 Tuberculosis (TB) Disease

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis.* The disease predominantly affects the lungs (pulmonary tuberculosis) but can affect any other organ in the body (extra pulmonary TB). TB-like disease also affects animals caused by other mycobacterial species. Bovine tuberculosis, which is caused by *Mycobacterium bovis* also causes TB in humans, but has decreased as a public health problem since the introduction of milk pasteurization and improved animal husbandry (14, 15).

Mycobacterium tuberculosis is an airborne pathogen that can spread from person to person including through coughing, sneezing or having close contact with an infected individual. The main signs and symptoms of TB disease include persistent cough, weight loss, loss of appetite, night sweats, and fevers. TB is a global public health issue, however the majority of cases occur in South Asia and Sub Saharan Africa.

About a quarter of the global population is infected with the causative bacterium, *Mycobacterium tuberculosis,* and therefore considered to harbour latent infection which can develop into active disease months or years after the initial infection (16).Latent TB infection (LTBI) is defined by WHO as

"a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB" (17). People with LTBI do not feel sick and are not contagious. However, if the TB becomes active, disease transmission can then occur to other people, therefore treatment to eradicate the infection is essential to prevent disease in infected individuals and to interrupt transmission chains to reduce disease burden.

1.2.1 History of TB

TB disease has been known by many various names since ancient times including consumption, phthisis and the 'white plague'. In Nepali, TB is known as chayarogh, although the term TB is commonly used nowadays. TB infection is believed to have spread across human populations through trade routes. Domesticated animals such as goats, cows also probably served as transmission sources (18). The pathological signs of TB have been discovered in Egyptian mummies from around 3000 and 2400 BC, indicating that TB is indeed one of the most ancient of human diseases (19). TB was widely considered a death sentence until the German microbiologist Robert Koch discovered the causative agent of the disease in 1882: *Mycobacterium tuberculosis, or koch's bacillus*. TB epidemics were rampant throughout Europe and North America during the 18th and 19th centuries and it has been referred to as the "Captain Among these Men of Death", a name which reflect both its ubiquity and its high mortality. In Europe and North America, public health measures were initiated to combat the spread of diseases including TB, and socioeconomic conditions improved , which

drove a steep decline in TB incidence in the Western industrialized nations through the twentieth century (20, 21).

The Bacille Calmette-Guerine (BCG) vaccine was first administered in 1921 BCG vaccine is very effective for preventing severe disease in infants and children (22, 23). However, protective efficacy of BCG wanes over time, and the vaccine is not effective in protecting adults from TB disease, although efficacy estimates have varied widely between studies. (24, 25). The development of effective antituberculosis drugs, which began with the discovery of streptomycin in 1944, initiated the modern era of tuberculosis chemotherapy. Wealthy countries like Europe and North America were able to overcome the tuberculosis epidemic because of the discovery of antituberculosis drugs and better socioeconomic conditions during the 1950s – 1970s, however the TB epidemic continued unabated in poorer countries. The emergence of HIV in the 1980s precipitated a dramatic exacerbation of TB epidemics, because untreated HIV infection progressively destroys the innate immune system and increases susceptibility to TB. Multi Drug Resistant-Tuberculosis (MDR-TB) also began to be reported from multiple settings during the 1970s -1980s. The rise of MDR-TB and TB-HIV problems raised concerns for the wealthy countries with fears of resurgence of TB disease at the end of 1980s.

TB cases rose worldwide during the mid-1980s and the World Health Organization (WHO) declared that TB was a global emergency for the first time in history in 1993 (26-28).

Over 40% burden of global TB incidence is in the South East Asia region with over 170,000 MDR-TB cases, accounting for almost 40% of the global MDR TB incidence. Of the incident MDR TB cases in 2021, only 64,970 were detected and only 58,181 were enrolled in treatment. High TB burden countries in the SEA region are Bangladesh, India, Indonesia, Myanmar, Democratic People’s Republic of Korea, and Nepal (29). 9.9 percent of MDR-TB cases were Extensively Drug Resistant-TB (XDR-TB) (30).

Prior to the discovery of effective TB drugs, TB patients were screened for TB with tuberculin test, chest x-ray and BCG vaccination and isolated in “sanatorium care” to control the TB epidemic (20). Social taboo, discrimination, and fear to transmission of disease to family members led to a policy of isolating and TB patients in sanatoria.

Chemotherapy to treat TB was discovered in the 1940s and “long course treatment” which is 12-18 months TB treatment were provided to TB patients (28). Six months “short-course chemotherapy” treatment regimen was developed in a series of clinical trials in the 1970s. The sputum test has been recommended as the main diagnostic test for national TB programmes since 1974 (20). WHO proposed the “Directly Observed Treatment Short-course (DOTS) strategy in 1994 to fight the TB problem as per the statement of “the global emergency of TB” with five components – political commitment, quality assured sputum microscopy, standardized short course chemotherapy for all cases of TB under Directly Observed Treatment (DOT), uninterrupted supply of anti-TB drugs, recording and reporting system (28). The DOTS strategy was subsequently implemented in public health services as National Tuberculosis Programmes (NTPs) in most of the highly affected countries (31).

1.2.2 Causative Agent - Mycobacterium Tuberculosis

Robert Koch discovered *Mycobacterium tuberculosis* in 1882 and recognised its role in causing tuberculosis. Bovine TB was discovered and differentiated from the human strain by Theobald Smith in 1898. These two strains are pathogenic to humans (32). The closely related organisms are *M. africanum, M. bovis, M. microti, and M. smegmatis* are classified as the *M. tuberculosis* complex. These are also pathogenic to humans.

1.2.3 Modes of Transmission

Tuberculosis is primarily transmitted through droplet nuclei and droplet infection from pulmonary tuberculosis patients (33). Agent, host, environment and social factors all contribute to the transmission of TB disease.

Host factors such as malnutrition and comorbidities, including diabetes, HIV/AIDS, silicosis, hypothyroidism, hyadrenalism, can increase susceptibility to tuberculosis disease because the immune system is weakened (immunocompromised status). Smoking is a significant risk factor for TB disease due to lung damage.

Environmental factors such as poorly ventilated housing or living in overcrowded conditions, and poor air quality also increase the risk for tuberculosis.

Social factors are also important in TB epidemiology. The prevalence of tuberculosis is higher in population groups with low socioeconomic status , large family size, lack

of knowledge about the mode of spread. Occupations with increased TB risk include healthcare workers, particularly those in respiratory medicine, miners and construction workers. (15, 32). Poverty and infections are interrelated to each other and therefore poverty is a powerful determinant of tuberculosis. Poverty is also associated with lack of basic health general knowledge, adherence of TB treatment, modern health services utilization (34). Poverty fuels TB and TB fuels poverty.

1.2.4 Signs and Symptoms

The major signs and symptoms of tuberculosis are persistent cough (more than 2 weeks), haemoptysis, night sweats, fevers, chest pain, loss of appetite, weakness or fatigue, and weight loss. Latent TB infection is asymptomatic (16). Extrapulmonary TB (EPTB) patients may exhibit diverse symptoms, depending upon the affected site. Extrapulmonary TB symptoms may include pain associated with the affected area, low-grade fever, swelling of affected organs like lymph nodes, prolonged fever of unknown origin, chills, weakness, dyspnoea and malaise (35).

1.2.5 Diagnosis of TB disease

Tuberculosis disease should be diagnosed through complete medical history (present and past history, signs and symptoms), physical examination, chest X-ray and laboratory tests. The aim of laboratory tests is to identify the *Mycobacterium tuberculosis* bacteria in sputum, or other appropriate clinical sample.

Chest radiograph is used to detect chest abnormalities such as lesions in the lungs. Chest radiograph cannot be used to confirm the diagnosis of TB and must be interpreted by an experienced radiologist. Computer assisted reading of Chest X-rays for tuberculosis has advanced significantly in the last five years, and more than 12 commercial software solutions are now on the market. These may be used to identify anomalies on the chest radiograph, but cannot confirm a TB diagnosis (32). Following identification of an abnormal chest X-ray, the diagnosis should be confirmed through identification of *Mycobacterium tuberculosis* in a clinical sample

Sputum smear microscopy to detect the presence of acid-fast bacilli (AFB) is a simple, inexpensive technique and the primary method for diagnosis of pulmonary tuberculosis in low- and middle-income countries (LMICs), including Nepal. However it has significant limitations, particularly regarding low sensitivity of the test, which is

only around 50% of active pulmonary TB cases (36). Sensitivity is lower for children, people living with HIV/AIDS, extra pulmonary TB. Sputum smear cannot confirm *Mycobacterium tuberculosis* infection because Mycobacteria other than tuberculosis (MOTT) also stain positive on acid fast smear. Culture or molecular tests are required to confirm the presence of M. tuberculosis. However, culture is either unavailable or prohibitively expensive in majority of high burden settings and in practice sputum smear microscopy alone is still used as the primary diagnostic test for TB in the majority of high burden countries. While MOTT represent a significant proportion of AFB positive cases in low TB incidence countries, in high incidence countries an AFB positive smear is presumed to indicate active TB disease and testing for MOTT and is only conducted if the patient fails to respond to antituberculous chemotherapy. Smear microscopy is also not able to detect drug resistant TB (7).

All patients should be tested for drug resistance to ensure effective treatment, but this is not feasible for high burden countries and drug susceptibility testing is usually only carried out for treatment failure cases in Nepal and other LMIC. (37).

In the context of LMICs, many TB patients are undiagnosed, untreated and continue to be infectious, more sensitive diagnostic tests, tools are now widely available, including molecular diagnostic tests such as GeneXpert MTB/RIF test, myco-bacteriological culture. Clinical algorithms have also been evaluated and refined to detect TB more accurately, particularly for paediatric, HIV-associated and extrapulmonary TB (38).

GeneXpert MTB/RIF is a cartridge based molecular diagnostic test for the rapid diagnosis of TB disease which was first brought to market in 2010. It is also able to detect Rifampicin (RIF) resistance in less than 2 hours, whereas cultures can take 2 to 6 weeks and is not available in many places. In Nepal, mycobacterial culture is only available in the capital city, Kathmandu. GeneXpert MTB/RIF assay has many advantages such rapid time to result, quickly identify multi drug – resistant TB (MDR TB) through rifampicin resistance as a marker, minimal technical training needed to run the test (37) and therefore, WHO has urged to all the countries to expand access to rapid molecular tests for the detection of tuberculosis and drug resistant TB. Dr Tereza Kasaeva, Director of WHO's Global TB Programme, states that "The use of rapid molecular assays as the initial test to diagnose TB is recommended instead of

sputum smear microscopy as they have high diagnostic accuracy and will lead to major improvements in the early detection of TB and drug-resistant TB". She also emphasized that rapid molecular tests are urgently needed to ensure universal access, reducing transmission and increasing accurate treatment (39) .

The WHO consolidated guidelines and the associated operational hand book recommend GeneXpert MTB/RIF assay (Cepheid, USA), GeneXpert Ultra assay and Truenat assay (Molbio Diagnostics, Goa, India) to use as the initial test to diagnose pulmonary TB and to detect rifampicin resistance which replaces smear microscopy and culture. GeneXpert Ultra is a new cartridge for the GeneXpert assay which has increased sensitivity, but slightly reduced specificity. It is particularly suitable for diagnosis of paucibacillary samples, including pediatric, extrapulmonary and HIV-associated TB cases. The GeneXpert-XDR cartridge is also available to expand detection of drug resistance to a further six antituberculous drugs: isoniazid (INH), fluoroquinolones (FLQ), second-line injectable drug (SLID) (amikacin, kanamycin, capreomycin) and ethionamide (ETH). The GeneXpert-XDR cartridge does however require a more advanced 10 colour machine to process and therefore requires replacement of existing GeneXpert technology to be applied within health systems. The Truenat assay (MolBio Daignostics, India) is a new molecular test withy slightly more complex hands-on processing required, and marginally lower sensitivity than GeneXpert. Truenat MTB and MTB Plus can detect M. tuberculosis in clinical samples, whereas Truenat MTB-RIF Dx also detects resistance to rifampicin (12).

1.2.6 Diagnosis of Latent TB Infection

More than a quarter of the world population is infected by *Mycobacterium tuberculosis complex* (MTBC), with no evidence of clinically manifested TB disease (40). Infected persons are increased at risk of developing TB disease (40) and therefore TB preventative treatment (TPT) is useful to eradicate the infection and prevent the development of TB disease (41).

Latent tuberculosis infection (LTBI) is mainly diagnosed by tuberculin skin test (TST) also known as the Mantoux test or Hain test. In high income countries the IFN-y release assays (IGRA) are used for the diagnosis of latent TB infection. These tests are more expensive and complex to perform, but are not confounded by prior BCG vaccination. A test for latent TB must be combined with medical evaluation to exclude

active TB disease because neither TST nor IGRA are able to differentiate between latent and active infection(41). If an individual has a negative LTBI result combined with a history of exposure to an active TB case, they should receive counselling on signs and symptoms of TB and be advised to present for further testing if symptoms develop. LTBI treatment is essential to prevent TB disease and is more cost effective than treating TB disease(41).

New TB antigen-based skin tests (TBST) have recently been developed for the diagnosis of tuberculosis infection which were found to be accurate, acceptable, feasible and cost-effective for detection of TB infection compared with IGRA and TST(42). These tests may represent a simpler alternative to the conventional tuberculin skin test (TST) and Interferon-Gamma Release assays (IGRAs) but are not yet widely available in high volume. (42).

1.2.7 Treatment of Tuberculosis

TB drugs should be easily available free of cost to every patient. The Nepal National TB Management Guidelines state: “For TB patients to be effectively treated, TB patients must be given the right drugs in the right combinations, appropriate dosage, administered correctly and regularly for the appropriate duration of time under observation” (35). Incomplete treatment puts the patient at risk of relapsing, developing bacterial resistance and also increases the risk of infection in the community with resistant organisms and spread of TB to other people (15). Some challenges with adherence of TB patients are the long duration of TB treatment regimens, lack of awareness, inadequate nutrition, poverty, and side effects of drugs. Bactericidal drugs are Rifampicin (RMP), INH, Streptomycin, Pyrazinamide. Bacteriostatic drugs are Ethambutol, Thioacetazone (15). The standard first line regimen for TB applied by most national TB programmes, is 2 months of daily isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of daily rifampicin and isoniazid. (2HRZE/4RH). Identified drug resistant cases should ideally be managed according to the drug susceptibility profile of the individual case. In practice, many national TB programmes apply a standardised MDR TB regimen for cases identified as resistant to rifampicin. Although pragmatic due to lack of capacity for second line drug susceptibility testing, such approaches can amplify drug

resistance and lead to both treatment failure, and ongoing transmission of drug resistant strains.

Standard pulmonary TB cases should have follow up examination of sputum at 2 months, end of 5 months and at the end of treatment (6 months) to monitor the treatment progress. The treatment regimen for Extra pulmonary TB patients (EPTB) depends on the form of extra pulmonary TB. Nine to 12 months treatment should be considered for the complicated, severe forms of EPTB (35). TB treatment is usually administered through health systems as Directly Observed Treatment (DOT) to ensure effective treatment. TB patient who are not able to attend the treatment Center regularly because of various reasons such as long hours walking from home are often considered for schemes such as Community Based DOT (CBDOT). Community volunteers or family members can supervise the treatment at or near the patients home.

1.2.8 Multidrug-resistant tuberculosis (MDR-TB)

Multi Drug Resistant (MDR)-TB is defined as resistance to the first line TB drugs Isoniazid and Rifampicin. MDR TB is one of the major threats to TB control program in many countries, including Nepal. Multidrug-resistant tuberculosis (MDR-TB) is a critical public health issue and the leading killer due to antimicrobial resistance globally. The WHO Global TB Report estimates that globally 3-4% of all TB cases are resistant to at least isoniazid and rifampicin (multi drug resistant TB or MDR TB).The first systematic Nepal prevalence survey in 2018 revealed an incidence of TB in Nepal that is 1.6 times higher than the previous estimate, and consequently Nepal was recognised as one of MDR TB burden countries, Nepal was added to the WHO list of high MDR TB burden countries in 2021 and a full TB drug resistance survey is planned for 2023. .

Resistance to a broader spectrum of TB drugs is an increasing problem and has also been classified by WHO to enable development of clinical management guidelines, and monitoring of incidence. There are two major categories beyond MDR TB: pre XDR-TB and XDR-TB.

The definition of pre-XDR-TB adopted by WHO in 2021 is: “TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that fulfil the definition of

MDR/RR-TB and which are also resistant to any fluoroquinolone". The definition of XDR-TB has also been revised to pre-XDR-TB plus at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid) (43).

Shorter regimens, including the 'Bangladesh regimen' have recently been developed and shown to be effective in randomized controlled trials such as the STREAM, NIX-TB, BPal and NeXT trials (44). These regimens represent a significant advance in MDR TB treatment, with reduced toxicity and removal of the need for daily injectable drugs.

The current guidelines for Nepal recommend shorter standardized treatment regimen (SSTR; 4-6 Am Mfxh Eto Hh Cfz E Z / 5 Mfxh Cfz E Z), longer regimen 1 (Bdq(6), 18 Lfx,Lzd,Cfz,Z) and longer regimen 2 (Bdq (12),18Lzd, Cfz, Cs,Z) (35).

In 2022, the World Health Organization announced approval of novel drug-resistant tuberculosis regimens including a novel 6-month treatment regimen based on bedaquiline, pretomanid and linezolid (BPaL). BPal in combination with moxifloxacin (BPaLM) can be used in patients aged 15 years or more with MDR/RR-TB or pre-XDR-TB. If a patient receiving BPaL combination therapy has a slow response to therapy, a 3 months extension is possible which would bring the total duration to 9 months (45). These newer regimens are generally better tolerated with dramatically shorter durations than the old 18+ month regimens, which can significantly improve treatment outcomes due to improved completion rates. Shorter regimens also substantially reduce the broader long-term social, psychological and economic consequences of MDR TB.

However, transition to newer, shorter TB regimens within national TB programmes has been hampered by lack of adequate capacity for high-quality second line drug resistance testing. Patient advocacy groups are campaigning strongly for scale-up and improved access to these improved regimens.

1.2.7 Directly Observed Therapy Short Course (DOTS)

DOTS is a core component of the WHO STOP TB strategy. DOTS is used widely through existing primary health care network and is has been considered one of the successful components of TB control programmes standardization. However technical, logistical, operational and political aspects of DOTS play a crucial role to ensure success (31). Directly Observed Treatment, Short Course (DOTS) started in Nepal from 1996 with the standard five elements; case detection by sputum smear microscopy, regular drug supplies, standard recording and reporting system, assessment of treatment outcomes and standard short course chemotherapy administered under standardized case management conditions (46).

The main purpose of DOTS is to increase treatment completion, reduce drug resistance and relapse, and support to TB intervention to reduce the transmission in the community (31). However, despite providing drugs free of charge at point of care, many people affected by TB struggle to reach TB services and DOTS clinics for daily drug administration. TB patients often have low socioeconomic status and therefore unable to regularly attend for medication at the DOTS Centre because of challenges such as having to work or risk losing self-generated income or employment, being the main source of income for the household, or difficult geographical terrain (distance, lack of or roads transport). Lack of knowledge of TB patients can be a common reason for dropping out of treatment (47, 48), with patients not aware that the full regimen must be completed to achieve a cure. The management of MDR TB is more complex, requiring longer treatment courses, toxic and expensive second line drugs (49). The causes of high morbidity and mortality among TB cases in Nepal are multifactorial, including longer duration of treatment, alcohol consumption during treatment, inadequate intake of nutritious diets, private pharmacy prescribe and distribute anti TB drugs without national guideline, private medical practitioner prescribe the TB drugs as not align with national protocols and also social issues such as poverty, illiteracy, stigma, cultural beliefs, traditional healers, distance from health facilities (50-52).

1.2.8 Diagnostic Gap in Tuberculosis

TB is the leading infectious disease killer worldwide, overtaken briefly by COVID during its peak in 2020-2021.

The World Health Organization (WHO) estimates that 10 million people develop tuberculosis (TB) disease annually, of which four million were either unreported or remain undiagnosed and untreated in 2020 (53). TB was responsible for the deaths of 1.5 million people in 2020, the majority of which occurred among vulnerable people residing in low and middle income countries (LMICs) where health services are severely under resourced (1).

For multidrug resistant TB, the diagnostic gap is even more severe. Approximately half a million people are affected by multi-drug resistant TB every year, and only one in three people with MDR TB are being diagnosed and treated through national TB programmes (14). Some progress has been made on MDR TB testing, detection and treatment since the scale-up of rapid molecular based testing for rifampicin resistance, which can be used as a marker for MDR TB. Sixty percent of bacteriological confirmed TB patients were reported to be tested for rifampicin resistance globally in 2019, although this is probably an overestimate.

Systematic screening for TB symptoms among people living with HIV is an essential component of an effective TB strategy and strongly recommended within WHO guidelines for countries. In 2019, data from 86 countries showed 7% of people reported to be newly enrolled in HIV treatment were also diagnosed with TB. Of 172 countries reporting data, there was a 12% increase in new and relapse TB patient with documented HIV test result compared to 2018.

Early diagnosis and prompt, accurate treatment are essential components for high quality health services (54). While progress in access to TB diagnostic services is being made, the pace of progress is slow and intensified investment and service provision is urgently required to close the diagnostic gap and reach the 40% of TB cases not accessing diagnosis through national TB programmes every year.

Barriers to access for individuals with active TB in TB care cascade in LMICs are multifaceted and include hard to reach health facilities, stigma, limited availability of TB diagnostic tests, limited availability of doctors and laboratory technicians, inadequate knowledge about TB, insufficient financial and human resources, unable to register for treatment after diagnosis, unable to complete treatment, experience TB recurrence or death after having completion of therapy. High quality innovative action-

oriented research to understand and address and close these gaps in the care cascade (55).

The diagnostic capacity of the health care system (health system level) and services utilization from community (patient level) are essential factors to achieve universal health coverage (UHC). Highly trained human resources in place, alongside leveraging new technologies are essential to fulfill the diagnostic gap. People with tuberculosis are trapped in a vicious cycle of poverty.

Early diagnosis and prompt, accurate treatment are essential components for high quality health services (54). While progress in access to TB diagnostic services is being made, the pace of progress is slow and intensified investment and service provision is urgently required to close the diagnostic gap and reach the 40% of TB cases not accessing diagnosis through national TB programmes every year.

We need to make faster progress to prevent, detect and treat TB in order to close the diagnostic gap and ensure that every case, everywhere receives early diagnosis and is supported to complete appropriate chemotherapy to achieve a cure.

Screening and testing for TB remain major challenges for fragile, under-resourced health systems. Although coverage of access to TB diagnostic facilities is relatively high, these facilities are often very simple and rely on both passive self-referral by symptomatic individuals and the insensitive diagnostic test of sputum smear microscopy. Therefore, many individuals do not present to health services, or receive a false negative diagnosis with a sputum smear negative result

1.2.9 Prevention and Control

Prevention of TB infection and control progression from infection to disease are essential component to reduce TB incidence. TB preventive treatment, treatment of people with latent TB infection, house hold contacts/social contacts of people with TB and other risk groups, vaccination of children with BCG vaccine. Health Promotion such as improvement of living standard through social development is crucial in reduction of tuberculosis. It includes availability of well ventilated, lighted, personal hygiene, environmental sanitation, good nutrition, compatible working conditions, healthy habits (32). Specific Protection such as the protective measures are immunization (BCG vaccination) however it makes small protection for TB prevention,

chemoprophylaxis, isolation of cases, behaviour change and disinfection. Early Diagnosis and Prompt Treatment are another important interventions. Many cases are hidden in community because of the stigma and spreading in geometrical progress. As per WHO, Government is implementing passive case finding and active case finding strategy to utilise the modern health services. TB confirmation was made by sputum examination and radiography. Effective chemotherapy is the best means of reduction of TB infection in the community (32).

Global TB Report (2019) mentioned that major health care interventions of TB prevention are TB prevention treatment, prevention of transmission of *M. tuberculosis* through infection prevention and control and BCG (bacille Calmette-Guerin) vaccine to children. Latent TB is defined that *M. tuberculosis* is persistence in human body but not clinically manifested evidence of active TB disease. Latent TB should be treated properly. WHO recommended treatment regimens are Rifapentine and isoniazid once a week for 3 months (3HP) which are popular in different parts of the world, rifampicin plus isoniazid daily for 3 months (3RH), rifampicin once a day for 4 months (4R), and isoniazid once a day for 6 months (6H) or longer duration (14). This is a novel regimen that is not widely used yet. BNMT Nepal is planning to introduce this novel regimen first time in Nepal with close coordination with the Government of Nepal - NTCC and MoHP.

WHO also updated the recommendations of two other TB preventive treatment regimens – 4R in high burden settings and isoniazid and rifapentine (1 HP) once a day for 1 month. This novel regimen will be published soon along with operational guidelines at the country level (14).

1.3 Global Scenario of TB

Tuberculosis (TB) is one of the top ten causes of death in the world. TB remains a global public health crisis and major economic burden, disproportionately affecting lower- and middle-income countries. Although a steady reduction of TB prevalence worldwide of between 1-3% per year has been achieved in the last decade, at the current glacial pace the disease will continue to claim millions of lives and cost billions of dollars to the global economy before elimination is achieved.

TB remains a global public health threat and major economic burden, disproportionately affecting lower- and middle-income countries. In 2021 WHO estimated 10.6 million people (95% UI: 9.9–11 million) fell ill with TB globally. This represents an increase of 4.5% from the 10.1 million estimates in 2020, due to the impact of the COVID-19 pandemic on TB control programmes globally. Similarly, COVID-19 reversed years of slow but steady progress in declining TB incidence of around 2% each year. In 2021 the TB incidence rate (new cases per 100 000 population per year) is estimated to have increased by 3.6% compared to 2020, a small but devastating rise after years of slow decline.

In 2021, eight countries accounted for more than two thirds of global TB cases: India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and Democratic Republic of the Congo (2.9%) About 40% of TB cases are concentrated in South Asia (Nepal, India, Bangladesh, Pakistan, Bhutan, Myanmar, Afghanistan, Sri Lanka and Maldives) (56).

In 2021, tragically, TB deaths also rose for the first time in a decade due to the impact of the COVID-19 pandemic. Between 2005 and 2019, TB deaths steadily decreased. In 2021, there were an estimated 1.6 million deaths due to TB.

TB is a major cause of mortality among people living with HIV and therefore WHO disaggregates deaths in HIV-infected and uninfected individuals. 1.4 million deaths were estimated in HIV-negative people (95% uncertainty interval [UI]: 1.3–1.5 million) and 187 000 (95% UI, 158 000–218 000) among HIV-positive people. This was an increase of 0.1 million compared to the 1.5 million deaths in 2020. The first milestone of the End TB Strategy was originally set in 2015 as a 35% reduction in TB deaths between 2015 and 2020. Considerable progress had been made towards this milestone prior to COVID, but much of the gains were lost during the pandemic and the net reduction in TB mortality between 2015 and 2021 was consequently only around 6%(1).

1.3.1 The Sustainable Development Goals

In 2000 the UN declared the Millennium Development goals ‘Health for all 2000’ for 2000-2015 which included targets for HIV and malaria reduction, but no specific target for TB. In 2015 the millennium development goals were succeeded by the Sustainable Development Goals (SDGs), with 17 Broad overarching goals. SDGs encapsulate a

broad agenda to transform our world. The consolidated goal on health is SDG 3, defined as “Ensure healthy lives and promote well-being for all at all ages”, Target 3.3 of SDG 3 , explicitly mentions TB: “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne diseases and other communicable diseases” (57). The terms “ending epidemics” has been an important element of global health strategies developed by WHO, End TB Strategy and the Joint United Nations Programme on HIV/AIDS (UNAIDS) for the post-2015 era. The WHO’s End TB strategy envisions a world free of TB (Zero deaths, disease, and suffering due to TB) with a goal to end the global TB epidemic. There are multiple links between the different SDGs goals. TB, poverty and nutrition are closely interrelated to each other. Similarly, income loss, improvement of living conditions, equal rights to health care treatment, gender equality, cultural barriers, climate change are also interrelated to each other and therefore multisectoral efforts need to be addressed comprehensively to achieve the TB free world and ultimately SDGs goals (58). Several efforts with important events set out and drafted road map to meet SDGs will accelerate the end of tuberculosis. Time line for action for major events are WHO end TB Strategy established 2014, UN SDGs adopted 2015, the WHO Global Ministerial conference on ending TB in the sustainable development era 2017, UN high-level meeting on TB 2018, Global Fund replenishment conference; Global plan to end TB update 2019, End TB Strategy milestones due; UN Secretary-General’s report on progress towards UNHLM on TB commitments 2020, UNHLM targets due 2022, End TB Strategy milestones due 2025, SDGs due; End TB Strategy milestones due 2030, End TB Strategy targets due 2035.

1.3.2 The End TB Strategy

The ambitious global strategy for TB elimination is known as the ‘END TB strategy’ and was also launched in 2014to integrate with the SDG(3, 59, 60).

The End TB strategy had a vision of “a world free of TB – zero deaths, disease and suffering due to TB by 2035”. It was followed by the Moscow Declaration to End TB, and The Political Declaration at the UN high-level Meeting on TB in 2018.

It has been recognized that multi sectoral efforts are required to end the TB epidemic. “Multisectoral accountability framework” developed during WHO Global Ministerial conference 2017 and also includes high level political commitment from national and

global level (61). Despite the efforts of Government and external development partners, TB still remains one of the leading causes of death in the world

The World Health Organization (WHO) End TB Strategy was adopted by all the WHO member states at the World Health Assembly in 2014 and made vision of “a world free of TB – zero deaths, disease and suffering due to TB by 2035”. The strategy goals aimed at achieving universal health care and social protection, no TB – affected households facing catastrophic costs due to TB. 95% reduction in the absolute number of TB deaths and 90% reduction in the TB incidence rate in compared with the 2015 baseline. The overall goal is to “End the global TB epidemic” (**Error! Reference source not found.**).

Table 1.1:WHO END TB Strategy and Global Target to END TB

Vision	**A WORLD FREE OF TB** **- Zero deaths, disease and suffering due to TB**			
Goal	**END THE GLOBAL TB EPIDEMIC**			
Indicators	**Milestones**		**Targets**	
	2020	**2025**	**SDG 2030**	**END TB 2035**
Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of TB-affected households facing catastrophic costs due to TB (level in 2015 unknown)	0%	0%	0%	0%

Source: WHO Global TB report, 2020

WHO End TB Strategy emphasizes early diagnosis, including universal drug susceptibility testing (DST) and systematic screening of contacts and high-risk groups as vital strategies to reduce the case detection gap (60). WHO also recommends active case finding (ACF) among selected high risk groups such as household

contacts, people living with the human immunodeficiency virus (PLHIV), prisons and urban slum dwellers (38).

The status of TB scenario in different regions, is shown in table 1.2

Table 1.2:Key indicators for monitoring the implementation of the End-TB Strategy

Estimates for 2017	**Global**	**SEARO**	**Nepal**
Incidence all forms	133/100,000	226/100,000	152/100,000
TB Mortality	17/100,000	32/100,000	23/100,000
Treatment success rate	81%	75%	91%

Source: The WHO Global TB Reports 2018

1.3.3 Moscow Declaration to end TB

WHO and the Ministry of Health of the Russian Federation co-hosted the first global ministerial conference convened on TB on 16-17 November 2017. Member states committed in four areas: advancing the TB response within the SDG agenda, ensuring sufficient and sustainable financing, pursuing science, research and innovation and developing a multi sectoral accountability framework (14).

1.3.4 The Political Declaration at the UN High-level Meeting on TB in 2018

UN high level meeting (UNHLM) on TB was convened in New York on 26 September 2018 with the title on United to End TB: An Urgent Global Response to a Global Epidemic. The main objective of the meeting was reaffirmed the members about political commitment and accelerate the progress on SDGs, End TB strategy and Moscow Declaration (14). It has been revealed that political will is largest gap in the fight against TB and set ambitious targets and endorsed the political declaration by world leaders.

Global Plan to end TB 2018 - 2022: The Paradigm Shift prepared plan to set up the steps and in order to track the end TB. The plan aims to reach the targets of the UNHLM Political Declaration by 2022 and achieved the SDGs of ending TB epidemic by 2030. The TB UNHLM Political declaration builds further commitments for further finding and treating TB to achieve 90-(90)-90 people-centred global targets. The global

plan articulates to reach at least 90% of people in need of TB treatment and prevention, reach at least 90% of people in need of treatment and prevention among vulnerable, underserved, at risk population and achieve at least 90% treatment success (58). All the countries should fulfill their UNHLM commitment with the involvement of the Government and relevant stakeholders and therefore leave no one behind.

1.4 TB in the South Asian Context

Evidence suggests that missed diagnosis of TB is prevalent in South Asia and about 43% burden of TB incidence in SEA(29) (56). This maintains a reservoir of infectious people, a potential source of onward transmission and a significant challenge to eradication of the disease. One third of the world population or about 4.9 million prevalent TB cases are resided in South East Asia Region. Huge economic impact of TB occurred in their productive years (62, 63) however WHO annual report (2016) revealed that 41% of the global burden of TB incidence in South East Asia Region. India and Indonesia have the largest number of cases 23% and 10% of the global total respectively. In Nepal, TB cases will be booming after having the prevalence survey.

About 40% of TB cases are concentrated in South Asia (Nepal, India, Bangladesh, Pakistan, Bhutan, Myanmar, Afghanistan, Sri Lanka and Maldives) with 4,028,165 cases and TB deaths 38% (681,975 deaths) of the global burden. South Asia accounts a third of global MDR TB burden estimated at about 184,336 multi drug resistance (MDR) TB cases among notified TB cases. It has been estimated that 70% of the MDR patient are not treated in South Asia region and spreading to general population in geometrical progress (54, 56). 27% of the world's TB cases are concentrated on India (14).

Table 1.3:Estimates of TB Burden in the SAARC Region 2019

Country	Population ('000)	Incidence		Total TB Mortality	
		Number (Best estimate)	Rate* (Best estimate)	Number	Rate*
Afghanistan	38,000	72,000	189	9,920	26
Bangladesh	163,000	361,000	221	38,150	23
Bhutan	760	1,300	165	141	19
India	1,366,000	2,640,000	193	445,500	33
Maldives	530	190	36	11	2
Nepal	290,00	68,000	238	17,220	59
Pakistan	217,000	570,000	263	43,900	20
Sri Lanka	21,000	14,000	64	774	4
Total	1,835,290	3,726,490	203	555,616	30

*Source: WHO Global Tuberculosis Report 2020, *Rates are per 100 000 population*

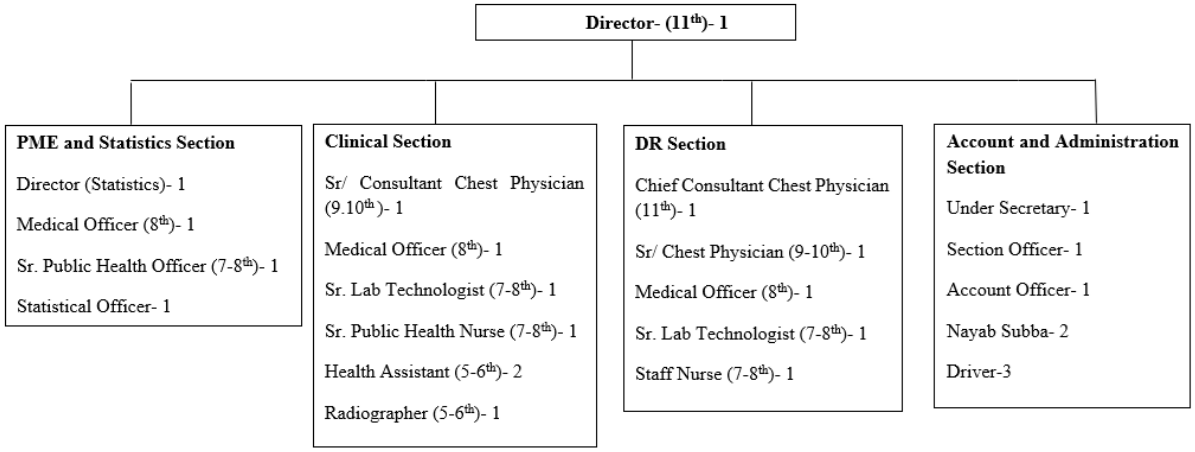
1.5 TB Control Programme in Nepal

In Nepal, The TB control programme was started by the Government of Nepal from “Tokha Sanatorium” to care for TB patients in 1937. The sanatorium was situated in the north of Kathmandu valley. The Central Chest Clinic (CCC) was established to diagnose and treat TB patients on domiciliary basis on 1951. Ultimately the National Tuberculosis Control programme started with a tripartite agreement between government of Nepal, WHO and UNICEF in 1965. A preventive and promotive programme started to be delivered during that time and Japan International Cooperation Agency (JICA) supported the government to establish the National Tuberculosis Centre (NTC) in Thimi, Bhaktapur at central level and Regional Tuberculosis Centre (RTC) at the regional level in Pokhara in 1989.

The National Tuberculosis Control Center (NTCC) is under the umbrella of the Ministry of Health & Population and Department of Health Services (DoHS) and provincial and local governments deliver preventive, promotive, curative and palliative health care services along with planning, monitoring and evaluation, human resource, and financial management. The TB programme is vertical however it has been integrated and implemented within the health systems of the Government of Nepal through 135 public hospitals, 2168 non-government organizations, 196 primary health care centers (PHCCs), 3806 health posts and 51,402 female community health volunteers (FCHV) (64). The DOTS strategy was adopted as the national policy for TB control in 1996, and DOTS based TB control services were provided in all the 75 districts.

As per DoHS annual report (2019/20), TB services were operated through 4,955 TB treatment centers. There are 765 microscopy centers and 72 GeneXpert centers as diagnostic services in the country. Treatment services for drug resistant (DR) TB are provided through 22 drug resistant TB treatment centers and 86 sub-centers and 7 DR TB hostels. At the central level, culture and drug susceptibility testing services are provided by the TB reference laboratories at the National TB Centre (NTC), Bhaktapur, and GENETUP/NATA, Kathmandu(65). The National Strategic Plan (NSP) to End TB (2021/22-2025/26 has been formulated to be used as a policy guideline in federal level, provincial and local levels (59).

Figure 1.1: Ministry of Health and Population, National Tuberculosis Centre, Organogram



1.6 TB in Nepal

Nepal is struggling to eliminate TB. TB is the 7th leading cause of death, and the, number one killer of the infectious diseases, killing at least 46 Nepali people daily. Nepal's National Tuberculosis Centre (NTC) reports that 15 million people, almost half of the population, are infected with TB (66). The first national TB prevalence survey for Nepal in 2018 showed that TB cases were dramatically higher than previously estimated by WHO. Previous estimates were based on incomplete data from small studies and case notifications. The TB burden was 1.6 times higher than previously estimated by WHO. The survey revealed that about one hundred and seventeen thousand (117,000) people are living with TB disease in Nepal and about sixty-nine thousand (69,000; male 67% and female 33%) people develop tuberculosis in Nepal every year, with 17,000 deaths. The national prevalence of TB is 416 people in every 100,000 and there are 245 new TB cases for every 100,000 people in Nepal each year (the incidence of TB). This means that around 35,000 TB cases are 'missing' from national notification data in Nepal each year (4).

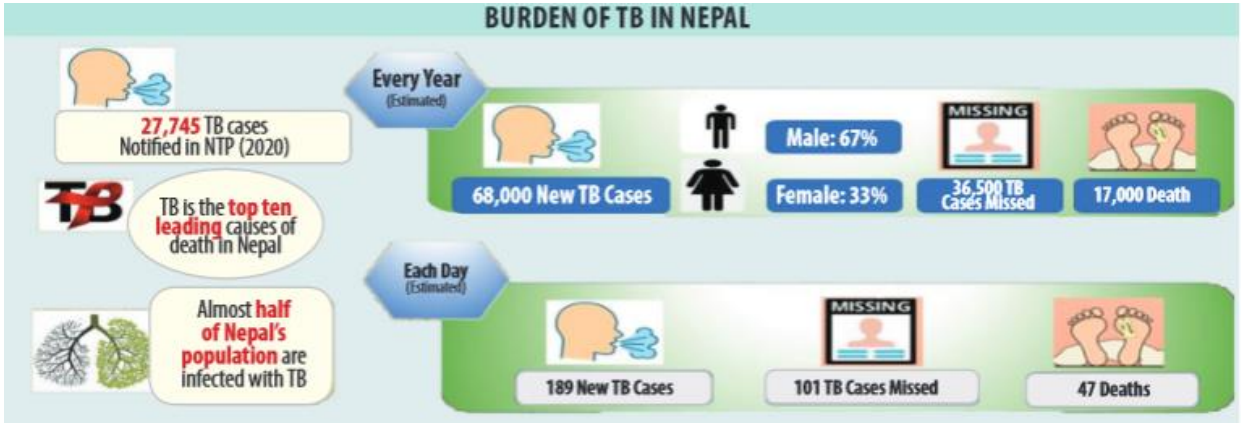
Table 1.4: Comparison of TB burden estimates for Nepal before and after the 2018 national prevalence survey.

Year	Incidence (all forms)	Prevalence (all forms)	Mortality (HIV -ve& +ve)
2018 New estimates	69,000 (245 per 100k)	1,17,000 (416 per 100k)	17,003 (9,000-26,000)
2018 Prior estimates	42,000 (151 per 100k)	60,000 (215 per 100k)	5,500 (3,900 - 7,400)
Revised burden, higher by:	1.6	1.8	3.1

Each day, there are 189 new TB cases new cases, 47 deaths, with 101 TB cases missed from diagnosis each day in Nepal (66) (**Error! Reference source not found.**).

These cases are not notified in the government system and it is largely unknown whether they are receiving the correct care and treatment. Many will receive incorrect diagnosis and care from private providers. There is a high risk of developing drug resistant TB with incorrect treatment and this is extremely difficult to treat - the drugs for drug resistant TB can have severe side effects which can lead to life-long disability- including deafness. The medicines for MDR TB usually have to be taken for over a year, although shorter, better tolerated regimens are now becoming available.

Figure 1.2:TB burden in Nepal



Source: NTCC Tuberculosis Profile FY 2076/77 (2019/20)

Urgent action with innovative interventions, and systematic implementation of effective tools are needed to accelerate the TB response in Nepal to achieve the End TB targets (4).

The Nepal National Strategic Plan (NSP) TB 2015 - 2020 set the goal aligned with SDG goal aims to reduce the incidence of current status 158 case per 100,000 (2015 where TB NSP started) to 20 cases per 100,000 by 2030. The target breakdown is shown in table 1.4. However little progress has been made, with TB case notification remaining largely stagnant and MDR TB increasing. The COVID-19 pandemic severely disrupted TB services and caused case notification to plummet. Although case notification recovered to pre-pandemic levels in 2022, there remains a significant case detection gap.

Table 1.5: SDG Goal: Reduce incidence of current status 158 case per 100000 to 20 cases per 100000 by 2030

Indicator	**2015**	**2019**	**2022**	**2025**	**2030**
Incidence/100000	158	85	67	55	20

Table 1.6:TB Indicators in Nepal, India, Bangladesh and Pakistan

	Nepal	**India**	**Bangladesh**	**Pakistan**
Population	29 million	1.342 billion	149 million	185 million
Incidence	156 per 100,000 population	211 per 100,000	225 per 100,000	270 per 100,000
Mortality	20 per 100,000 population	32 per 100,000 population	45 per 100,000	23 deaths per 100,000
TB Treatment Coverage	70%	63%	62%	69%

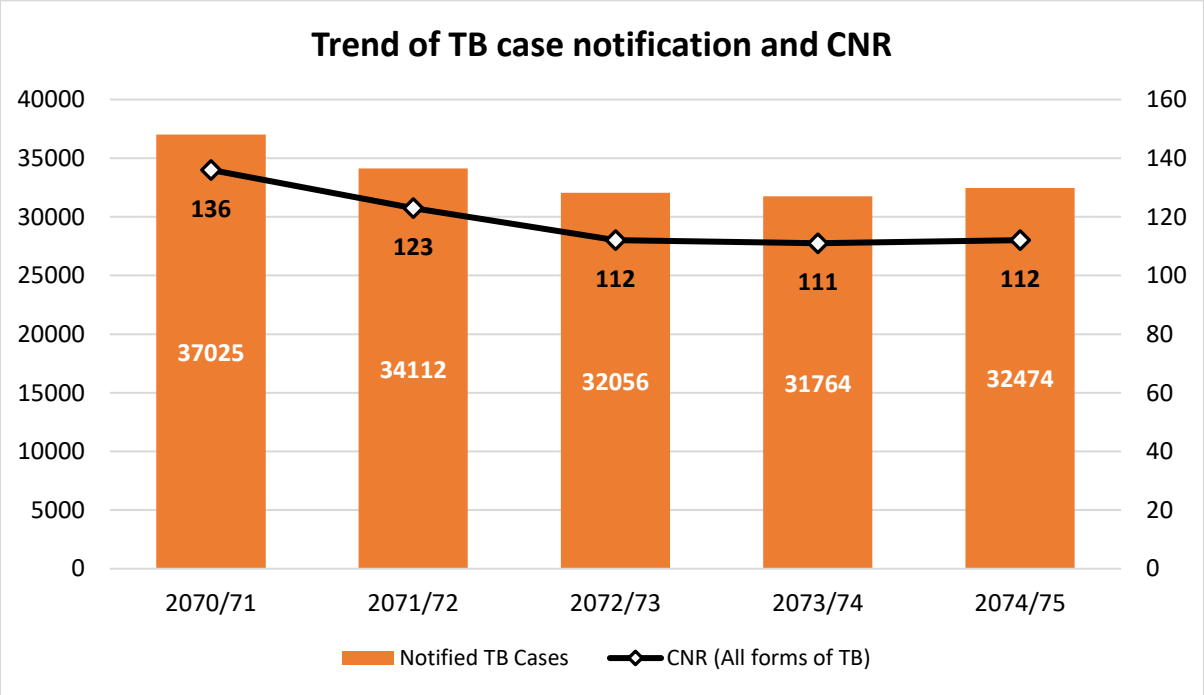
Source: Annual reports (Population, Incidence, Mortality)

1. Nepal NTP Annual report 2017
2. TB India Report 2018
3. Bangladesh Census 2011
4. Pakistan NTP Annual Report 2016

TB Treatment Coverage Source: WHO Global Health Observatory data repository apps.who.int/gho/data/view.main.57060ALL

WHO recommends that new innovation are key to fight tuberculosis especially innovations on strategy, diagnostics, new drugs and universal access to health services (63). Active case finding (ACF) is of proven benefit for people with tuberculosis and their close contacts with patients and community people. However, evidence of the most effective methods to implement ACF is lacking.
TB National Strategic Plan (NSP) 2016 – 2021 set the vision of TB free Nepal with the goal to decrease the TB incidence in Nepal by 20% by 2021 in comparison to the baseline value of 2015. Case notification rates have been stagnant in the last decade (table 1.6) and the 3 year trend was 112,111,112 per 100,000 people per year (2072/73, 2073/74, 2074/75 nepali calendar [2015/2016, 2017/2018, 2018/2019 international calendar) respectively when this thesis began. Annual TB case notification rates have continued to decline, exacerbated by COVID-19.

Figure 1.3:Trend of TB case notification and CNR



Source: NTP Annual Report 2074/75 (2018)

Nepal must close the case detection gap by diagnosing and treating every case of TB with high quality care. The country will not achieve the target to increase case notifications by at least 20,000 additional cases by 2025 as described in the country's National Strategic Plan.

In Nepal, National Tuberculosis Care Center (NTCC) is the main responsible body to deliver the tuberculosis program under the Department of Health Services (DoHS) and Ministry of Health & Population (MoHP). Main responsibilities are formulating programme policies, strategy, planning, monitoring and quality assurance (66). In the context of decentralized systems, Nepal has aligned the roles and responsibilities in various level the quality service provisions of tuberculosis services respectively. National level (NTP) - TB technical working group (TWG) in National Tuberculosis Programme, Provincial Health Directorate (PHD) office, District level, Local level (Palikas), Health Facility and Health Worker levels, DOT/Treatment Provider at the Community level (CB DOT Provider), Patient and Community level (35).

In Nepal, the health facilities are under the authority of the Provincial Health Directorate. Public health services including TB programme are delivered by 11 central level hospitals, 125 provincial hospitals, 77 health offices, 198 primary care centers, 3,808 health posts, 374 urban health centers, 299 community health units, 59 other health units. There are also 11,974 primary health care and outreach clinics, 15,853 EPI/outreach clinics and 51,420 female community health volunteers provide health service in Nepal (66).

1.7 Impact of Covid-19 Pandemic on TB

In 2020, The world, including Nepal, faced double burden of two pandemics: Covid-19 and Tuberculosis. The mode of transmission is similar in both diseases, both can present with respiratory systems and both cause infection related morbidity and mortality. Both diseases cause major disruption such as socio-economic effect including catastrophic costs to individuals and households, isolation, stigma and discrimination.

There was a big decline in TB case notification in high burden countries including Nepal. Many countries reported a decrease of 50 percent in TB notifications. India reported big drops of number of TB cases notifications. Approximately half a million TB cases were not detected in 2019 (12). The Covid-19 pandemic destroyed fragile and struggling TB programme interventions Major investment efforts and TB funds have been diverted to manage the Covid-19 pandemic, and shown that funding can be mobilized for infectious diseases if political commitment is strong. There is an

urgent need to continue to mobilize funding for innovative research, effective interventions, better tuberculosis management, universal health coverage (67, 68).

Covid-19 has caused major disruptions and yet also new opportunities and advances in infectious disease management programmes as well. Real time data gathering through covid-19 apps, artificial intelligence, tele health and digital, drug support services, people and delivery systems such as E-pharmacy, contact tracing while responding to covid-19 were rapidly developed and deployed. Many improvements can be applied to the TB programme intervention including social and behavioral aspects, masks for TB patients and health care workers like covid-19 protection. Such interventions and, digital tools can be used, to address the TB pandemic.

1.8 Passive Case Finding

People affected by TB are usually aware about their symptoms if they are diagnosed by passive case finding (PCF). PCF is defined as the symptomatic patients who seek medical care services on their own at health facilities to detect TB. It has been widely promoted in developing world with DOTS strategy (69). PCF is sufficient in low TB prevalence areas and therefore other case finding strategy may not be required if health facilities are functioning effectively (70). Many TB endemic countries rely on passive case finding to detect the TB cases however this strategy is not adequate to detect the undiagnosed TB cases in the community. Research revealed that many TB cases were missed by the health system and spreading infection in families and communities (10, 71). Many people with presumptive TB do not seek medical care at health facilities and even TB affected people face multiple barriers along the pathway to illness, diagnosis and treatment because of multiple reasons such as long distance to health facilities, financial constraints, poverty, stigma, discrimination, health systems delays, opening hours of health facilities, health professionals behavior etc. and therefore advocacy, awareness, communication, social mobilization and community based active case findings are needed for the utilization of health services. PCF for TB has not been adequate (72). PCF using sputum smear microscopic is not sufficient. Many surveys including prevalence surveys in different countries revealed that there are many undiagnosed TB cases and seeking care and diagnosis problems. Early diagnosis and treatment of smear positive TB cases are prime priority of reducing transmission. Passive case finding have many barriers such as reaching the

poorest, hard to reach areas and vulnerable groups, costs, accessing quality care. ACF reduce TB transmission and reduce the TB incidence, reduce catastrophic costs, contribute to reduce suffering (73).

1.9 Barriers and Delays to Seeking Care of Tuberculosis

Delays in diagnosis of tuberculosis may lead to severity, mortality and enhance transmission in the community (74). Priority is given to passive case finding in developing countries like Nepal. It is based on diagnosing infectious (suspected) cases of tuberculosis usually through direct microscopy of sputum specimens obtained from persons who present themselves in the health facilities (75). The national TB control programs directly observed treatment with short course (DOTS) strategy emphasizes passive case finding which may lead to delay diagnosis (WHO, 2003). Other hand, active case finding may also not improve the efficacy of the existing global DOTS strategy (76). Further research is needed to for the responsible of delay in diagnosis of TB. Studies revealed that health care seeking behavior is one of the barriers to delay on TB case diagnosis (77). Current case finding strategies under the DOTS strategy adopted globally need to be revised.

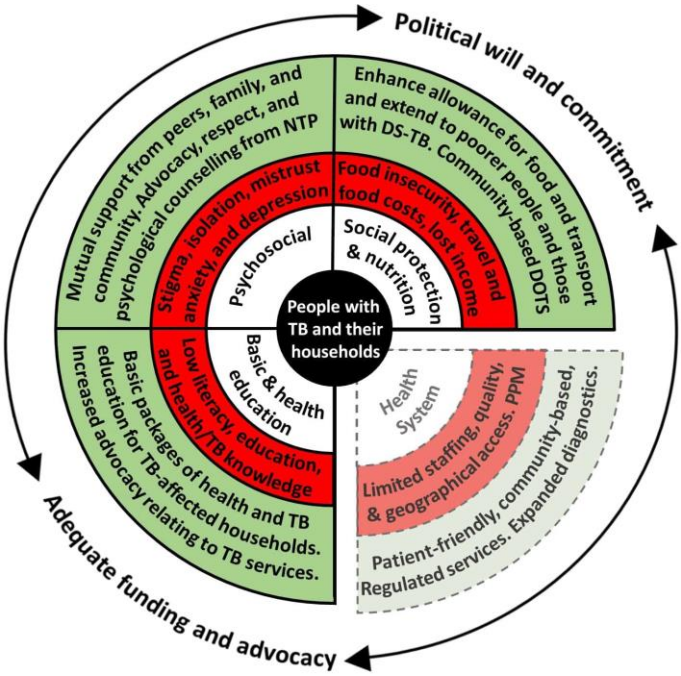
Studies conducted in Asia, Sub Saharan Africa and South America revealed that active case finding approaches may increase in tuberculosis case finding if we conduct in appropriate setting however it is only for the short term (78). Tuberculosis case detection may increase on house-to-house screening, organizing tuberculosis diagnostic clinics in high prevalence of undiagnosed disease. These people may have high treatment success rate and less default however there was no sufficient evidence to increase tuberculosis case detection from only health promotion intervention (78).

Samal J (2016) revealed that health seeking behavior and delays are important aspects in terms of timely treatment and completion of treatment. Level of knowledge of service users (patient), treatment delay, financial constraint, health system delays are responsible for early treatment and diagnosis (79).

Asia is like a reservoir of Tuberculosis (TB). The WHO Global TB Report documents the have highest number of TB cases in India and China in the world (26% and 12% respectively). About 2.9 million cases (75%) cases either not diagnosed or diagnosed but not reported in national tuberculosis program (NTP) in 12 countries including India,

Pakistan, Bangladesh, China, Philippines, South Africa, Myanmar, Indonesia, Democratic Republic of the Congo, Mozambique, Nigeria and Ethiopia (38). Enormous social and economic disruption and series of serious consequences can cause from TB in the society (80). There are two types of delays factors such as patient and provider delays associated for tuberculosis diagnosis and treatment in Asia. Patient delays significantly correlated with low income (costs), long travel time (distance), geographical terrain, male, unemployed, rural residence, hemoptysis, positive sputum smear and provider delays are related with health systems or doctor delays, diagnostic delays and treatment delays. Patient makes first visit to traditional practitioner when they become sick, just stay at home or pray to god which makes prolonged delays in diagnosis (81, 82).

Figure 1.4: Barriers (red circle) and facilitators (green circle) to TB diagnosis and care in Nepal(83)



Delays are significantly responsible for the disease prognosis, complications, transmission in the community, higher mortality, emergence of multidrug-resistant TB ((84-89). Among the health seeking point of view, males are more likely to seek health care earlier than females. Gender related barriers and delays in TB diagnosis and treatment services are mostly that women experienced larger social stigma and financial hardships then men. Gender specific barriers are further challenging to

overcome therefore innovative intervention are required to address these issues (90-92). TB control program have to identify the reasons for delays to improve the TB control strategies. Government has given priority 1 (P1) programme for TB control and prevention to subsidies the epidemic situation of TB (90). Very few research conducted in research in health seeking behavior, further research study needs to be focused in the Asia.

1.10 Active Case Finding

Active Case Finding promotes early diagnosis and treatment of communicable diseases (Covid-19, TB, measles, HIV/AIDS, STI, Hepatitis A, B, rabies, flu, MRSA, pertussis, Ebola, shigellosis etc.) which helps to prevent further transmission of infectious diseases (7, 93).

During the later half of the 20th century, WHO promoted a passive case finding approach to TB for LMIC, with the underlying hypothesis that diagnosis and treatment of the most infectious (smear positive) cases would be sufficient to reverse the TB pandemic and drive elimination. It was also strongly believed that active population wide screening approaches were too expensive and not feasible in LMIC. By the millennium, it was clear that TB was not declining and that a more active strategy was required Renewed interest developed in active case finding approaches for TB.

WHO defines, TB ACF as the “systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly” (71). ACF has also been defined as systematic screening of TB outside of health facilities (10). When systematic screening is applied to high-risk groups or populations in high burden settings TB ACF can be a cost-effective tool (94).

ACF is instigated by the health service provider (provider initiated) rather than by service utilization (demand side). ACF may also provide an opportunity to support people who do not seek health care. The reasons for not seeking health care can be summarized in the three delays models.

1. Delay in decision to seek care due to financial implications, poor understanding of complications, risk factors, professional patient relationships, cultural and traditional beliefs

2. Delay in reaching care due to distance to health facilities, availability of and transportation of costs, poor roads and infrastructure, geographical terrain
3. Delay in receiving adequate health care due to poor health facilities infrastructure, lack of medical supplies, inadequate trained staffs, inadequate referral systems

An approach to or intervention for active case finding that integrates both the patient demand side and the health care supply side interventions could significantly enhance the care offered by a local, regional or national TB programme (79, 81, 95).

Health interventions are often applied via vertical systems in low-income countries however integration of services can be more cost effective, comprehensive and patient friendly. Interventions which are often managed vertically include TB, HIV programme, general health, mother and child health, nutrition, communicable, non- communicable diseases, respiratory diseases, mental health. TB and HIV programmes should be particularly integrated at all levels to ensure effective bidirectional screening and diagnosis of HIV-associated TB (60).

ACF can benefit patients and the community and can improve equitable access to healthcare overall by strengthening health systems (10). ACF has been shown to reduce patient morbidity, mortality, prevent transmission and burden of TB and economic consequences due to earlier diagnosis. However, stakeholder engagement (Government, International/National non-government organization (I/NGOs), bilateral, multilateral organizations, civil society) and operational research evidence from the perspectives of the individual, the community/organization and the health system are needed to inform ACF policy implementation at all levels (72, 73).

Enhanced case finding (ECF) is a term often used to describe strategies which utilize information provision, educational, behavioral change communication (BCC) or training strategies in affected communities to improve awareness of TB symptoms and knowledge of location of appropriate health centres providing TB services. The aim of ECF strategies is to encourage symptomatic or high risk individuals to attend health services for screening and are more useful in high TB incidence areas (96).

Screening for active tuberculosis disease can improve early TB case detection, reduce barriers in diagnostic delays and early treatment and ultimately reduce *Mycobacterium tuberculosis* transmission in the community. However, implementation is complex and

in a systemic review Kranzer et.al (2013) concluded that communities and individuals may not necessarily benefit from active screening of TB disease. ACF programmes need to be appropriately designed to the context and ensure linkage to care and cure for those diagnosed with TB.

Within a well functioning TB programme, PCF will be responsible for the majority of TB case notifications (97). However, ACF can diagnose TB cases earlier, at a less infectious and less severe disease stage, improve equity of access, reduce gender disparities in access to care and reveal high burden of undetected of tuberculosis in population subgroups (17). Within well designed programmes, ACF and PCF are complementary synergistic interventions, to detect tuberculosis and close the case detection gap (97). Although concerns are often raised that individuals diagnosed through ACF will not access or complete treatment, a systematic review showed treatment outcomes among people identified through screening ACF and PCF are similar (98). The main components of effective ACF include high quality TB diagnosis, treatment, management and support for patients, prioritization of high risk groups, appropriate algorithm, ethical principles. Factors influencing successful implementation of ACF can include forced screening, health system weaknesses, individual and community level participation, stigma and discrimination, socio cultural factors, lack of knowledge about tuberculosis among healthworkers and the affected community (99).

Since the millennium, there have been a large number of TB ACF studies, using different strategies in different countries. Many of these have been funded by a large STOPTB partnership programme, TB REACH, which also funded the ACF intervention described in chapters 3 and 5 of this thesis, under TB REACH wave 5. Populations targeted for ACF screening have including prisons, homeless shelters, nursing homes, slum areas, impoverished areas. Screening approaches have included house to house screening, household contact screening, social contact screening, symptoms screening in clinical and community settings, microscopic camps in hard to reach areas. Different diagnostic algorithms have also been implemented, including verbal screening, chest X-ray screening, clinical diagnosis, molecular diagnostics and triage testing. An alternative strategy has been private sector engagement. Many people experiencing TB related symptoms self present at pharmacies or health service providers in the private sector. Through improving the TB screening at such centres,

TB case recognition can be increased. Differing models of private sector engagement have been tested, including incentives for referral, free gifts to screening participants, or subsidized screening and case retention. Through partnership with private healthcare providers such as pharmacies and private clinics, TB cases diagnosed in the private sector are notified and included in national case notification data, thus closing the case notification gap.

The implementation of ACF through TB REACH has dramatically increased the number of cases detected in Ethiopia (100) and Cambodia, in the context of extremely weak underlying national TB programs (101). The implementation of ACF by Britain Nepal Medical Trust (BNMT) under TB REACH wave 2 in 15 Nepalese districts detected 968 additional cases in one year (102). The ACT series of studies by Marks et al in Cau Mau province of Vietnam have shown reductions in TB prevalence through repeated intensive systematic community screening for TB using chest X-ray and GeneXpert testing(103, 104).

The Active Case Finding in Tuberculosis trial (ACT2) in Vietnam have shown that the implementation of ACF in addition to strong passive case finding (PCF) not only increased TB case detection, from 703 per 100,000 population in the control districts to 1,788 per 100,000 population in the intervention districts, but also reduced all-cause mortality in intervention districts from 1.7% (control districts) to 0.6% (intervention districts; relative risk, 0.60; 95% CI, 0.50 to 0.80; P<0.001) (103). ACF also had an estimated incremental cost-effectiveness ratio of US$544 per DALY averted (95% CI 330–1375) (104).

However, increases in overall notification at the national level have not been shown through small-scale, shorter term projects, thus justification for national TB programs and global funders to invest in ACF remains weak.

The Zambia, South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) trial conducted in Zambia and Western Cape province of South Africa was designed to show if ACF could effectively increase TB case notifications at the national level, and close the case detection gap. The trial implemented community based enhanced case finding (ECF) or house hold counselling and TB/HIV prevention services at the house hold level in a 2x2 factorial design. (105). The adjusted prevalence ratio for the

comparison of ECF versus non-ECF intervention groups was 1·09 (95% CI 0·86-1·40), showing no significant effect of the intervention.

These field studies reveal the complexity of ACF interventions and conflict with theoretical modeling data which suggests ACF interventions should have significant impacts on both TB notifications and long term prevalence.

For example a study by David Dowdey et.al (2013) which modeled ACF interventions of private sector engagement in Pakistan suggested that the theoretical intensive, multifaceted, sustained TB case finding intervention could reduce the TB burden (TB incidence and mortality) in densely populated urban areas of South Asia with as much as 40% reduction of TB prevalence. Large randomized implementation trials in South Asia are lacking regarding about TB case finding (106).

ACF, particularly when poorly implemented may have negative consequences. The costs per case diagnosed are substantially higher for ACF than PCF, which is an important consideration for severely under-resourced health systems with multiple demands for financing. However, in the long term modeling studies suggest ACF is a highly cost-effective public health intervention, due to the cascade in cases and consequences averted from every TB case diagnosed (107, 108).

ACF intervention is not effective in a general population with a moderate TB prevalence but community based active case finding is an effective strategy to detect TB in high-risk groups and therefore a blanket approach in the screening process may not applicable in the community. Household or close contacts or index cases are usually the highest risk group and should be prioritized for TB screening. Beyond this category, the highest risk groups, and therefore highest yield groups for ACF, will vary by context. Priority high risk groups for a particular context can be determined by review of grey literature such as TB/HIV prevalence survey reports, NTP annual report and population groups prioritized may include prisons, slum areas, homeless, migrants, elderly, Diabetes mellitus patients (109).

The World Health Organization (WHO) has set the target to end the global tuberculosis (TB) epidemic by 2035. The Directly Observed Treatment Short - Course (DOTS) strategy and the subsequent Stop TB (DOTS expansion) are estimated to have saved more than five million lives (61) however the number of tuberculosis cases continues to rise and TB remains one of the leading cause of death globally (10). Passive case

finding is not adequate to end the tuberculosis (TB) epidemic by 2035. There needs to be significant improvement in existing case detection strategies. Active case finding (ACF) TB strategies can be an important complimentary strategy to passive case finding (PCF) in terms of early diagnosis and treatment, unattended (those not using modern health services), prevent the infectiousness and transmission. ACF interventions are usually feasible in all settings, however these interventions need to be context specific (110).

In Nepal, the expansion of ACF is a key part of the Strategic Interventions to increase TB Case Notification (111). The National TB Programme (NTP) has planned to expand ACF activities through the implementation of microscopy camps, screening of household and social contacts of index TB patients and scaling-up of Gene Xpert testing (111). Nepal has continued to face challenges in crucial areas, such as increase of case detection, poorly functioning health system and high dependence on international funds (45% of the total budget) (17, 112). Furthermore, an important proportion of TB patients seek care in the private sector due to weak public services (112), increasing the chance of financial hardship for the most vulnerable.

Previous cost and cost-effectiveness studies conducted in Nepal evaluated community-based *vs* family member directly observed treatment short-course (DOTS) for TB control (113) and direct costs of outpatient visit to obtain TB diagnosis (114, 115).

1.11 Stigma and discrimination associated with TB disease

Severe stigma surrounding TB remains a substantial barrier to access to care globally. Due to the infectious nature of TB, campaigns to raise TB awareness may inadvertently increase stigma. Many cultures, including some Nepali groups, can view a disease such as TB as a punishment for sin, leading to intense stigma and self-shaming. Such entrenched cultural attitudes are difficult to displace.

A study showed over 60% of patients attending a DOTS clinic in Dharan Municipality Nepal experienced stigma during their TB illness and treatment(116). Many patients were stigmatized even attending the DOTS clinics, or other medical services, often by

healthcare workers themselves, due to lack of knowledge and awareness (116). Stigma exacerbates the issues faced by people affected by TB. Those affected often report staying away from work, or being fired due to TB. Women are often excluded or fear exclusion from potential marriages, are expelled from the family home or are divorced as a consequence of TB. Divorce or separation from a husband has severe consequences for women in South Asia where single women have almost no social or economic autonomy. The majority of patients attempt to conceal the diagnosis of TB due to related stigma and social discrimination. Most of the patients felt ashamed, shame, embarrassed, less respect, impaired self-esteem, isolated, badly treated at their home and community. These factors often lead patients to attend a DOTS clinic distant from their residence, and to give false identities to avoid being disclosed as TB patients (117). Often relatives, friends and neighbors are not aware that TB is no longer contagious after having a few weeks of treatment (118).

TB patient knowledge about causative agent, disposal method of sputum and body fluid, prevention of tuberculosis can also be improved through effective behavior change communication which should be provided to patient, family members, community and service providers and therefore empower both TB affected individuals and their families to feel a sense of agency and reduce both internal and external stigma(119).

1.12 Poverty and Tuberculosis

Tuberculosis (TB) mostly affects the poorest, most vulnerable members of a society. Poverty increases the risks that a person will get sick with TB. In turn, TB can make people and their families a lot poorer. Accessing TB care is expensive. TB patients often pay high out-of-pocket costs or lose income in seeking a diagnosis. TB patients may also sell important household items or take out loans to cope with high costs. A recognition that, despite free at point of access TB diagnosis and treatment through national TB programmes, the majority of TB patients were incurring severe costs which could precipitate households into extreme poverty, resulted in WHO initiating several national TB patient costing surveys. This highlighted the issue, including the long term impact on households of selling essential income-generating assets (such as livestock or farming tools), or taking out usurious loans. TB can precipitate a spiral of poverty for affected households. When this results in children being withdrawn from education

early, the consequences can be multi-generational (7, 120, 121). Some forms of social protection, patient supports interventions are essential to support the TB patient and their household such as social welfare/cash transfers, food support, transport voucher, disability grant/sickness insurance, housing support, income generation programme, policy to eliminate discrimination and avert the spiral of poverty (7).

1.13 Catastrophic Costs

WHO defines “catastrophic costs” when more than 20% of the annual household income of a TB patient is spent on TB diagnosis and treatment. Many TB patients and families are facing financial risks especially direct and indirect costs (120, 122). The World Health Organization’s (WHO) End TB Strategy aimed to end the catastrophic costs that TB patients experience by 20200. This goal was not achieved, with very little progress made, and a renewed focus will be needed to achieve elimination of catastrophic costs by the still ambitious target year of 2030 (10). The positive impact of reducing the catastrophic costs on treatment outcomes has been reported in several low and middle-income countries. Systematic review of published or reported interventions in 2018 showed a relatively strong effect of social protection *vs* no social protection, with OR: 1.77 [95% CI: 1.57–2.01] (123). Active case finding (ACF) has been recommended by international agencies as a supportive strategy to reduce the financial barriers faced by TB patients (10, 102).

Despite the evidence supporting ACF policies, there is a lack of data showing the impact of ACF on patient costs. The World Health Organization (WHO) has been advocating strongly for research evidence from diverse settings to inform policy development to achieve the zero catastrophic costs milestone (38).

The costs incurred by people affected by TB are determined by analyzing the direct medical costs (drugs, tests, consultation fees, hospital charges), non-medical direct costs (transportation, food, accommodation) and indirect costs (time and income loss). Systematic review of patient costing surveys revealed that income loss is often the largest financial risk for patients. Coping mechanisms of TB patients can include taking out usurious loans, using savings, reducing food consumption, withdrawing children from school to work, selling household items and transfers from relatives. Therefore

social protection interventions and appropriate income replacement are crucial for TB patients and their affected families (122).

Catastrophic costs were calculated in the first studies into this issue only as direct out of pocket expenditure (124), however indirect costs represent over half of the economic burden of household (122). The indicator of catastrophic costs due to TB now includes indirect costs and is calculated as household income before and after having TB, including direct income loss due to TB. The earning capacity of the patient due to the number of hours spent in seeking care or unable to work due to TB can be calculated in hourly income. However, catastrophic costs are measured using different methods such as human capital approach (125), equality of wages method, output related approach. Human capital approach is the most commonly used method. An "individual's time (or loss of productive time from treatment and illness) is valued based on their estimated productive output based on their reported income *prior* to being ill (by multiplying the estimated productive time lost due to treatment and illness with the reported income *prior* to being ill)" (10). Alternatively, The minimum wages (general average wage) rate can be used rather than patient's wage to calculate the value of the time loss (126).

Some methodological challenges for the analysis of catastrophic TB costs need to be addressed. Self-reported income may not always be an appropriate measure of household income. It may lead to under reporting of income and over reporting of expenditures, costs. It can be verified by hospital, pharmacy bills, vouchers but these are not usually available from patients. Country specific studies or National demographic and household survey assets questions can be adopted to construct socioeconomic status index, household asset questions. The second methodological challenge is estimating patient's productivity loss – indirect costs and third challenge is the threshold used to determine whether costs incurred by patients are catastrophic or not (10). "Catastrophic total costs" does not implicitly measure the total TB related costs for patient and household. It does not capture the loss of income due to disability, health seeking, health care visits, hospitalization, stigma, discrimination. Individual disease such as TB make limited sense to measure financial protection of households and therefore only use in "TB catastrophic total costs" not applicable to compare the population-based indicators of catastrophic expenditures in the country.

There are a lot of evidence gaps regarding catastrophic costs. Care seeking costs such as dissaving is one of the major problems in catastrophic cost which largely affects socioeconomic status and health outcomes (127). Long term consequences of catastrophic costs lead to risks of further illness poverty trap and therefore adverse effects on TB yield rate and transmissions, multi drug resistance (128). Increasing health care coverage, socio economic interventions including social protection, such as cash transfer intervention can reduce the catastrophic costs and prevent households from financial hardship, vulnerability and further poverty (120, 129).

The WHO End TB Strategy 2014 recommended to measures catastrophic costs as the total costs incurred more than 20% threshold of the annual house hold income and this definition has been applied in this thesis. However, low income countries, including Nepal, have often used a threshold of more than 10% of household income to define catastrophic costs, due to the fragility of household incomes for those near or below the poverty line. Tanimura *et.al* (2014) emphasized that whatever the threshold of catastrophic costs used, it is important to understand the contributing factors.

The Global TB strategy will be impossible to achieve without proper implementation of social protection and universal access to general health services (130). Universal health coverage (UHC) means that every human being can access and use their high-quality health services including preventive, promotive, curative, rehabilitative and palliative health services without suffering from financial hardships. Health as a fundamental human right was enshrined in 1948 and expanded with the concept of UHC at the Alma Ata conference in 1978 (14). The Sustainable development goals (SDGs) applied all the health-related matters as cross cutting issues and aims to improve better health and protection of the poorest people. There are a lot of inequality in health status between developing and developed countries. UHC moto is to reach the essential health services to reach the door steps of all the people and community without discrimination whether people live in urban or rural areas, rich or poor, male or female, any religions, castes or ethnicities (14). UHC provides financial protection of citizens due to ill or sickness and implemented through legislation, regulation and taxation. UHC was started from Germany as sickness fund and other countries also started as financial protection coverage (131). About 44 million households (more than 150 million individuals) are suffering from catastrophic health care expenditure

worldwide and about 25 million households (more than 100 million individuals are forced into poverty by catastrophic costs (132).

More than two third of the Nepalese population depend on out of pocket expenditure (133). Some initiatives have been piloted such as free health services to poor people, community-based health insurance, community drug programmes, Aama programme, subsidy to disadvantage and marginalized population, social health insurance scheme in reproductive, maternal, new born, child health, infectious disease control, non-communicable diseases and other essential health services. However a successful long term model has not been established yet. There is utmost need to design effective financial protection scheme for Nepal aligning with the principles of UHC (134).

Poverty and tuberculosis are inextricably connected. The poor are more prone to get TB because of crowded homes, poor nutrition, vulnerable working conditions, comorbidities, less access to treatment and diagnostic facilities (135). Quality health service provision, accessibility not very far from their home may be extension of community DOTS nearby their door steps, flexible working hours, improvement of patient and community awareness. DOTS program should be introduced in private clinics, encouraged home visits to address the working people, severely ill patient and elderly people (136).

Within Nepal, a small study conducted in 2008 showed the majority of TB patients incur costs for transportation to medical services, food, accommodation, clinics fees while accessing diagnosis and the overall expenses were about one week of their national income per capita in country. The highest expenditure was incurred by patients attending the private clinics (115). Individuals having signs and symptoms such as chronic cough and active untreated TB usually are forced to travel on buses while infectious and transmit in geometrically progression to other people. Therefore more accessible TB services can reduce the TB transmission in multifaceted ways.

The studies reported in this thesis, chapters 5 and 6, aimed to establish the prevalence, intensity and components of costs incurred by TB patients in Nepal, and to establish if ACF is an effective strategy contributing to reduced patient costs for TB in the Nepali context.

1.14 Rationale and Justification of the Thesis

The WHO End TB Strategy has emphasized that one of the key strategies for accelerating TB elimination is the scale-up of systematic screening for TB, also known as Active Case Finding (ACF). This is a central component of ensuring early diagnosis for all people affected by TB, and to achieve the ambitious targets of the UN High Level Meeting.

My thesis study was conducted through BNMT Nepal as a component of the TB REACH Wave 5 and IMPACT TB projects which implemented active case finding for TB. During this time, I was Executive Director of BNMT. After more than 23 years working experience in health system strengthening and tuberculosis sector, I experienced directly the challenges facing the TB control programme, and the wider health system in Nepal, and became passion to support government in efforts to eliminate TB. The case detection gap is one of the most urgent challenges facing the national TB control programme and therefore these two projects aimed to evaluate the potential of ACF strategies to reduce the diagnostic gap in Nepal. Through TB REACH wave 5, I aimed to determine if the use of GeneXpert as a diagnostic test for ACF could substantially increase the yield, compared to the cheaper smear microscopy test which is still the most commonly applied TB diagnostic test in Nepal. One Genexpert machine was established in the district hospital of each of the districts implementing GeneXpert. Through the IMPACT TB study, I them aimed to evaluate if an ACF strategy screening social contacts of index cases would result in significant yields. The case finding coverage using GeneXpert was further intensified in IMPACT TB by installing three 4-module GeneXpert machines in each district, at primary health centres, in addition to the district hospital.

The second major theme of my thesis was to evaluate the degree and intensity of costs incurred by TB patients in Nepal, and to determine if ACF is an effective strategy to reduce these costs through earlier diagnosis and improved patient-centric care. During TB REACH wave 5, I conducted a cross sectional survey following the WHO patient cost survey protocol. This methodology collects patient cost data at a single timepoint, and has limitations in capturing the full scope of costs, particularly during the treatment continuation phase. Therefore, during the IMPACT TB project implementation, I conducted a patient cost survey using a longitudinal design, with data collection at three timepoints during TB treatment. The Nepali NTP has now planned a national patient costs survey. The results of such a survey will be a key

driver for the development of Social protection policies for which are inclusive of, and sensitive to, people affected by TB.

ACF has been chosen as the focus of this PhD research because its implementation is a national priority in Nepal. Nepal has struggled to improve case notification for tuberculosis in recent years, and in recent years has witnessed a decline in case notification rather than an increase. While a large body of evidence exists to support early detection and treatment of TB, resource-limited settings continue to face major barriers to scale-up, inhibiting the comprehensive implementation of such proven interventions.

It has been recognized that although TB smear microscopy and TB treatment are provided free at the point of access, patients incur significant costs in seeking a TB diagnosis, through lost income, transport costs nutritional supplements and payment for additional diagnostic tests such as chest X-ray or clinic visits and treatment. If the sum of all of these incurred costs is above 20% of the annual household income, they are termed catastrophic costs. As TB patients are often the poorest members of our society, they are most vulnerable to the consequences of catastrophic costs and can be pushed into using coping strategies including usurious loans, forced to sell vital assets or losing their homes and the ability to economically support their household. This research project will evaluate the costs incurred by patients in obtaining a TB diagnosis, as well as comparing different active case finding strategies to the current passive case finding model.

The World Health Organization's (WHO) End TB Strategy aims to end tuberculosis (TB) by 2035. Similarly, the UNHLM, September 2018 also set ambitious targets including diagnosing and treating 40 million people with TB by 2022. Yet, low-income countries such as Nepal are unlikely to achieve this goal without a dramatic increase in technological, financial and human resources.

In Nepal, an estimated 69,000 people per year are suffering from TB, but half are not diagnosed and treated by the National TB Programme. Active case-finding (ACF) is an essential component of a comprehensive strategy to find those "missing cases", treat and prevent TB. In Nepal, the National TB Center (NTC) and organizations such as the Birat Nepal Medical Trust (BNMT), HERD, JANTRA and Save the Children have

piloted different models of ACF, but there is no single agreed method for ACF and coverage of ACF is limited at a national level.

In June 2019, the WHO Joint Monitoring Mission Expert Review team recommended Nepal move towards using GeneXpert nationwide as the first diagnostic test for TB. GeneXpert is an automated molecular diagnostic test that can identify *Mycobacterium tuberculosis* DNA and resistance to rifampicin. Using GeneXpert in Nepal may increase case notifications and achieve the goal of diagnosing 20,000 additional cases by 2025, as outlined in the TB National Strategic Plan (NSP).

The IMPACT TB project evaluated the health systems costs and yields of ACF using either GeneXpert or smear microscopy as the primary diagnostic test in Nepal. It has been noted that GeneXpert test is a better diagnostic tool than microscopic. ACF using GeneXpert detects more cases than smear microscopic.

Active TB case-finding (ACF) can help TB patients and their families to decrease costs and potentially reduce transmission. ACF makes care accessible and helps to find and treat TB patients earlier. In Nepal, the National TB Center (NTC) and organizations such as the Birat Nepal Medical Trust (BNMT), HERD, JANTRA and Save the Children are implementing ACF.

The IMPACT TB project adapted WHO's TB patient costing survey to compare the costs experienced by patients diagnosed through ACF and passive case-finding. Such evidence can inform the design and implementation of policies to reduce financial barriers to accessing and engaging with TB treatment, care and prevention measures.

The National TB Center (NTC) has recently conducted the first ever TB prevalence survey in Nepal, results showed that it has been almost 1.6 times higher TB prevalence than previously estimated.

Active case-finding (ACF) is an essential component of a comprehensive strategy to detect, treat and prevent TB. Given Nepal's diverse geography and ethnic composition, ACF is particularly important to ensure equitable access to TB diagnosis and care among the most vulnerable populations. However, poorly implemented ACF can draw resources from passive case-finding.

ACF projects have shown mixed results in Nepal and it is key to learn lessons from failed approaches while improving and scaling up successful ones. The

BNMT/IMPACT TB project evaluated the yields of ACF using GeneXpert (Chitwan and Dhanusha) or smear microscopy (Mahottari and Makwanpur) as the primary diagnostic test. Also, the BNMT/TB REACH Wave 5 project implemented ACF using GeneXpert (Bardia, Gulmi, Kapilvastu and Pyuthan) or smear microscopy (Acham, Argakhachi, Doti and Salyan). The results of both projects show strong additionality and lessons for scale-up.

CHAPTER 2: Methods

2.1 Geographic Location of the studies

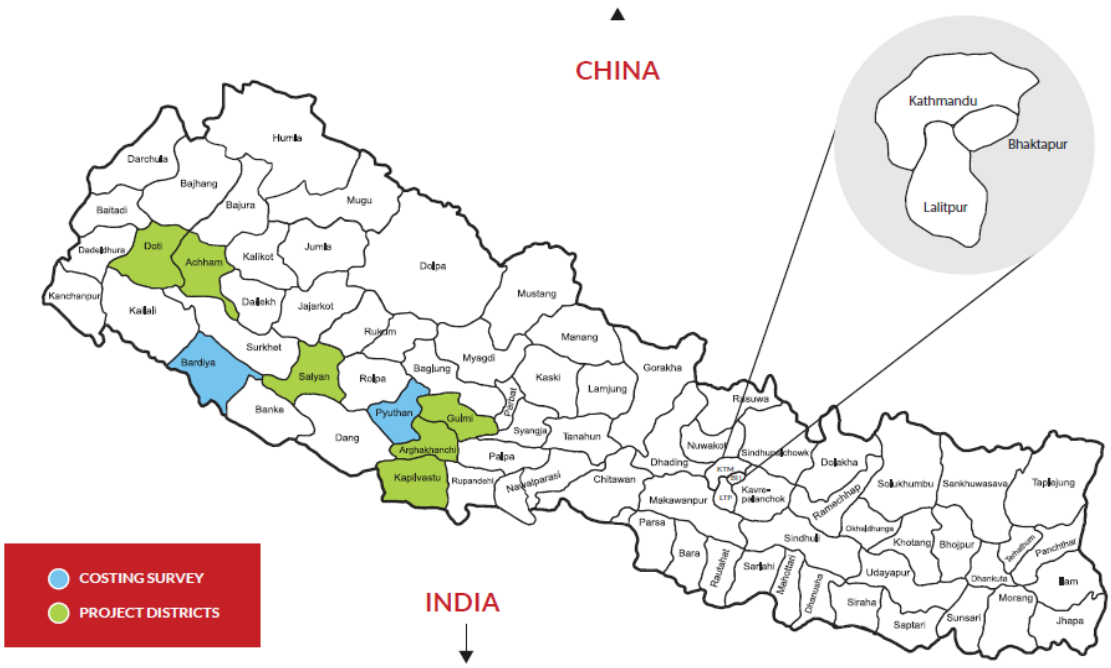
Nepal is a landlocked country in South Asia. The three principle geographic terrains are the Himalayas (himal) in the north, (including Mount Everest the highest peak in the world), the mid hills (pahad) and the flat plains in the southern belt which are known as terai. Gautam Buddha was born in Lumbini, Nepal. Nepal is the home of multi-ethnic, multi-lingual, multi-cultural, multi-religious people with common aspirations and living in diverse geographical regions. There are 125 ethnic groups, speaking 123 different languages. Nepal is a low-income country with a population of 29 million people and a gross domestic product of USD 689 per capita (133). However, the country is very rich in culture. Nepal reduced the multidimensional poverty index (MPI) from 30.1% in 2014 to 17.4% in 2019 which represents a 42% reduction over five years, and reflects the rapid development of Nepal during this period. However, there are significant and growing disparities between urban and rural areas, and between regions. The far west and remote mountainous regions remain the poorest (137) (133).

Nepal prevalence survey revealed that the TB burden is almost 1.6 times higher than has been previously estimated by WHO. About one hundred and seventeen thousand (117,000) people are living with TB disease in Nepal and about sixty-nine thousand (69,000) people develop tuberculosis in Nepal every year. Over half these TB cases were undiagnosed, with forty-seven persons are dying every day because of TB in Nepal (4). Health care services in Nepal are provided by public and private sectors however a large number of people are not receiving quality health services in rural areas of Nepal because of several reasons such as poverty, distance, transportation, lack of awareness, stigma, socio-cultural believes, lack of human resources, inadequate trainings of healthcare staff etc.

The federal democratic republic of Nepal comprises 7 provinces and is divided into 77 districts.

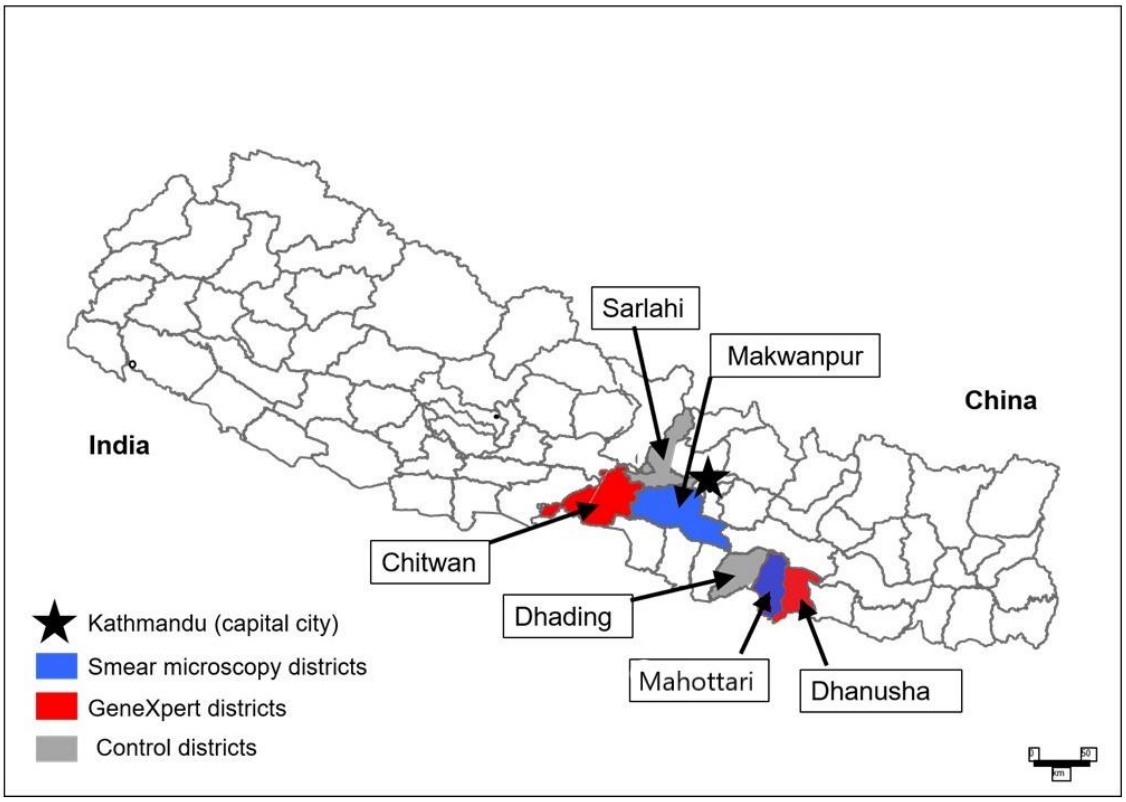
The TB REACH study reported in this thesis (chapter 3 and 4) was conducted in western part of Nepal, covering 8 districts: Bankey, Bardiya, Salyan, Pyuthan, Acham, Doti, Argakhachi, Nawalparasi, shown in figure 2.1.

Figure 2.1:TB REACH districts coverage and costing survey districts, Nepal, 2018



The IMPACT TB study reported in chapters 5 and 6 was conducted in central region covering 4 districts: Chitwan, Mahotari, Dhanusha, Makwanpur, shown in figure 2.2.

Figure 2.2: Map of Nepal showing location of intervention and control districts for IMPACT TB active case finding



2.2 Health System in Nepal

Basic health care is a fundamental right of citizens. The Nepal National health policy 2019 (2076) was formulated to ensure access to high quality health services for all citizens in the context of the new federal governance system.

The Nepal Health Sector Strategy (NHSS) 2015-2020 is the principal strategy document of the health sector for five years. Similarly, the National Strategic Plan to End Tuberculosis in Nepal 2021/22-2025/26 outlines the national Tb Programme strategy. The Government of Nepal, Department of Health Services (DoHS) are provide different programme interventions through their health facilities, including the national immunization programme (NIP), integrated management of neonatal and child hood illnesses, nutrition, nutrition in emergencies (NIE), safe motherhood and newborn health, family planning and reproductive health, adolescent sexual and reproductive health, primary health care outreach clinics, malaria, kala-azar, lymphatic filariasis, dengue, leprosy, health related rehabilitation and disability management, zoonoses, tuberculosis, HIV/AIDS and STI, non-communicable diseases, mental

health, surveillance and research, curative service, nursing capacity development, geriatric services and gender based violence management, bipanna nagarik aushadi upachar programme, female community health volunteers, inpatients/OPD services, health training, vector borne disease research and training, health education information and communication (NHEIC), health service management logistics management, health laboratory services, personnel administration, financial management, monitoring and evaluation, eye care, human organ transplant services, medico-legal services, health councils, health insurance, development partners support in health programs (65).

2.3 TB REACH ACF project implementation (Chapter 3)

The yield study was conducted in eight districts of Nepal from June 2017 to November 2018 supported by TB REACH wave 5 funding. BNMT installed one four-module GeneXpert machine for TB diagnosis at each of the district government hospitals in Pyuthan, Bardiya, Kapilvastu, and Gulmi districts. The other four districts: Arghakhanchi, Salyan, Doti, and Achham used the standard NTP smear microscopy (Zhiel-Neelsen) for TB diagnosis, which is the primary diagnostic method in Nepal. Five districts Bajhang, Bajura, Banke, Nawalparasi, and Palpa that had similar features, such as population size, geographic characteristics, and TB case notification rates, were selected as control districts by the external TB REACH monitoring consultant. Table 2.1 shows the District wise case notification rates (CNR for the intervention and control districts prior to the ACF implementation.

Table 2.1: District wise case notification rate (CNR) of bacteriological positive cases in study districts

Province	Implementation districts	Population[1] 2011	CNR B+[2] 2015/2016
Province 5 (Lumbini Province)	Kapilvastu	631159	98.9
	Pyuthan	237212	113.8
	Bardiya	459535	120.8
	Arghakhanchi	201055	128.3
	Gulmi	266635	110.6
Province 6 (Karnali Province)	Salyan	260990	91.6
Province 7 (Sudurpaschim Province)	Doti	213473	68.4
	Achham	276198	63.7
Total		2546257	
Province	Control districts	Population[1] 2011	CNR B+ [2] 2015/2016
Province 5 (Lumbini Province)	Nawalparasi	695484	107.5
	Palpa	254203	140.8
Province 6 (Karnali Province)	Banke	561497	158.1
Province 7 (Sudurpaschim Province)	Bajhang	211653	82.7
	Bajura	147526	67.8
	Total	1870363	

Unpublished data (2016). National Tuberculosis Control Center
Annual Report (2016). National Tuberculosis Program

The chief laboratory officer at NTCC provided the hospital laboratory staff in GeneXpert districts with a three-day training on the operation GeneXpert machines and in smear microscopy districts a 2-day refresher training on standard operating procedures for smear microscopy and quality control of sputum samples. Standard operating procedures for the smear microscopy and GeneXpert (Xpert MTB/RIF. Cepheid, Sunnyvale, CA) testing followed the standard Nepal NTP guidelines, which are based on the relevant WHO protocols and the manufacturer's standard operating procedures (35). Individuals diagnosed with TB were registered and treated under the routine NTP directly observed treatment short course (DOTS) services. If contacts

were negative for TB, they were counselled by the Community Health Volunteers (CHV) and were asked to contact community health volunteers if they developed any symptoms subsequently.

2.3.1 Case-Finding Strategies in TB REACH wave 5

The project employed three case-finding strategies: a) close contact tracing, b) TB camps in hard-to-reach areas, and c) screening at hospital OPD visits (in districts using GeneXpert). All strategies applied the same initial verbal symptom screening using eight questions:

1. Have you had cough for more than 2 weeks?
   Yes / No
2. Have you had fever during the last 2 weeks?
   Yes / No
3. Have you had night sweats for >2 weeks?
   Yes /No
4. Have you Lost your appetite during the last 2 weeks?
   Yes/ No
5. Have you experienced unexplained weight loss in the last 4 weeks?
   Yes /No
6. Have you noticed blood when coughing during in the last 2 weeks?
   Yes/ No
7. Have you been in contact with any TB infected person within 3 months?
   Yes/ No
8. Have you been diagnosed with tuberculosis in the last 2 years?
   Yes/ No

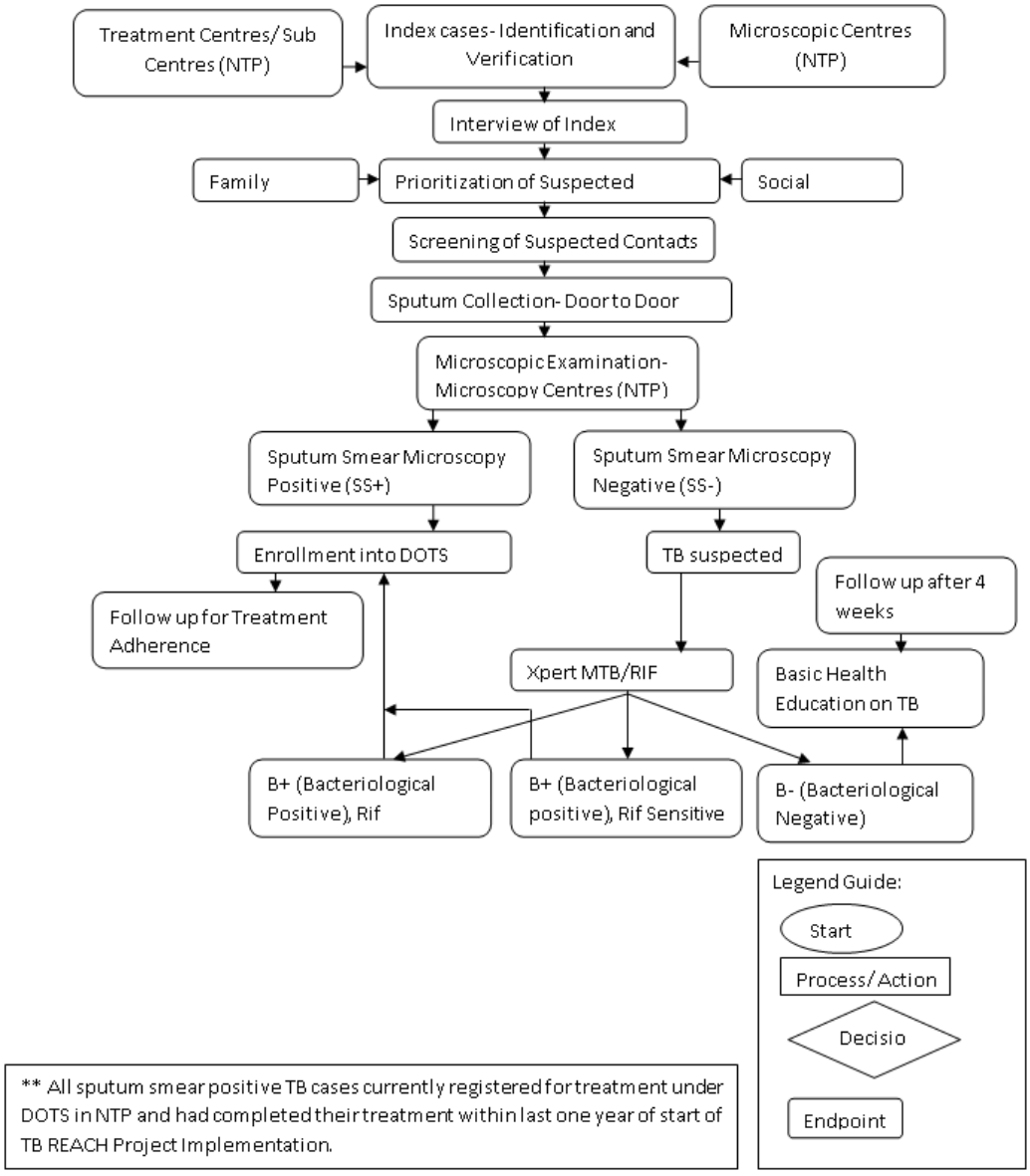
A positive response to any of these questions was an indication for TB testing by smear microscopy or GeneXpert MTB/RIF on sputum. Thirty CHVs in each district were trained in the three strategies, including symptom identification and treatment monitoring. The CHVs collected one morning voluntary sputum sample for GeneXpert testing or two samples (spot and morning) for smear microscopy. No sputum induction techniques were used, but participants were given instructions by CHVs on how to produce quality sputum. On the day of sample collection, the CHVs transported the samples to the nearest microscopy or GeneXpert testing center.

Close-Contact Tracing

CHVs contacted all index cases registered through the NTP in the preceding 12 months and interviewed them to identify name and address of their close contacts.

The algorithm for contact tracing is shown in figure 2.1. With consent from the index case, the CHV then visited the contacts to screen for cardinal TB symptoms such as cough for more than two weeks, fever, unknown weight loss, night sweats, and lack of appetite (71). The volunteers collected the morning and on-spot sputum samples of individuals having at least one of these cardinal symptoms and transported the samples to the nearest testing facility.

TB



case finding Camps

TB camps were conducted in areas with poor access to TB services, selected in consultation with the government TB officer of the district. The areas were selected based on the high-risk populations such as people from disadvantaged communities,

Figure 2.3: Algorithm for TB REACH active case finding through contact tracing

ethnic minorities, and poor socioeconomic conditions. Awareness raising campaigns on TB signs and symptoms were conducted prior to the camps through house-to-house visit or mass media such as newspapers and radio. Local leaders and TB survivors also acted as champions to disseminate information on TB, the planned camp services, and testing to encourage at risk people to attend the camp. The same questionnaire survey was applied to screen camp attendees for TB symptoms. CHV collected sputum samples from symptomatic individuals which were tested by either by GeneXpert or smear microscopy, according to the district.

Screening at Hospital OPD

Verbal symptomatic screening at the hospital OPDs were performed by medical doctors only at the four district hospitals where GeneXpert was installed. Patients who visited the OPD of the district hospital in the four GeneXpert districts for any kind of consultation or diagnosis were screened for symptoms using the eight questions and if symptomatic, were tested for TB.

Five districts Bajhang, Bajura, Banke, Nawalparasi, and Palpa that had similar features such as population size, geographic characteristics, and TB case notification rates were selected as control districts by the external TB REACH monitoring consultant. In these districts, routine passive case finding was implemented following the standard NTP protocols, supplemented by limited household contact tracing supported by the Global Fund (35).

2.3.2 Statistical Analysis of TB REACH project yield

Screening and Diagnosis of TB Cases

Diagnosed cases were cross verified from the laboratory registers. The primary outcome of the analysis was the yield rate from the three strategies, which was calculated as the number of cases diagnosed divided by the total number of individuals tested. To further evaluate the strategies, the study also compared the number of contacts required to screen (NNS) and the number of contacts required to test (NNT) to identify a TB case from each strategy.

Comparison of Yield from GeneXpert vs. Smear Microscopy

We excluded Salyan and Arghakhanchi districts from the comparative study of yield between GeneXpert and smear microscopy. During the project implementation, the

National TB Control Center (NTCC) provided a GeneXpert machine to Salyan district hospital for diagnosis. Similarly, the project discontinued Arghakhanchi district one year after the implementation because of continued delays in project initiation.

The yield rate from smear microscopy and GeneXpert were compared for close-contact tracing and TB camps. Hospital OPD-based screening was not included in the comparison as tests through GeneXpert were performed only in the four GeneXpert districts.

Additionality in District Level TB Case Notification Rates

The Nepal NTP reports TB cases on a trimester basis (3 × four-month reporting periods each year). We obtained case notification data disaggregated by age group and gender of all intervention and control districts from the NTP database.

The contribution of the project to the NTP notification was determined by the additionality method used by TB REACH, which is calculated by subtracting the cases notified during the baseline period from the cases notified during the implementation (108). The baseline covered the period 16 July 2016 through 15 June 2017, and the implementation period started on 16 July 2017 until 15 Nov 2018.

Second, to calculate the predicted case notification data of the intervention year in both intervention and control districts, we performed a trend analysis using linear regression method for the preceding three-year case notification data. We then applied the adjusted additionality method, which calculates the difference between the expected values during the months of implementation compared to the actual notification among bacteriological cases. We compared the trimester data as well as the consolidated data of the intervention period with the estimated case notification data for both intervention and control districts. The changes in number and percentage from the analyzed data provided the additionality in the intervention and control districts. We compared the additionality of the intervention and control districts and calculated the total additionality.

Finally, we used the double difference method to evaluate the yield (unadjusted and adjusted) from the strategies.

2.4 IMPACT TB ACF implementation

2.4.1 Study setting

From 1st November 2017 to 31st October 2019, the IMPACT TB project implemented ACF in four districts of Central Nepal:Chitwan (population 579984; 2.2% of the national population), Makawanpur (population 420477, 1.6% of national population), Mahottari (population 627580, 2.4% of the national population) and Dhanusha (754777, 2.8% of the national population) (32). Dhanusha and Mahottari are flat plains regions bordering India (known as the Terai in Nepal), while Makawanpur and Chitwan districts have a mixed terrain of hills and lowland Terai (33).

Dhading and Sarlahi, were purposively selected as the two control districts implementing only the routine National tuberculosis control programme activities. Figure 2.1 shows the location of the study districts.

2.4.2 Study population TB

The study population included all social contacts of index TB patients who had been diagnosed in the 12 months preceding IMPACT TB implementation (January-December 2016). During IMPACT TB implementation, household contacts of index cases in the study districts were screened by the Global Fund supported activities of the National TB Programme. Social contacts are individuals who do not belong to the same household but have shared close space with index TB patients during the three months prior to the diagnosis of the index case with TB (34). We included contacts age 18 years and above who provided written informed consent for screening participation. Child contacts were referred to the appropriate National TB Programme services for evaluation.

2.4.3 ACF Intervention IMPACT TB

All activities were implemented in consultation and coordination with the local health authorities. Thirty Community Health Volunteers were recruited (CHV) in each project district and received training to identify and screen the social contacts of index cases with informed consent. TB case finding was carried out in the four districts through three strategies; a) close community contact tracing (b) door-to-door screening in high risk areas and c) mobile diagnostic camps in hard to reach areas. In all cases, individuals were screened first by eight verbal questions to identify symptomatic individuals for testing. TB symptoms included in the questionnaire were the presence

of cough for more than 2 weeks, blood in cough, fever, night sweats or weight loss, chest pain, and had TB in the past two years.

Individuals responding positively to any one of the questions were advised to take a test for TB. GeneXpert MTB/RIF was used for TB testing in Chitwan and Dhanusha districts. BNMT Nepal installed three GeneXpert machines in each of these districts at government health facilities strategically located to maximize population coverage for the district. GeneXpert locations were determined in consultation with the government health service personnel and community stakeholders at district and provincial level to ensure appropriate space and human resources to support the service. Makawanpur and Mahottari implemented ACF using standard NTP Zhiel-Neelsen smear microscopy for TB testing. BNMT Nepal supplied 11 new Olympus microscopes in these districts to replace faulty microscopes in the existing network. Training and refresher courses for laboratory staff in GeneXpert or Ziehl-Neelsen smear microscopy were conducted in the relevant districts.

Close community contact tracing IMPACT TB

A list of index patients, both drug sensitive and drug resistant, was obtained from the government health facilities. These index cases were visited by CHVs at their homes and interviewed with consent to identify their social contacts for screening Social contacts were then contacted, invited to participate and if informed consent was granted, were verbally screened for TB symptoms using the eight question symptom evaluation. Participants with one or more symptoms of TB were counselled to provide a sputum sample for testing, which was collected and transported to the nearest testing center by the CHV. In microscopy districts two samples were collected; the first ‘on the spot’ and the second in the early morning of the following day. For each index case, at least ten social contacts were screened by the CHVs. The collected sputum samples were sent for free laboratory testing to either the microscopic center or GeneXpert center according to the intervention district. All those who tested positive were traced back and brought to the health facility for TB treatment free of cost under NTP.

TB case finding camps IMPACT TB

Mobile TB case finding camps were conducted targeting geographically disadvantaged and remote communities with a high TB burden in the intervention

districts. These camps were conducted in coordination with district public/health offices and local health facilities. CHVs conducted verbal community screening for TB symptoms Sputum samples were collected and sent for testing either in GeneXpert or microscopic centers according to the intervention districts. Those testing positive for TB were followed up by the respective CHVs and enrolled in the nearest DOTS center for treatment. These camps also included awareness on TB signs, symptoms and methods of prevention.

2.4.4 Data management and analysis IMPACT TB

Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (KNCV) TB Foundation and BNMT developed a custom web portal for data entry and management. Data from index lists, screening forms and laboratory forms were entered by the district based community mobilizers trained by the KNCV TB Foundation. Data analysis was performed on R (version 3.5.1, R foundation for Statistical Computing).

2.4.5 TB Yield and Additionality analysis IMPACT TB

Notification rates were compared using official government notification data between districts implementing ACF using GeneXpert, ACF using smear microscopy testing or districts implementing only the standard National TB Programme activities..

Yield rates were also compared for the different active case finding strategies implemented in the districts. Number needed to screen (number of individuals testing positive for TB/total number of individuals verbally screened) and number needed to test (number of individuals testing positive for TB/number of individuals submitting sputum sample for testing) was calculated and compared for GeneXpert and smear microscopy active case finding strategies.

TB cases are reported by the Nepal NTP using a trimester system (3 x four-month reporting periods each year). We obtained official case notification data for the intervention and control districts from the NTP database.

To evaluate the additional TB case notification achieved overall by the project, and disaggregated by diagnostic method applied (smear microscopy or GeneXpert), we applied the additionality method used by TB REACH projects. This is first calculated by subtracting the cases notified during a baseline period two years previous to the

intervention (15 July 2015-14 July 2017) from the cases notified during the period of active implementation (15 July 2017- 14 July 2019) (138). This is the crude additionality. Nepali government data notification for the National TB Programme is based on a trimester system, reporting each year from July 15-July 14.

Second, to calculate the predicted case notification data for each district in the intervention years we performed trend analysis using linear regression method for the preceding three-year case notification data. We then applied the adjusted additionality method, which calculates the difference between the expected and recorded values during the months of implementation, to determine the adjusted additionality.

Finally, we created a generalized linear mixed methods model fit to determine the relative increase associated with each intervention (GeneXpert or smear), while incorporating the variation arising from each district. The model employs a poisson distribution to model TB notification over time and treats time as a fixed variable using the trimester variable.

2.5 Cross sectional patient costs evaluation TB REACH wave 5 (chapter 5)

This TB patient cost study was conducted in two districts of the BNMT TB REACH Wave 5 project in Nepal, which aimed to increase case notifications of TB through the implementation of ACF models (June 2017 – December 2018). The BNMT TB REACH project was implemented in eight districts, with four districts applying GeneXpert for diagnosis (Pyuthan, Bardiya, Kapilvastu, and Gulmi) and four districts using smear microscopy (Doti, Achham, Argakhachi and Salyan).

The ACF model adopted three strategic interventions to identify TB patients: (1) contact tracing of social contacts; (2) TB camps for remote populations and (3) screening at outpatient departments (OPDs) of public hospitals. Household contacts were not evaluated in this TB REACH study because this was being carried out in the project areas as part of The Global Fund activities of the NTP.

This TB patient cost survey was conducted in two districts where the GeneXpert intervention was implemented: Pyuthan and Bardiya, Province No. 5. Pyuthan is a hilly district covering an area of 1309 km² and has a population of 228 102 inhabitants

(139). It is classified as a district with a medium TB burden by the NTP, with 285 cases registered in 2017 (111). Bardiya is a lowland Terai district covering an area of 2025 km^2 and has a population of 426 576 inhabitants (139). The district is classified as having a high TB burden, with 601 cases registered by the NTP in 2017 (111). There is one government hospital in each district. In Bardiya, there are 29 health posts and three primary healthcare centers. In Pyuthan, there are 44 health posts and two primary healthcare centers. During the TB REACH project, 16 and seven TB camps were held in Bardiya and Pyuthan districts, respectively.

2.5.1 Study design and sampling TB REACH cross sectional patient cost evaluation

Three ACF interventions were applied in the TB REACH project. Details of the interventions are given section 2.3.1.

A cross-sectional study to evaluate patient incurred costs was conducted between June and August 2018. As no data from Nepal were available to inform a sample size determination, we set a sample size based upon a previous cost survey conducted in the Philipines (TB FIT: *Filipino Impact Assessment of new tuberculosis diagnostics*) (140), which was sufficient to demonstrate an effect.

One hundred patients were included in this study in a 1:1 ratio (PCF: ACF, 50 consecutive ACF and 50 consecutive PCF patients in each district). ACF patients who were between two weeks and three months into the intensive phase of TB treatment were selected from a study database of all patients diagnosed via ACF strategies. PCF patients were identified from the treatment registers at DOTS centers in each district. No eligible patients declined participation.

2.5.2 Inclusion criteria TB REACH cross sectional patient cost evaluation

All adult (≥ 18 years) new and relapse TB cases registered in government facilities and who were residents of Nepal were eligible for inclusion.

2.5.4 Time horizon TB REACH cross sectional patient cost evaluation

Costs were collected at one point in time during the intensive phase of treatment. The interviewers collected information regarding costs incurred during the pre-treatment period (that is, from the onset of the first reported TB symptom until the first visit to a health facility for initiating TB treatment) and during the intensive phase of treatment

until the date of the interview. (That is, within 60 days of treatment initiation for new cases and 90 days for relapse cases). Costs incurred during the intensive phase were extrapolated according to the number of remaining days of treatment: costs incurred from treatment until the date of interview x the proportion of the intensive phase to be completed; for example, if a patient was interviewed on the 30th day (half of intensive phase completed for new cases), the cost incurred until the day of the interview was multiplied by two (proportion of intensive phase to be completed = 60/30) (141).

2.5.5 Data collection TB REACH cross sectional patient cost evaluation

The WHO TB patient costing questionnaire was adapted for this study. The questionnaire included questions on clinical parameters; demographic variables; information on employment and household composition; socioeconomic position; healthcare utilization, including the number of visits and costs (direct medical and non-medical) incurred during each visit in all types of health institutions; time and income lost (indirect costs) while seeking and receiving care; individual and family income; coping mechanisms, such as loans taken, assets sold; and the financial and social impacts of TB on patients and families.

The questionnaire was translated into Nepali and was pre-tested on seven patients undergoing TB treatment in Bardiya and Pyuthan. Minor corrections to the Nepali version of the questionnaire were made following this pilot testing. CHWs were trained in informed consent procedures and to administer the interviews. They were allocated to areas where they had relationships of trust in the community. CHWs prepared a list of TB patients diagnosed through ACF and PCF during the intervention period and contacted them to schedule an interview at their home or at the health facility. Those diagnosed via household contract tracing in The Global Fund program were not included in either group because the study's aim was to compare the TB REACH interventions with passive patient presentation. Eligible individuals were invited to participate, informed about the purpose of the study orally and by a written patient information sheet (PIS), and were given an opportunity to ask questions. The PIS was read to individuals with low literacy levels. Written informed consent was obtained, or a thumbprint for those unable to sign, following standard Nepali practice. Compensation of 500 Nepalese rupees (NPR) (approximately USD 4.5) was provided for the time taken to complete the questionnaire (approximately 90 minutes).

Data completeness and consistency of information were assessed after each interview and were cross-checked with the patient treatment card. Data quality control was performed by the district TB coordinators, a research associate, and the data manager.

2.5.6 Data entry and analysis TB REACH cross sectional patient cost evaluation

The WHO definition was applied to estimate the proportion of TB-affected households experiencing catastrophic costs: that is, the total costs (direct plus indirect) of seeking TB diagnosis and care which exceeds 20% of the annual household income (141). We calculated the prevalence (that is, the proportion of patients with total costs > 20% of annual household income) and the intensity of catastrophic costs (using the positive overshoot method; that is, the average degree by which catastrophic costs exceed the 20% threshold) (142) for each group. Income loss, and individual and household income were self-reported by patients. Time loss was also self-reported by patients and converted to monetary values using the human capital approach applying hourly and monthly minimum wages of USD 0.62 and USD 4.67, respectively (143). Costs were collected in NPR and were converted to USD applying the average exchange rate from OANDA during the data collection period (NPR 1 = USD 0.00903) (https://www1.oanda.com/) (144).

Data were entered by a trained technician into a bespoke web tool hosted by Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (KNCV) TB Foundation and BNMT. Data analysis was performed using Stata version 15 (StataCorp, College Station, Texas 77845, USA). The mean imputation approach was used to handle missing data and missing values were replaced by the mean value of the costing items (145). The patients in each study arm were compared on socioeconomic and clinical characteristics. The impact of ACF on costs was determined by analyzing: (1) income changes and social consequences of TB; (2) median costs per cost component: that is, direct medical costs (drugs, tests, consultation fees, hospitalization charges), non-medical direct costs (transportation, food, accommodation), and indirect costs (time and income loss); (3) median cost per period of analysis (that is, the pre-treatment and intensive phases); and (4) proportion of direct and indirect costs per period of analysis.

The chi-square test was applied to test the difference in proportions of categorical variables. The non-parametric Wilcoxon-Mann-Whitney test was used to compare continuous variables (that is, costs). The Mantel-Haenszel analysis was performed to assess if the association between catastrophic costs and type of diagnosis (ACF vs PCF) was modified by other variables (gender, age, disease category, poverty line, dissaving, financial and social impacts). Stratified and pooled *OR*s and 95% *CI*s were reported together with the *P*-value for the homogeneity test (146). All *P*-values below 0.05 were considered statistically significant.

A sensitivity analysis was performed to assess the impact of varying the threshold for catastrophic costs (10%, 20%, 30%, 40%, 50%, and 60%) on the prevalence of catastrophic costs for ACF and PCF patients. The prevalence of catastrophic costs was also calculated using only the total direct costs as a proportion of the household annual income.

The effect of recall bias was also assessed in both groups. Median and interquartile costs were calculated for ACF and PCF patients interviewed within one month and after one month of treatment initiation.

2.6 Longitudinal patient costs evaluation IMPACT TB (chapter 6)

2.6.1 Study design and setting Longitudinal patient costs evaluation IMPACT TB

A longitudinal TB Patient Cost Survey was conducted between April 2018 and October 2019 within the IMPACT TB project. The survey was conducted in four districts of Nepal covering both rural and urban areas, hilly and lowland Terai regions: Dhanusha (population 754 777; 2.8% of the national population) and Mahottari (population 627 580; 2.4% of the national population) in Province 2, and Makwanpur (population 420 477; 1.6% of the national population) and Chitwan (population 579 984; 2.2% of the national population) in Province 3. Makwanpur, Mahottari and Chitwan districts are considered high burden TB districts, i.e. case notification rate (CNR) >120, and Dhanusha is classified as medium TB burden district, i.e. CNR between 75 and 120. These districts reported 2061 TB cases in 2018, which accounts for 11% of all reported TB cases in Nepal (66).

2.6.2 Sample size calculation and sampling

At the time of study design, there were no studies comparing ACF and PCF incurred patient costs on which to base an effect size estimate. Therefore, we took a pragmatic approach and sample size was based upon previous TB patient costing surveys in other countries that showed a sample of 100 patients is sufficient to capture the spectrum of TB patient costs incurred (147). Allowing for an expected attrition rate of 20% in the study sites, 121 patients were therefore recruited for each study arm (ACF and PCF). TB patients diagnosed through ACF and PCF were registered at IMPACT TB database and at the treatment registers at Directly Observed Treatment Short-course (DOTS) centres, respectively. A research associate checked the list of patients diagnosed in both databases monthly and consecutively selected participants until reaching the target sample size in each arm. Patients were recruited from April 2018 to January 2019.

2.6.3 Inclusion criteria Longitudinal patient costs evaluation IMPACT TB

Adults, ≥18 years old, with laboratory bacteriological confirmed pulmonary TB (new, retreatment or relapse), resident of Nepal, with written informed consent provided were eligible for this study. Drug-resistant TB patients were excluded from this study due to time and budget constraints.

2.6.4 Interventions Longitudinal patient costs evaluation IMPACT TB

PCF is the current practice implemented by the NTP in Nepal. Symptomatic individuals seek healthcare by self-presentation at healthcare facilities, which includes a network of health posts, primary health centers and government district hospitals. PCF pathway includes (1) patients are aware of their symptoms and access health facilities, (2) patients are evaluated by health workers who recognize the symptoms of TB and (3) patients are referred to diagnostic centers to collect sputum sample and perform a TB test (71). In Nepal, sputum smear microscopy is the standard diagnostic test within the NTP, with GeneXpert available in some centers and currently reserved for priority groups. The NTP is prioritizing the scale-up of GeneXpert testing (111).

Full details of the community-based ACF model applied are given in section 2.4.3(148).

2.6.5 Data collection tool longitudinal costing study IMPACT TB

The WHO TB Patient Costs Survey (KNCV Tuberculosis Foundation, World Health Organization and Japan Anti-Tuberculosis Association, 2008)(149) was adapted to the Nepli context and translated into Nepali during the TB REACH study described in chapter 5. The patient costing tool was further adapted to a longitudinal design and piloted in 16 patients for the IMPACT TB longitudinal costing evaluation. The survey collected socio-economic data, direct medical costs (e.g. drugs, tests, medical fees), direct non-medical costs (e.g. transportation, accommodation and food) and indirect costs (e.g. lost time and income loss) and information on the social and economic impact of TB. After piloting, the survey was used by trained CHWs to conduct paper-based interviews at the location preferred by the patient, usually the residence of the patient or at a health facility. Interviewers followed a standard operating procedure manual developed by the project team. Completed questionnaires were then reviewed by a research associate and district program coordinators. CHWs were advised to contact patients to clarify or correct any missing or incomplete information. Participants were compensated for their time (~60 minutes) with 500 Nepalese rupees (NPR) (~US$4.5) for each interview.

2.6.6 Patient costs, time horizon longitudinal costing study IMPACT TB

Patient costs were collected at three time points. The first interview was conducted during the intensive phase (between 2 weeks and 2 months of treatment initiation) and collected data on costs incurred during pre-TB diagnosis (since the onset of TB symptoms) and treatment period until the date of the interview. Two subsequent interviews collected information on costs incurred during TB treatment, covering the time since the preceding interview. The second interview was applied during the continuation phase of treatment (between 3 months and 4 months) and the third at the end of treatment (sixth month of treatment). Therefore, costs incurred during TB illness from the time of symptom onset (self-reported by patients) to the time of TB treatment completion were calculated.

2.6.7 Data entry and analysis longitudinal costing study IMPACT TB

Questionnaires were entered by trained study staff into a dedicated study database designed by IMPACT TB consortium partners at KNCV Tuberculosis Foundation, Netherlandsa.

Socio-economic profile

The living standard was assessed using the indicators recommended by the government of Nepal to evaluate multidimensional poverty, i.e., education level, and proportion of patients included in the study with access to electricity, drinking water, sanitation and asset ownership (143).

Patient costs

Mean costs with 95% confidence intervals (CIs) and median costs with the interquartile range were estimated by cost type (direct medical, direct non-medical and indirect costs) and by treatment period (pretreatment and treatment). Total costs were calculated by summing all costs incurred during the pretreatment and treatment periods. Direct costs were calculated by summing all costs in each category (medical and non-medical). Indirect costs comprised lost income and lost time seeking diagnosis and care. Lost income was calculated using the human capital approach (143), applying self-reported length of time absent from work, 2018 Nepali monthly minimum wage (US$121.05), the labour force participation rate (49%) and unemployment rate (1.2%) (133). Lost time was converted to a monetary value by applying hourly (US$0.62) and daily (US$4.67) minimum wages (143). Costs were collected in the local currency, NPR, and were converted to US$ applying the average exchange rate from OANDA during the data collection period (NPR 1 = US$0.009) (https://www1.oanda.com/) (144). Participants who could not be located for the second or third interviews were considered lost to follow-up and were excluded from the analysis.

To evaluate uncertainty in costs, one-way sensitivity analysis was performed. Total costs were calculated by varying direct medical, non-medical and indirect costs according to the upper and lower limit of their CIs (150).

Socio-economic impact

Income changes, employment status, poverty headcount (151), self-reported social impact (food insecurity, social exclusion and others), self-reported sense of relative economic status (e.g., feeling poorer) and use of coping strategies were analysed throughout the treatment.

Catastrophic costs

The prevalence of households with catastrophic costs was determined for the WHO threshold for TB (total cost >20% of the annual household income). Catastrophic costs were calculated according to the annual household income self-reported before the onset of TB. Catastrophic costs and pretreatment costs were not calculated for retreatment and relapse TB cases as we were not able to accurately determine pretreatment costs for this group due to the length of time elapsed between initial TB diagnosis and the interview.

Statistical analysis

Data analysis was performed using Stata version 15 (STATA, Statacorp, TX, USA). Frequency distributions and descriptive statistics such as mean/median were calculated. Chained multiple imputation (152) was used to estimate missing costs data (Supplementary Table S1). Ten multiple imputed data sets with five iterations were generated. The variables gender, age, type of provider, district and ACF/PCF were included in the imputation model. Chi-square and Fischer's exact test were applied to test differences in proportions of categorical variables. Wilcoxon rank-sum test was used to compare costs between ACF and PCF. P-values ≤0.05 were considered statistically significant.

The association between catastrophic costs and high costs, i.e. costs above the 75th quartile incurred during the pretreatment and treatment periods (114), and adjusted by baseline characteristics (i.e. ACF/PCF, sex, age, education level, employment status and patient income) was explored through multiple logistic regression. Odds ratios (ORs) with 95% CIs were estimated.

We fitted an interaction term between ACF/PCF and treatment phase using a generalized estimating equation (153) to evaluate the effect of ACF on the socio-economic characteristics throughout TB treatment: unemployment, food insecurity, social exclusions, to be poorer/much poorer, coping strategies, patient and household

incomes and poverty headcount. We used the CHEERS (154) checklist when writing our report.

2.7 Ethical Review and approvals

Ethical approvals for the yield study and Costs study (TB REACH project) were received from the Liverpool School of Tropical Medicine (LSTM) UK [N 17-019] and the Nepal Health Research Council [149/2017]. Ethical approval of IMPACT TB were approved by the Liverpool School of Tropical Medicine UK (N. 17-019) and the Nepal Health Research Council Ethical Committees (Reg. no. 138/2017). All participants received a written Patient Information Sheet and an oral explanation about the study. Written informed consent was obtained from participants before each interview. Data were anonymized for the analysis.

CHAPTER 3: Comparative Yield of Tuberculosis during Active Case Finding Using GeneXpert or Smear Microscopy for Diagnostic Testing in Nepal within TB REACH wave 5 implementation

3.1 AIMS Chapter 3

The study aimed to compare the yield of bacteriological confirmed TB using either smear microscopy or GeneXpert as the primary diagnostic test and to further compare the yields of the NTP recommended three case finding strategies. The study also evaluated both the crude and adjusted additionality to TB case notifications achieved from ACF interventions in the study districts.

3.2 Abstract chapter 3

Objective: This study compared the yield of tuberculosis (TB) active case finding (ACF) interventions applied under TB REACH funding.

Methods: Between June 2017 to November 2018, Birat Nepal Medical Trust identified presumptive cases using simple verbal screening from three interventions: door-to-door screening of social contacts of known index cases, TB camps in remote areas, and screening for hospital out-patient department (OPD) attendees. Symptomatic individuals were then tested using smear microscopy or GeneXpert MTB/RIF as first diagnostic test. Yield rates were compared for each intervention and diagnostic method. We evaluated additional cases notified from ACF interventions by comparing case notifications of the intervention and control districts using standard TB REACH methodology.

Results: The project identified 1092 TB cases. The highest yield was obtained from OPD screening at hospitals (n = 566/1092; 52%). The proportion of positive tests using GeneXpert (5.5%, n = 859/15637) was significantly higher than from microscopy testing 2% (n = 120/6309). (OR = 1.4; 95%CI = 1.12–1.72; p = 0.0026). The project achieved 29% additionality in case notifications in the intervention districts demonstrating that GeneXpert achieved substantially higher case-finding yields.

Conclusion: Therefore, to increase national case notification for TB, Nepal should integrate OPD screening using GeneXpert testing in every district hospital and scale up community-based ACF of TB patient contacts nationally.

3.3 Background Chapter 3:

WHO recommends a rapid molecular diagnostic such as GeneXpert MTB/RIF (Cepheid, USA) as the first diagnostic test in any presumptive TB case (6). However, the relatively high cost of GeneXpert compared to traditional smear microscopy diagnosis has limited uptake by many low-income countries. The test is often only applied to groups at high risk for multidrug-resistant TB (MDR-TB) and HIV positive cases. Nevertheless, if routinely applied, accurate rapid diagnostic tests have great potential for increasing case identification and early treatment. We, therefore, sought to compare the difference in case-finding yields of ACF strategies applying either traditional smear microscopy or GeneXpert testing, which is the primary diagnostic test in Nepal. We also compared the yield of three different case-finding interventions in Nepal: (1) district hospital OPD screening, (2) community-based social contact tracing of known index TB patient, and (3) TB camps in remote or underserved populations.

Nepal is a Himalayan country in South Asia with a vibrant diverse culture and a significant burden of TB (annual incidence 245/100,000) (4). The NTP provides routine free TB diagnosis and treatment services using the passive case-finding (PCF) model with sporadic ACF activities implemented under varying models and in different geographical areas, by the NTP and partner organisations (66). Difficult geographical terrain, inadequate knowledge on TB symptoms and services, and poverty have limited access to TB services among the general population, particularly in remote areas (155, 156). The 2019 Nepal prevalence survey estimated that 40,000 cases are missing from the NTP notifications each year (4). Therefore, the NTP strategy 2016-21 has prioritized ACF scale-up as a diagnostic strategy to complement PCF (157). The strategy recommended conducting screening among close contacts of index patients, TB camps, and hospital screening. Nevertheless, there remains a paucity of data on the yield of these strategies and inadequate evidence to drive comprehensive scale up within the NTP, with many competing priorities for government funding.

3.4. Results of TB REACH wave 5 ACF intervention

Overall, the ACF project intervention diagnosed 1,092 TB cases in 17 months in the eight districts. The project verbally screened 54,239 contacts or high risk individuals, identified 28,293 symptomatic individuals and tested 27,096 individuals. The cascade of screening to diagnosis of TB cases, disaggregated by ACF strategy, during the study period is shown in Figure 3.1. The age and gender disaggregation of identified cases is given in table 3.1. The majority of the individuals diagnosed with TB were male (752/1092; 69%). A fifth of those with TB was aged 65 years and above (230/1092; 21%).

Figure 3.1: Flowchart showing screening cascade results of the ACF intervention applied in TB REACH wave 5 project, disaggregated by ACF

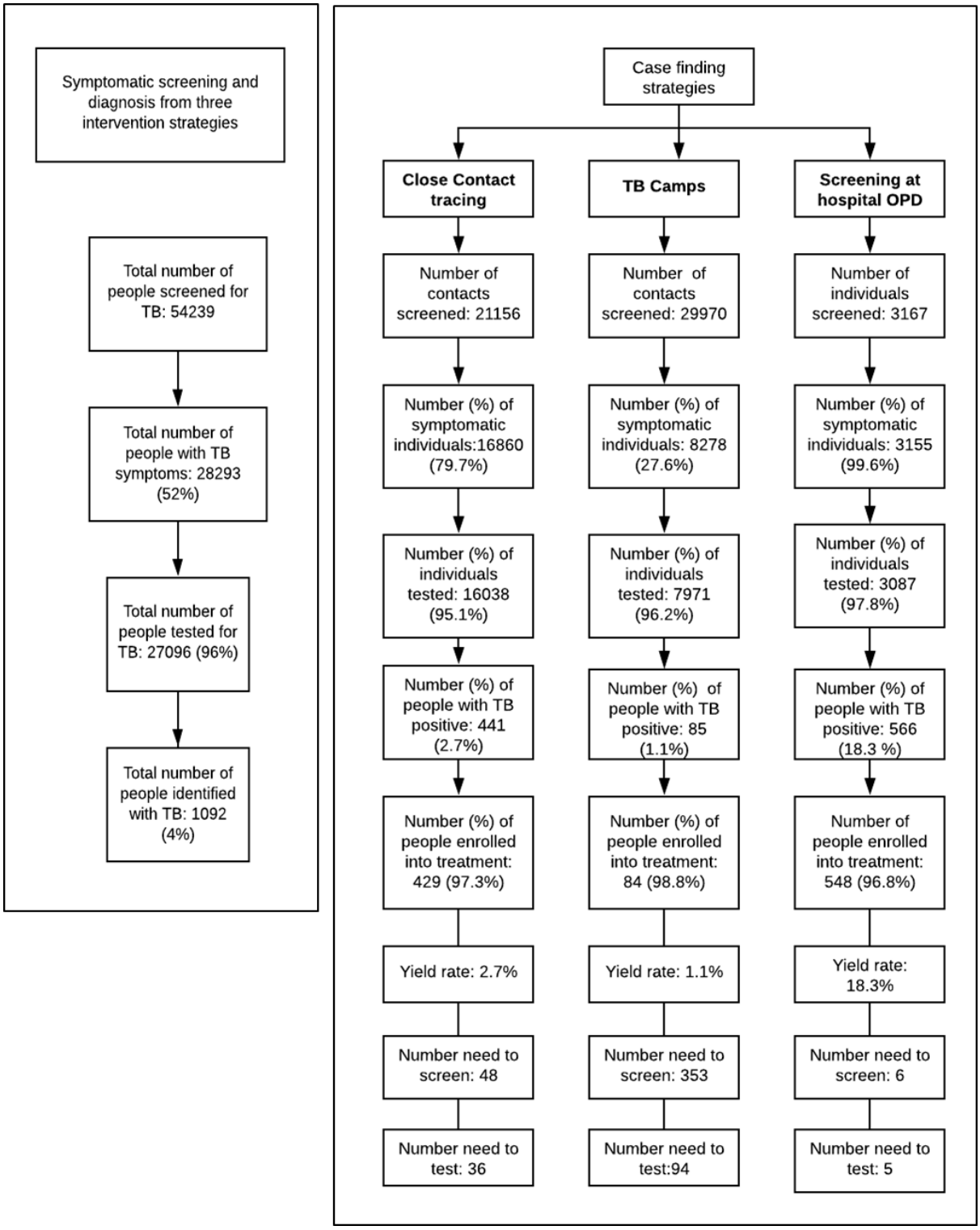


Table 3.1:Age and sex wise disaggregation of people diagnosed with TB through the TB REACH active case finding intervention

Age group	Male (%)	Female (%)	Total (%)
0-4	0 (0)	0 (0)	0 (0)
5-14	5 (0.7)	7 (2.1)	12 (1.1)
15-24	86 (11.4)	50 (14.7)	136 (12.5)
25-34	103 (13.7)	47 (13.8)	150 (13.7)
35-44	88 (11.7)	58 (17.1)	146 (13.4)
45-54	129 (17.2)	62 (18.2)	191 (17.5)
55-64	152 (20.2)	75 (22.1)	227 (20.8)
≥ 65	179 (23.8)	51 (15.0)	230 (21.1)
Total number of TB diagnosed B+ TB (SS+ Xpert)	752 (100)	340 (100)	1092 (100)

3.4.1 Comparison of Yield from GeneXpert vs. Smear Microscopy

Table 3.2 shows the indicators between the two diagnostic tools implemented in six districts for all the three interventions. The majority of the cases in the study were diagnosed using GeneXpert with yield rate 5.5% vs. 2% by smear microscopy. Using GeneXpert and smear microscopy, respectively, NNS was 38 and 93, and NNT was 18 and 53.

Table 3.2: Comparison of TB yields in intervention districts using GeneXpert or smear microscopy as TB diagnostic tool for active case finding intervention

Indicators	Districts Diagnosing TB with GeneXpert	Districts Diagnosing TB with Smear Microscopy
Total number of people screened	32,616	11,202
Total number of people with TB symptoms	16,060	6,575
Total number of people tested for TB	15,637	6,309
Total number of people diagnosed with TB positive	859	120

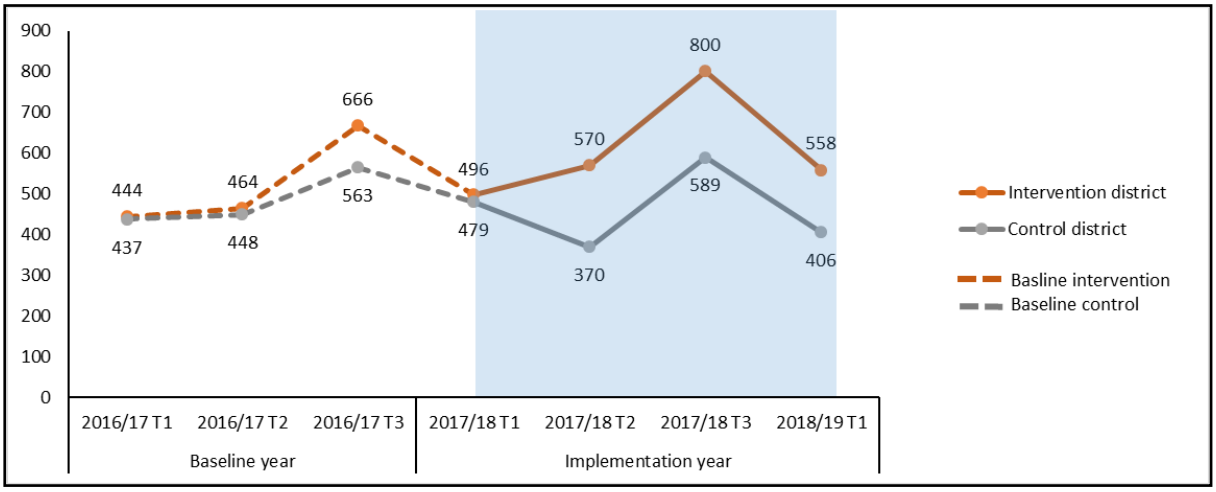
Yield rate (%)	Contact Tracing	3.2 (273/8567)	2.4 (103/4246)
	TB Camps	1.4 (58/4106)	0.82 (17/2063)
	Three interventions combined	5.5 (859/15637)	2 (120/6309)
Numbers needed to screen (NNS)		38	93
Numbers needed to test (NNT)		18	53

However, as districts using smear microscopy did not apply OPD screening as an intervention strategy, we further compared the interventions using contact tracing and TB camps only. The respective yield rate from GeneXpert and smear microscopy during contact tracing was 3.2% and 2.4%, and that for TB camps was 1.4% and 0.82%. The use of GeneXpert for TB diagnosis increased case detection (OR = 1.4; 95%CI = 1.12–1.70; p = 0.0026) (**Error! Reference source not found.**).

3.4.2 Additionality in Case Notification

Figure 3.2 shows the NTP case notification data for the intervention and control districts during the preceding year (2016/17) and the year of intervention (2017/18 and 2018/19). We calculated additionality and compared the case notification data with the corresponding trimester of the baseline year using unadjusted additionality methods for case notifications for bacteriologically positive TB in the implemented districts (**Error! Reference source not found.**). We consolidated the trimester data of intervention district and observed 406 additional cases (20.1%) in bacteriologically confirmed cases. During the same period, there was a decrease in case diagnosis in the control districts of −2.2%. Therefore, the additionality in the intervention districts contributed by the project was 22.3%. TB REACH standard method applied.

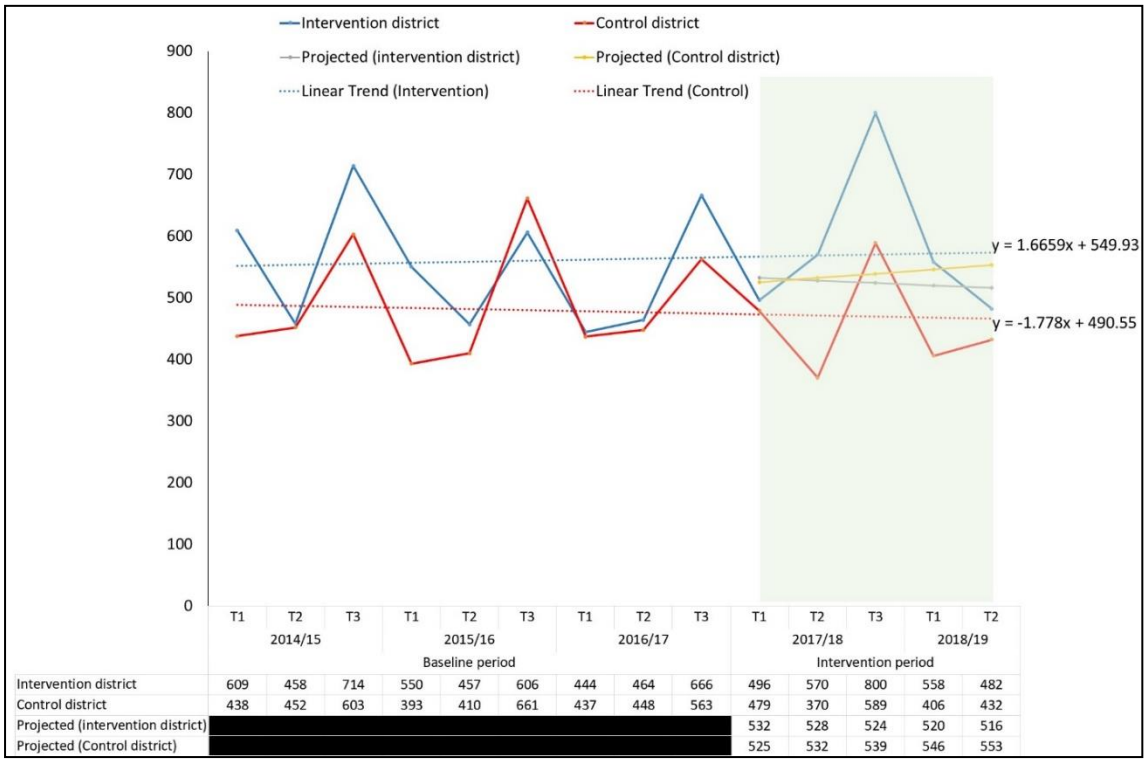
Figure 3.2: Comparison of case notification before and after implementation of active case finding (ACF) interventions (unadjusted data).



We also compared the case notification with the estimated three-year (2014/15–2016/17) trend-adjusted data. We identified additionality of 15.4% for bacteriologically confirmed TB and decrease of 13.9% in the control districts. The comparison showed the total increment in the case notifications in the implemented districts by 29.0% (Figure 3.3). Since 2014/15, we observed an annual declining linear trend case notification data in the corresponding trimester before intervention. Therefore, the results showed that the double difference was substantial in both unadjusted (22.3%) and adjusted additionality (29.0%).

The projected values for both intervention and control districts are forecasted values under the condition that no intervention was done (i.e. routine NTP was implemented). Thus, the projected lines are drawn for the intervention period based on the values preceding the intervention (3 years taken here). The overall trend lines are shown aggregated by control or intervention area for the complete five year duration.

Figure 3.3: Comparison of case notifications before and after implementation of ACF interventions (3-year trend-adjusted, i.e., estimated case notification).



	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2
	2014/15			2015/16			2016/17			2017/18			2018/19	
	Baseline period									Intervention period				
Intervention district	609	458	714	550	457	606	444	464	666	496	570	800	558	482
Control district	438	452	603	393	410	661	437	448	563	479	370	589	406	432
Projected (intervention district)										532	528	524	520	516
Projected (Control district)										525	532	539	546	553

NB: projected data lines for intervention and control districts estimate expected notifications during the intervention period for intervention and control districts projected from T3 2016/17 baseline if no intervention occurs.

3.3 Discussion chapter 3

This TB REACH wave 5 project successfully contributed 22% additionality to the NTP case notification in the project districts. Over 50% of the project yield was attributable to screening for TB symptoms in OPD attendees at the government district hospitals and subsequent testing by GeneXpert. Although this strategy is often not considered “active” case finding, in the Nepali context, at the time of the project, this was an extension of the standard National TB programme strategy. An OPD screening strategy known as the FAST strategy policy evolved since this work had been done and incorporated into the Global Fund-supported activities of the NTP in priority districts. The substantial yield of this strategy, when coupled with GeneXpert testing to maximise the sensitivity of the testing, demonstrates that there is an urgent need

for every district hospital in Nepal to be equipped with GeneXpert testing and to consistently implement TB symptom screening in OPD attendees.

A further major finding of the project was the substantial yield of cases (n = 230) in individuals >65 years of age. This is consistent with our previous TB REACH wave 2 project data November 2011 to June 2014 and the 2019 prevalence survey and shows that the elderly are among those high-risk groups unable to access existing TB diagnostic services (4, 102). National strategies to improve TB screening and diagnosis among the elderly should be developed and implemented and integrated with existing health services.

The 2019 prevalence survey in Nepal has revealed a high proportion of asymptomatic individuals with active TB; 70% of those identified were asymptomatic (4). While our study shows that substantial additionality can be achieved using a simple verbal symptom-screening tool, to achieve the END-TB strategy goals, this must be complemented by a scale-up in availability of chest X-ray diagnosis (6). Currently, there are rarely specialized radiographers available in remote districts of Nepal, and chest X-ray equipment is often nonfunctioning. The recent development of improved accuracy of computer-assisted chest X-ray reading for TB diagnosis presents an ideal opportunity for Nepal to address this gap (158).

In this study, we obtained a lower yield from TB camps, which were conducted in hard-to-reach areas. Nevertheless, it is important to conduct such camps as the study screened and tested a large number of people who are not able to access diagnosis in other ways. Such strategies improve equity of access to quality TB services, reduce patient incurred costs from TB illness in the most impoverished population groups, and are essential to “leave no-one behind” in countries with large remote rural populations (148, 159).

Our results showing the increase in case diagnosis by using GeneXpert is consistent with other studies that highlighted improved case detection through the use of sensitive molecular diagnostic methods (98). WHO now recommends molecular diagnostic tests such as GeneXpert as the first test of choice to investigate patients for TB; however, resource limitations are a major barrier to uptake in high TB burden or low resource settings. To achieve widespread scale-up of GeneXpert as a first line test for TB through national policies, cost-effectiveness studies are necessary to

quantify the relative costs of health systems approaches applying GeneXpert or smear. We are currently preparing a health system costing evaluation for publication. These studies will inform NTP to design and implement effective and sustainable case-finding strategies (160, 161).

To achieve the END TB strategy goals and close the global case detection gap, it is essential that all presumptive TB cases in high burden settings are tested by rapid molecular diagnostic methods. During the implementation of the project, Nepal underwent a major change in its political structure to a federal system, which included restructuring of the public health system administration. This affected the regular functioning of health workers, including those working in TB, and could have influenced the case notification in both intervention and control districts. The short duration of the project period exacerbates the weight of such external challenges. Therefore, to implement the ACF strategies, a significant period should be allocated prior to the project inception, especially for establishing human resources and rapport building within the health system to ensure optimal integration and synergy.

3.5 Conclusions chapter 3

This study demonstrated that ACF can effectively yield additional TB case notifications at the district level in Nepal, and contribute to closing the case notification gap. Substantial additionality in TB case notification was demonstrated through OPD screening and social-contact-tracing strategies. Higher yields were achieved using GeneXpert than smear microscopy for active case finding. Although TB camps had a relatively low yield, this strategy reaches remote populations and is an important component of a comprehensive TB case-finding strategy. Comprehensive cost-effectiveness studies that evaluate the monetary value of these interventions would better contribute evidence for the design and application of optimal NTP strategies to achieve the END TB targets (99, 162).

An intensification of the ACF strategy was evaluated in the subsequent IMPACT TB study reported in chapter 4, installing three GeneXpert machines in each of the ACF intervention districts applying GeneXpert testing. The IMPACT TB study focused on social contact tracing around index cases to avoid duplication of, and ensure synergy with, ACF activities implemented under the Global Fund programme.

CHAPTER 4: Additionality of GeneXpert or smear based active TB case finding among social contacts of index cases in Nepal IMPACT TB study

4.1 AIMS Chapter 4

1) Compare the yield of bacteriological confirmed tuberculosis using standard smear microscopy (Zhiel Neelson stain) or GeneXpert (rapid molecular test) as the primary diagnostic test, with three GeneXpert machines installed in each GeneXpert intervention district.

2) Evaluate the additionality (contribution to NTP) achieved from ACF interventions in the study districts.

4.2 Abstract chapter 4

Background: Forty thousand people with tuberculosis (TB) remain undiagnosed or unnotified in Nepal every year, to close the case notification gap the national TB Programme must improve strategies to identify cases in the community and enroll them promptly to treatment. The IMPACT TB project (www.impacttbproject.org) aimed to compare yield and additionality of community based active TB case finding strategies using either smear microscopy or GeneXpert testing as the diagnostic test.

Methods: Community based active TB case finding screening social contacts of index cases and high-risk groups was implemented in four districts of Nepal from July 2017-2019. Two districts (Chitwan and Dhanusha) applied GeneXpert testing and two districts (Makwanpur and Mahotarri) used smear microscopy. Two control districts implemented only the standard national TB control programme activities.

Results: The two districts implementing GeneXpert testing for ACF (Dhanusha and Chitwan) screened a total of 23,657 people for TB, tested 17,114 and diagnosed 764 TB cases, giving a yield of 4.5 %. The two districts implementing smear microscopy for ACF (Makwanpur and Mahotarri) screened a total of 19,961 people for TB, tested 13,285 and diagnosed 437 cases, giving an overall yield of 3.3%. The number needed to screen (NNS) was 31 and 45.7 for GeneXpert and smear districts, respectively. The number need to test (NNT) was 22.4 and 30.4 for GeneXpert and smear districts.

Adjusted additionality in TB case notifications was +20% (3985/3322) for the GeneXpert districts, +12.4% (3146/2798) for the smear districts and -0.5% (2553/2566) for the control districts.

Conclusion: Social contact tracing for TB using GeneXpert testing yielded an additional 22% to district level TB notifications in Nepal. Social contact tracing of TB index cases should be implemented throughout Nepal within the TB FREE initiative to close the notification gap and accelerate progress towards the END TB strategy targets(163).

4.3 Background Chapter 4

National TB Programmes (NTP) in LMICs heavily rely on diagnosing TB through passive case finding (PCF), and test for TB principally using smear microscopy in government health facilities (164, 165). Delays to diagnosis caused by PCF are multifactorial and include barriers to access TB services, lack of recognition of disease severity by the patient, the severe socioeconomic consequences of TB and health system constraints in the LMICs (166, 167). In addition, smear microscopy has a sensitivity of only around 50% for active disease and consequently many patients receive a false negative diagnosis, which leads to further delays in diagnosis and treatment. Delays in prompt treatment initiation can lead to sustained transmission, poor health outcomes, resistance to TB drugs or death (168, 169). However, newer diagnostic methods are available, including molecular testing approaches approved by WHO and recommended for scale-up (170, 171). To accelerate the elimination of TB and achieve the END TB strategy target to reduce TB incidence by 90% from its 2015 baseline, dramatically increased case notification is required (172, 173). WHO recommends both the scale-up of advanced molecular technology such as GeneXpert MTB/RIF and systematic screening of contacts of people with TB (174, 175). Evidence from low-and middle-income countries has shown increased TB diagnosis using GeneXpert among household and close contacts in LMICs (175-177).

Systematic screening of contacts by active case finding (ACF) is a global health priority and is identified as a key component of END TB Strategy for integrated, patient centred care and prevention (172, 173, 178, 179). WHO defines ACF as provider-initiated systematic screening and testing in the predetermined target groups, by assessing symptoms and using high accuracy tests, examinations and other procedures that can

be applied rapidly (174). ACF overcomes diagnostic barriers for the most vulnerable groups, reducing patient delay and pre-diagnosis costs for patients, and improving case detection rates, case notification and treatment outcomes (177, 180). Early diagnosis can shorten the infectious period, therefore, reducing transmission, incidence and prevalence (164, 173, 181-184). However, without appropriate contextual strategy, ACF activities can be a financial burden for health systems and also contribute to stigma, discrimination, and increase false-positive and false-negative results(181, 185, 186)). ACF needs to be implemented with sustainable strategies based on context, making optimal use of resources, balancing the potential benefits and challenges and supplementing existing PCF strategies rather than replacing them(164, 181, 182, 185-187).

Nepal is a low income country with TB incidence of 245 per 100,000 population(188). Although the NTP strategy 2016-2021 adopted both ACF and PCF approaches to diagnose new TB patients, to achieve the END TB target for Nepal, a comprehensive strategy needs to be designed and implemented to identify the 40,000 people with TB who remain undiagnosed or unreported each year in Nepal (188, 189). While WHO approved molecular diagnostics have higher sensitivity than smear microscopy, the costs, maintenance logistics and training required are considerable challenges or the national TB Programme in remote rural Nepal.

The IMPACT TB project compared the yield and additionality gained by applying either smear microscopy (in Makwanpur and Mahottari) or GeneXpert MTB/RIF (in Chitwan and Dhanusha) as the ACF diagnostic testing strategy among social contacts of TB cases. IMPACT TB aimed to compare the additionality gained at the district level through these two implementation models of community based active case finding in Nepal. The findings will inform. intensification strategies for scale up of active case finding of TB in Nepal under the TB FREE Nepal initiative of the National TB Programme(163).

4.4 Results IMPACT TB ACF intervention

In total, the IMPACT TB project verbally screened 41,388 for TB and diagnosed 1,201 TB cases with microbiologically confirmed TB across all four districts. This is an overall project direct yield of 2.9% (n=1,201/41,388). The government national TB programme

TB case notification data for the intervention and control districts (baseline and intervention years) in the IMPACT TB project is shown in table 4.1.

The two districts implementing GeneXpert testing for ACF (Dhanusha and Chitwan) screened a total of 23,657 people for TB and diagnosed 764 TB cases, giving a yield of 4.5 %. The number needed to screen (NNS) in these districts was 31.0 and the number needed to test (NNT) was 22.4.

The two districts implementing smear microscopy for ACF (Makwanpur and Mahotarri) screened a total of 19,961 people for TB and diagnosed 437 cases, giving an overall yield of 3.3%. The number needed to screen in these districts was 45.7 and the number needed to test was 30.4.

The majority of cases were identified through screening contacts of index cases: 33,767 people were screened from 3,122 index cases and through door to door high-risk community screening, and 5,442 were screened through 51 camps which identified 195 TB cases. This gave an overall yield of 3.6% though the camps. Twenty seven camps using GeneXpert testing yielded 105 cases among 2,460 tested (4.3% yield). Twenty four camps using smear microscopy testing yielded 90 cases among 2,982 tested (3.0% yield).

Table 4.1: National TB programme notification data for IMPACT TB intervention and control districts

		Baseline						Intervention							Baseline total	Intervention total	% change
Category	**District**	**2015/16**			**2016/17**			**2017/18**			**2018/19**						
		T 1	**T 2**	**T 3**	**T1**	**T2**	**T3**	**T1**	**T2**	**T3**	**T1**	**T2**	**T3**				
Evaluation-Xpert																	
	Chitwan	297	258	414	303	264	363	325	291	455	394	340	462		**1899**	**2267**	**+19.4%**
	Dhanusha	159	195	280	255	173	289	236	210	367	292	237	376		**1351**	**1718**	**+27.2%**
Total		456	453	694	558	437	652	561	501	822	686	577	838		**3250**	**3985**	**+22.6%**
Evaluation-Smear																	
	Mahotarri	251	288	351	288	230	312	263	252	389	234	281	306		**1720**	**1725**	**+0.3%**
	Makwanpur	241	201	291	288	185	236	208	234	257	188	218	316		**1442**	**1421**	**-1.5%**
Total		492	489	642	576	415	548	471	486	646	422	499	622		**3162**	**3146**	**-0.5%**
Control																	
	Sarlahi	293	311	497	363	303	369	341	304	419	359	322	258		**2136**	**2003**	**-6.2%**
	Dhading	62	104	113	84	84	101	105	79	105	70	90	101		**548**	**550**	**+0.4%**
Total		355	415	610	447	387	470	446	383	524	429	412	559		**2648**	**2553**	**-3.6%**

4.4.1 Additionality of IMPACT TB ACF interventions

Crude additional case notification for each district, and by testing strategy (GeneXpert vs. smear) are shown in table one. An overall additional crude notification of +22.6% was achieved for the GeneXpert districts, with a 0.5% decrease for the districts applying smear microscopy for ACF. During the same time period the control districts reported a decline in case notification of -3.6%.

The predicted case notification for each district based on the trend for the three years preceding the IMPACT TB intervention is shown in figure 4.2. Table 4.2 shows the predicted and actual notifications for each district, along with notifications aggregated by testing intervention (GeneXpert, smear or control), also shown graphically in figure 3. Overall, the three-year trend extrapolation would predict a case notification total of 3,322 for the GeneXpert districts, 2,798 for the smear districts and 2,566 for the control districts. The actual notifications during the intervention period were 3,985 for GeneXpert districts, 3,146 for smear districts and 2,553 for the control districts. This gave an adjusted additionality of +20% (3985/3322) for the GeneXpert districts, +12.4% (3146/2798) for the smear districts and -0.5% (2553/2566) for the control districts.

The adjusted additionality method (table 4.2) revealed a strong variation between the two districts implementing smear microscopy, with Mahotari district reporting a +56.4% increase in notifications compared to the predicted notification based on the trend. Makwanpur district, in contrast, reported a -16.2% decrease in actual notifications during the implementation period compared to the predicted trend.

The mixed effects model estimated a relative increase associated with the implementation of GeneXpert based ACF of 1.15 [95% CI 1.07 to 1.25] and a relative increase associated with smear based ACF of 1.04 [95% CI 0.95 to 1.14]. Thus, there was a statistically significant increase of 15% in TB notifications attributable to the GeneXpert based ACF, and a 4% increase in TB notifications in the smear based ACF districts when fitting the data to the mixed effects model.

Table 4.2: Predicted and actual case notifications by district, and aggregated by testing strategy (smear or Genexpert).

		Predicted						Intervention							Predicted total	Intervention total	% difference
Category	**District**	**2017/18**			**2018/19**			**2017/18**			**2018/19**						
		T 1	**T 2**	**T 3**	**T1**	**T2**	**T3**	**T1**	**T2**	**T3**	**T1**	**T2**	**T3**				
Evaluation-Xpert																	
	Chitwan	326	327	327	328	329	330	325	291	455	394	340	462		**1967**	**2267**	**+15.3%**
	Dhanusha	231	229	227	225	223	220	236	210	367	292	237	376		**1355**	**1718**	**+26.8%**
Total		557	556	554	553	552	550	561	501	822	686	577	838		**3322**	**3985**	**+20.0%**
Evaluation-Smear																	
	Mahotarri	199	194	188	183	172	167	263	252	389	234	281	306		**1103**	**1725**	**+56.4%**
	Makwanpur	264	271	279	286	294	301	208	234	257	188	218	316		**1695**	**1421**	**-16.2%**
Total		463	465	467	469	466	468	471	486	646	422	499	622		**2798**	**3146**	**+12.4%**
Control																	
	Sarlahi	346	340	335	329	324	318	341	304	419	359	322	258		**1992**	**2003**	**+0.5%**
	Dhading	95	95	95	96	96	97	105	79	105	70	90	101		**574**	**550**	**-4.2%**
Total		441	435	430	425	420	415	446	383	524	429	412	559		**2566**	**2553**	**-0.5%**

Figure 4.1: National TB Programme notification data by district for three years prior to IMPACT TB intervention and predicted linear trendline for

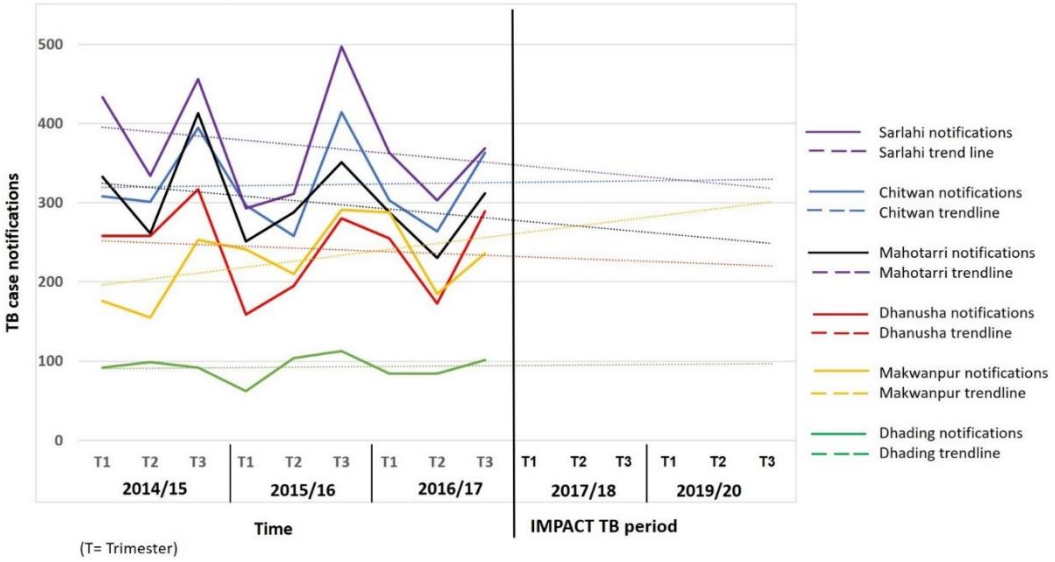
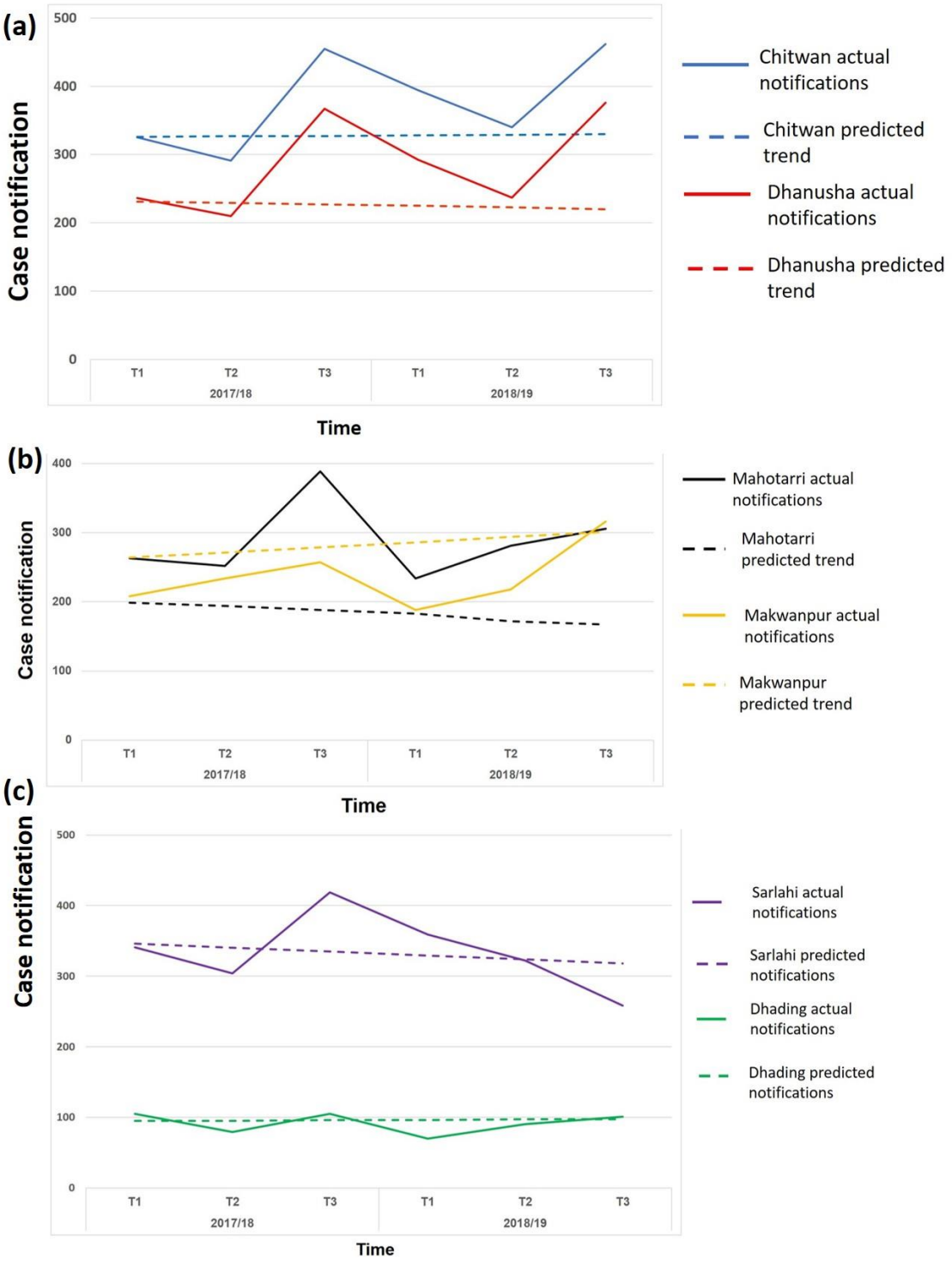


Figure 4.2: Achieved case notifications and predicted linear trend during the IMPACT TB intervention for (a) GeneXpert active case finding districts (b) smear microscopy active case finding districts and (c) control districts



4.5 Discussion of IMPACT TB yield analysis

Conducting active case finding among social contacts and high-risk population groups using GeneXpert testing resulted in substantial additional yield and additionality in Nepal. The active TB case finding projected 13% overall additionality to the NTP case notification in the intervention districts. A twenty percent adjusted additionality was shown in the IMPACT TB districts applying GeneXpert testing, when using the TB REACH double difference method to estimate additionality. Crude yield comparison (+22.6%) and the mixed effects modeling (+15%) also showed a strong additionality for GeneXpert based active case finding. Strong additionality was shown for both the districts implementing GeneXpert testing, Chitwan and Dhanusha.

The crude yield comparison of notifications in districts using smear microscopy testing showed a -0.5% decrease. However, when the adjusted additionality method was applied which takes account of the three year trend in the districts prior to the intervention, the smear districts showed an adjusted additionality of +12.4%. This is due to the decreasing trend in TB notifications in these districts prior to the IMPACT TB intervention. However, the two smear districts reported dramatically different results, with Mahotari district showing an adjusted additionality of +56%, and Makwanpur showing a decrease of -16.2%. During the IMPACT TB intervention period TB services in Makwanpur district were interrupted due to the sad death of the district TB and Leprosy Officer in a road traffic accident and a long delay in the appointment of a replacement. This variation in performance between the districts reflects the vulnerability of fragile health services to disruption and the need to build greater resilience into TB service delivery, particularly in rural areas(190). A larger evaluation area including more districts in each arm of the study would have allowed a more robust analysis of the factors influencing successful achievement of additionality.

This decreasing notification trend was also observed for the control districts (Sarlahi and Dhading) during the intervention period. Notifications in the control districts continued to decline by -3.6% during the two year IMPACT TB intervention. The mixed effects modelling also showed a relatively small additionality for the smear districts of +4%.

The number needed to screen, and number needed to test were also lower for GeneXpert testing compared to smear. For GeneXpert testing 31 people were

screened and 22 tested for every case detected, while for smear microscopy 46 people were screened and 30 tested for every person diagnosed. This result was expected due to the known substantially higher sensitivity of GeneXpert testing for tuberculosis(175, 176, 191, 192). However, it is important to quantify the difference given the substantial difficulties of obtaining and transporting samples for TB testing in rural Nepal, and the higher costs of GeneXpert testing. A health systems cost analysis of the IMPACT TB interventions is being prepared for publication. GeneXpert testing is also able to identify multidrug resistant TB (MDR TB) cases which smear microscopy is not(175). Only one in four MDR TB cases in Nepal is currently diagnosed and treated through the National TB Programme.

The TB case notification gap in Nepal is approximately 40,000 cases per year, with only 40% of cases diagnosed and treated through the National TB Programme (193). TB case detection plummeted due to the COVID pandemic, a situation which was observed in many high TB burden countries (190, 194-197). Unfortunately this has resulted in TB deaths increasing globally for the first time in a decade, with 1.5 million deaths due to TB in 2020 (198). Community based, patient centered health services were shown to be more resilient than centralized services during the pandemic (190). Active TB case finding through our network of community health workers reaches the most vulnerable members of a community and supports them to access and complete treatment for TB. The active case finding approach also reduces catastrophic health expenditure among households affected by TB(83, 180, 199). The elimination of catastrophic health expenditure is one of three key targets of the STOP TB partnership's END TB strategy, which Nepal has adopted(178, 200).

For every dollar invested in TB control programmes there is an approximate 59 USD return on investment in low and middle income countries(201). It is one of the most cost-effective public health interventions. Delivering 'people-centered care in the community' and universally replacing smear microscopy with rapid molecular diagnostics as the initial diagnostic test are two priority actions of the STOP TB global plan to END TB 2020-2023(201).

The IMPACT TB intervention analysis clearly shows that the active case finding approaches applying GeneXpert testing result in substantial additional notifications at the district level. 'Scale-up of activities of Active Case Finding among high risk and

vulnerable groups' is a priority of the five year strategic plan for tuberculosis in Nepal. but no case notification target is defined among the key performance indicators(202). Active Case finding in Nepal should be intensified to include social contacts of index cases as well as household contacts, and expanded to cover every district through GeneXpert testing, to maximize case notification and close the diagnostic gap (179, 184). The National TB Control Centre has recently launched the TB FREE Nepal initiative in 53 municipalities, with a plan to scale this up to all 753 municipalities throughout the country within four years (163, 200). Sustained political commitment will be necessary to achieve these ambitious goals. Comprehensive active case finding strategies will be an essential component of increasing TB notification in Nepal and progressing towards the END TB goals. In addition, community based active case finding supports equity of access to health services and health rights of people affected by TB through patient centred comprehensive TB care (203).

4.6 Conclusion

Social contact tracing for TB using GeneXpert testing yielded an additional 22% to district level TB notifications in Nepal. The additionality achieved in IMPACT districts implementing GeneXpert was not substantially higher than within the TB REACH project GeneXpert districts, despite the installation of 4 module GeneXpert machines at three locations within each district during IMPACT TB. During the IMPACT TB implementation, Global Fund supported the OPD based screening of TB cases in these districts via a strategy known as FAST (Find cases Actively, Separate safely and Treat effectively), which was implemented by another organisation(204). Therefore OPD screening was not included in the IMPACT TB interventions to avoid duplication and this may have reduced the yields of the ACF intervention.

The IMPACT TB and TB REACH interventions both demonstrated that social contact tracing of TB index cases results in high yields and should be implemented throughout Nepal within the government TB FREE initiative to close the notification gap and accelerate progress towards the END TB strategy targets(163). Social contact tracing is now being included in the next Global Fund TB application for Nepal, which will be submitted for implementation beginning March 2024.

CHAPTER 5: The Role of Active Case Finding in reducing Patient incurred Catastrophic Costs for Tuberculosis in Nepal: TB REACH wave 5 evaluation

5.1 AIMS Chapter 5

1) measure the prevalence and intensity of catastrophic costs incurred by TB patients in two districts implementing the TB REACH wave 5 ACF intervention.

2) compare costs incurred by TB patients diagnosed through either ACF and PCF to determine if ACF is a potential strategy to reduce the prevalence or intensity catastrophic costs for Nepali TB patients.

5.2 Abstract chapter 5

Background: The World Health Organization (WHO) End TB Strategy has established a milestone to reduce the number of tuberculosis (TB)- affected households facing catastrophic costs to zero by 2020. The role of active case finding (ACF) in reducing patient costs has not been determined globally. This study therefore aimed to compare costs incurred by TB patients diagnosed through ACF and passive case finding (PCF), and to determine the prevalence and intensity of patient-incurred catastrophic costs in Nepal.

Methods: The study was conducted in two districts of Nepal: Bardiya and Pyuthan (Province No. 5) between June and August 2018. One hundred patients were included in this study in a 1:1 ratio (PCF: ACF, 25 consecutive ACF and 25 consecutive PCF patients in each district). The WHO TB patient costing tool was applied to collect information from patients or a member of their family regarding indirect and direct medical and non-medical costs. Catastrophic costs were calculated based on the proportion of patients with total costs exceeding 20% of their annual household income. The intensity of catastrophic costs was calculated using the positive overshoot method. The chi-square and Wilcoxon-Mann-Whitney tests were used to compare proportions and costs. Meanwhile, the Mantel Haenszel test was performed to assess the association between catastrophic costs and type of diagnosis.

Results: Ninety-nine patients were interviewed (50 ACF and 49 PCF). Patients diagnosed through ACF incurred lower costs during the pre-treatment period (direct

medical: USD 14 vs USD 32, P = 0.001; direct non-medical: USD 3 vs USD 10, P = 0.004; indirect, time loss: USD 4 vs USD 13, P < 0.001). The cost of the pre-treatment and intensive phases combined was also lower for direct medical (USD 15 vs USD 34, P = 0.002) and non-medical (USD 30 vs USD 54, P = 0.022) costs among ACF patients. The prevalence of catastrophic direct costs was lower for ACF patients for all thresholds. A lower intensity of catastrophic costs was also documented for ACF patients, although the difference was not statistically significant.

Conclusions: ACF can reduce patient-incurred costs substantially, contributing to the End TB Strategy target. Other synergistic policies, such as social protection, will also need to be implemented to reduce catastrophic costs to zero among TB-affected households.

5.3 Introduction chapter 5

TB case finding (ACF) is an important complimentary strategy to passive case finding (PCF) in terms of early diagnosis and treatment, prevent the transmission and reducing the catastrophic costs.

The first published manuscript of this thesis examines the active case finding an effective strategy to reduce patient incurred catastrophic costs for tuberculosis in Nepal and also compare costs incurred by TB patients diagnosed through ACF and PCF.

The World Health Organization (WHO) End TB Strategy has established a goal to end the global tuberculosis (TB) epidemic. A key milestone to be achieved by 2020 is reducing the number of TB-affected households facing catastrophic costs to zero (10). A recent systematic review including studies of sufficient quality with low risk of bias conducted in Nigeria, Peru, China, and Moldova analyzed the effect of cash interventions on treatment outcomes. The review concluded that patients receiving a TB-specific cash transfer were more likely to have a positive clinical outcome than patients in the control group (odds ratio [*OR*]: 1.77; 95% confidence interval [*CI*]: 1.57–2.01) (123). However, cash transfers alone are unlikely to eliminate catastrophic costs. Active case finding (ACF) has been recommended by international agencies as a supportive strategy to reduce the financial burden faced by TB patients (10, 102).

Studies have shown the importance of scaling up ACF to eliminate the gap between estimated and notified TB cases. The degree of case finding within national TB programs varies globally and therefore ACF interventions may encompass a range of strategies depending on the underlying context. These can include: household or social contact tracing, door-to-door screening, or targeted screening of high-risk groups.

In Nepal, the implementation of ACF by the Birat Nepal Medical Trust (BNMT) under the STOP TB/TB REACH funding programme Wave 2 was conducted in 15 Nepalese districts and detected 968 additional cases in 18 months (from January 2013 to June 2014) (102). The ACF in Tuberculosis Trial (ACT2), which analyzed the impact of ACF using a household contact investigation of TB detection in Viet Nam, showed that the implementation of ACF, in addition to strong passive case finding (PCF), increased TB case detection from 703 per 100 000 population in the control districts to 1788 per 100,000 population in the intervention districts. Intensive household contact tracing was also found to reduce all-cause mortality in the intervention districts from 1.7% (control districts) to 0.6% (intervention districts; relative risk: 0.60; 95% *CI*: 0.50–0.80; $P < 0.001$) (103). The analysis found that household contact tracing is a highly cost-effective intervention when compared with PCF alone (USD 544 per disability-adjusted life year averted) (104).

The Zambia South Africa Tuberculosis and HIV/AIDS Reduction (ZAMSTAR) cluster randomized trial of enhanced TB case finding in the context of a high HIV prevalence failed to show an impact on culture-confirmed TB prevalence after four years of intervention (*OR* = 1.09, 95% *CI*: 0.86–1.40) (105). Furthermore, there is a lack of data to determine whether ACF can reduce patient-incurred costs. The WHO has been advocating strongly for research evidence from diverse settings to inform policy development to achieve the milestone of zero catastrophic costs (38).

In Nepal, the expansion of ACF is a key part of the Strategic Interventions to Increase TB Case Notification (205). The National TB Programme (NTP) has planned to expand ACF activities through the implementation of community TB screening camps, screening of household and social contacts of index TB patients and scaling up of GeneXpert® MTB/RIF testing (Xpert) (111). Nepal has continued to face challenges in crucial areas, such as a sustained case detection gap, a poorly functioning health

system and high dependence on international donor funding for health (45% of the total budget (17, 112). Furthermore, a significant proportion of TB patients seek care in the private sector due to weak public services (112), increasing the risk of financial hardship for the most vulnerable.

Previous cost and cost-effectiveness studies on TB conducted in Nepal have evaluated patient-incurred costs under either community-based or family member directly observed treatment strategies, short-course (DOTS) for TB control (113) and direct costs of outpatient visits to obtain a TB diagnosis (114, 115). This is the first study to evaluate and compare patient costs incurred through a diagnosis via ACF and PCF in the country. In a scenario of scarce financial resources, health economic evaluations play a key role in supporting the rational allocation of resources and informing evidence-based policy development. Therefore, the objective of this study was to compare costs incurred by pulmonary TB patients diagnosed through ACF and PCF, and determine the difference in prevalence and intensity of catastrophic costs between these groups.

5.4 Results of patient costing survey in TB REACH wave 5 patients

5.4.1 Patient characteristics

One hundred consecutively diagnosed TB patients were recruited. One PCF patient with extrapulmonary TB was excluded, thus the final sample was 99 patients: 50 diagnosed through ACF (three, 30, and 17 diagnosed via TB camps, OPDs, and contact tracing, respectively) and 49 diagnosed through PCF. All patients were interviewed during the intensive phase, within 14 to 90 days of treatment initiation, with 38% of patients interviewed during the first month of treatment. All eligible patients invited to participate gave written informed consent. Although MDR patients were included in the eligibility criteria, there were no MDR TB patients among those recruited. This is consistent with the MDR TB prevalence of < 1% in these districts.

No differences in the socioeconomic characteristics were found when comparing ACF and PCF patients (**Error! Reference source not found.**). The majority of patients were male (71%), consistent with the 2:1 ratio of males and females in national TB notification data. Twenty-five percent were aged over 65 years and 47% were farmers. The most common source of drinking water was piped (49%) and the majority had a

standard toilet (latrine) in the home (74%). Electricity (86%), a mobile phone (87%), and a bed (87%) were the most frequent assets reported (**Error! Reference source not found.**).

Figure 5.1: Socio-economic characteristics of TB patients diagnosed through ACF and PCF, Nepal, 2018

Patient features	ACF N= 50	PCF N = 50	All N = 100	P-value [1]
Sex	N (%)	N (%)	N (%)	
Female	18 (36)	11 (22)	29 (29)	0.123
Male	32 (64)	39 (78)	71 (71)	
Age group				
15-24	7 (14)	6 (12)	13 (13)	0.395
25-34	3 (6)	10 (20)	13 (13)	
35-44	9 (18)	8 (16)	17 (17)	
45-54	10 (20)	8 (16)	18 (18)	
55-64	10 (20)	6 (12)	16 (16)	
65+	11 (22)	12 (24)	23 (26)	
Education status[2]				
No education or illiterate	14 (28)	18 (36)	32 (32)	0.468
Literate	12 (24)	8 (16)	20 (20)	
Basic schools	20 (40)	16 (32)	36 (36)	
Secondary schools	4 (8)	7 (14)	11 (11)	
Master's	-	1 (2)	1 (1)	
Occupation				
Farmer	29 (58)	18 (36)	47 (47)	0.229
Homemaker	6 (12)	5 (10)	11 (11)	
Others	15 (30)	27 (54)	42 (42)	
Patient as main income earner				
Yes	19 (38)	17 (34)	36 (36)	0.677
Source of drinking water				
Piped	24 (48)	25 (50)	49 (49)	0.804
Well	1 (2)	2 (4)	3 (3)	
Other	25 (50)	23 (46)	48 (48)	
Toilets facilities				
No toilets	4 (8)	3 (6)	7 (7)	0.962
Ordinary toilet	36 (72)	38 (76)	74 (74)	
Public sewage	4 (8)	4 (8)	8 (8)	
Septic tank	6 (12)	5 (10)	11 (11)	
Assets[3]				
Electricity	43 (86)	43 (86)	86 (86)	1
Radio	18 (36)	24 (48)	42 (42)	0.224
Mobile phone	42 (84)	45 (90)	87 (87)	0.372
Table	22 (44)	22 (44)	44 (44)	1
Chair	23 (46)	25 (50)	48 (48)	0.689
Bed	44 (88)	43 (86)	87 (87)	0.766
Cupboard	14 (28)	17 (34)	31 (31)	0.517
Clock	14 (28)	14 (28)	28 (28)	1
Fan	18 (36)	18 (36)	36 (36)	1
Watch	20 (40)	22 (44)	42 (42)	0.685
Bicycle	22 (44)	18 (36)	40 (40)	0.414
Television	16 (32)	19 (38)	35 (35)	0.529
Livestock, small	37 (74)	40 (80)	77 (77)	0.476
Livestock, large	31 (62)	28 (56)	59 (59)	0.542

[1] Chi square

[2] Literate = able to only read and write, Basic schools = primary level/lower secondary level (1 to 8 year of education).

2 Other assets: refrigerator, ACF – 2 (4) and PCF - 4 (8); sofa, ACF - 1 (2) and PCF - 2 (4); computer, ACF – 1 (2) and PCF – 2 (4); motorcycle, ACF 4 (8) - and PCF – 2 (4); Animal-drawn cart, ACF – 5 (10), PCF 3 (6); thresher, ACF 1 (2).

5.4.2 Disease and treatment characteristics

No differences were documented in disease characteristics when comparing patients diagnosed by ACF or PCF. The majority of patients were classified as new TB cases (83%) and no patient reported a HIV positive status. A similar proportion of both groups (ACF vs PCF) visited private health services during the pre-treatment period (37% vs 41%) and sought diagnosis using public services (52% vs 54%). The average number of visits to health facilities during the pre-treatment period (2.3 vs 2.6) and the average number of follow-up visits after treatment initiation (0.2 vs 0.4) were lower among ACF patients. However, statistical significance was reached only for follow-up visits (P = 0.026). The average number of weeks between the first symptom and treatment initiation was similar for ACF and PCF patients (8.4 vs 8.8, P = 0.638) (Table 5.1).

Table 5.1: Disease and treatment characteristics of TB patients diagnosed through ACF and PCF, Nepal, 2018

Characteristics	ACF N= 50	PCF N = 50	All N = 100	P-value [1]
Treatment status	N (%)	N (%)	N (%)	
New	42 (84)	41 (82)	83 (83)	0.790
Retreatment/Relapse	8 (16)	9 (18)	17 (17)	
HIV Status				
Not tested	8 (16)	4 (8)	12 (12)	
Negative	39 (78)	41 (84)	80 (80)	0.469
Unknown	3 (6)	4 (8)	7 (7)	
Hospitalization				
Pre-diagnosis	4 (8)	10 (20)	14 (14)	0.099
Intensive phase	0	1 (2)	1 (1)	-
Type of service visited, pre-diagnosis				
Microscopy camps	8 (7)	0	8 (3)	
Cross border service [2]	0	1 (1)	1 (0.5)	
Pharmacy/Herbalist	5 (4)	5 (4)	10 (4)	0.031
Private clinic/hospital	42 (37)	55 (41)	97 (39)	
Public health facility	59 (52)	72 (54)	131 (53)	
Type of service visited, treatment				
No health facility	14 (23)	21 (33)	35 (28)	
Private clinic/hospital	7 (11)	13 (20)	20 (16)	0.102
Public health facility	40 (66)	30 (47)	70 (56)	
Number of visits	Mean (SD)	Mean (SD)	Mean (SD)	
Health facility visits – pre-diagnosis	2.3 (1.1)	2.6 (1.6)	2.5 (1.4)	0.380
Health facility visits – intensive phase	0.9 (0.9)	0.9 (0.9)[3]	0.9 (0.9)	0.500
Follow-up visits - Intensive phase	0.2 (0.6)	0.4 (1.0)	0.3 (0.7)	0.026
Days of hospitalization				
Pre-diagnosis	5.3 (3.8)	8.1 (7.0)	7.5 (6.4)	0.638
Number of weeks between 1st TB symptoms and treatment initiation	8.4 (8.0)	8.8 (11.3)	8.6 (9.8)	0.931

[1] Two-sample Wilcoxon rank-sum (Mann-Whitney) test and Chi square
[2] Patient crossed the border to get assistance in India

5.4.3 Income changes and social consequences

PCF patients reported a higher economic impact due to TB treatment when compared with ACF patients, with 20% of PCF patients declaring being much poorer after TB treatment initiation, while among ACF patients this proportion was 2% (P = 0.016). TB resulted in a substantial decrease in the individual and household incomes of individuals diagnosed by either ACF or PCF. However, the higher impoverishment rate among PCF patients did not appear to be a consequence of income reduction: there was no difference in the income reduction between the diagnostic groups, but rather time loss and out-of-pocket expenses (further details below). The individual income reduced by 75% and 74% for ACF and PCF patients, respectively. The reduction in the household income was 37% and 38% for ACF and PCF patients, respectively. The poverty headcount during the intensive treatment phase also increased substantially in both diagnostic groups: 160% and 167% for individuals diagnosed by ACF or PCF, respectively. A quarter of all patients (26%) reported food insecurity as a consequence of TB (Table 5.2).

Table 5.2: Income changes and social consequences of TB in patients diagnosed through ACF and PCF Nepal, 2018

Item	ACF N= 50	PCF N = 50	All N = 100	P-value [1]
Income (USD)	Mean (SD)	Mean (SD)	Mean (SD)	
Individual income prior TB	79 (88)	70 (83)	80 (85)	0.602
Household income prior TB	196 (111)	182 (184)	189 (151)	0.052
Current individual income[2]	20 (44)	18 (37)	19 (40)	0.951
Current household income[2]	123 (101)	113 (174)	118 (142)	0.080
Working hours per week				
Prior TB	31 (28)	29 (29)	30 (29)	0. 584
Current[2]	5 (11)	4 (11)	4 (11)	0. 643
Catastrophic costs				
Intensity [3]	61 (53)	88 (172)	76 (132)	0.6713
	N (%)	N (%)	N (%)	
Prevalence [4]	20 (45)	24 (61)	44 (53)	0.143
Employment status prior TB				
Unemployed	2 (4)	5 (10)	7 (7)	
Formal paid work	4 (8)	7 (14)	11 (11)	
Informal paid work	24 (48)	17 (34)	41 (41)	0.475
Housework	15 (30)	13 (26)	28 (28)	
Others	5 (10)	8 (16)	13 (13)	
Current employment status [2]				
Unemployed	13 (26)	18 (36)	31 (31)	
Formal paid work	-	2 (4)	2 (2)	
Informal paid work	5 (10)	2 (4)	7 (7)	0.310
Housework	29 (58)	23 (46)	52 (52)	
Others	3 (6)	5 (10)	8 (8)	
Poverty headcount [5]				
Before TB	5 (10)	6 (12)	11 (11)	0.749
Current[2]	13 (26)	16 (32)	29 (29)	0.509
Dissaving strategies [2]				
Loan	14 (28)	22 (44)	36 (36)	0.096
Sale of assets	4 (8)	5 (10)	9 (9)	0.727
Social impact [2]				
Food insecurity	13 (26)	13 (26)	26 (26)	1
Loss job	2 (4)	4 (8)	6 (6)	0.400
Interrupted schooling	4 (8)	2 (4)	6 (6)	0.400
Social exclusion	10 (20)	7 (14)	17 (17)	0.424
Others	4 (8)	1 (2)	5 (5)	0.169
Financial impact[2]				
Much poorer	1 (2)	10 (20)	11 (11)	
Poorer	26 (52)	22 (44)	48 (48)	0.016
Unchanged	23 (46)	18 (36)	41 (41)	

[1] Chi square
[2] Intensive phase
[3] Intensity of catastrophic costs measured as median-positive overshoot beyond the 20% threshold
[4] Percentage of patients with total costs> 20% of annual family income (WHO)
[5] Number of families living with an annual income per capita below NPR 12,000 (2011 prices) (http://www.thepovertyline.net/nepal

5.4.4 Costs incurred by TB patients

For the pre-treatment period, ACF patients reported lower direct medical (USD 14 vs USD 32; *P* = 0.001), non-medical (USD 3 vs USD 10; *P* = 0.004), and indirect (USD 4 vs USD 13; *P* < 0.001) costs, the latter measured using the human capital approach (that is, based on time loss). The median total costs in this phase were also lower for ACF patients, although not statistically significant (USD 132 vs USD 172, *P* = 0.103) (Table 5.3).

During the intensive treatment phase, ACF patients also incurred lower direct non-medical (USD 0 vs USD 1), indirect (USD 55 vs USD 60), and total (USD 85 vs USD 104) costs. However, statistical significance was found only for direct non-medical costs (*P* = 0.034).

The median total cost (pre-treatment plus intensive phase) was also lower for ACF patients, particularly for direct medical (USD 15 vs USD 34, *P* = 0.002) and non-medical (USD 30 vs USD 54, *P*=0.022) costs. The total direct costs were 65% lower for ACF patients compared with PCF patients (USD 40 vs USD 115, *P* = 0.001) (Table 5.3).

Table 5.3: Median costs per TB patient (USD) during pre-diagnosis and treatment period in patients diagnosed through ACF and PCF, Nepal, 2018

Cost item	ACF (N = 50)	PCF (N = 50)	Total (N = 100)	P-value[2]
Pre-diagnosis period	Median (IQR)	Median (IQR)	Median (IQR)	
Direct medical costs				
Consultation fee	0.0 (0.0-0.1)	0.2 (0.0-4.5)	0.0 (0.0-1.0)	0.003
Radiography	0.5 (0.0-3.2)	3.2 (0.0-9.9)	1.6 (0.0-5.6)	0.003
Lab tests	1.1 (0.0-3.4)	2.7 (0.0-5.7)	1.8 (0.0-4.1)	0.092
Medicines	5.9 (0.0-16.8)	18.3 (1.5-36.7)	8.1 (0.5-25.6)	0.021
Other medical	0.0 (1.8-4.5)	3.3 (1.4-6.6)	2.7 (0.0-5.8)	0.013
Total direct medical	14.3 (4.5-27.7)	31.6 (11.0-79.1)	19.2 (6.3-46.3)	0.001
Direct non-medical				
Transportation	3.3 (0.9-7.2)	5.4 (1.8-15.5)	3.7 (1.8-10.4)	0.031
Food	-	0.0 (0.0-10.8)	0.0 (0.0-2.7)	0.006
Total direct non-medical	3.4 (1.8-10.4)	9.7 (2.7-37.9)	5.4 (2.1-22.4)	0.004
Indirect costs				
Time loss[1]	4.4 (1.9-8.1)	13.4 (5.6-21.8)	7.8 (3.7-15.0)	<0.001
Income loss	51.4 (0.0-240.1)	30.7 (0.0-201.8)	40.6 (0.0-212.9)	0.629
Total indirect	63.5 (5.0-255.1)	43.3 (14.3-248.2)	51.1 (8.4-251.6)	0.430
Total cost pre-diagnosis	132.3 (22.6-258.0)	172.3 (59.9-405.4)	147.3 (41.6-304.9)	0.103
Intensive phase				
Direct medical costs				
Consultation fee/charges	-	-	-	-
Radiography/lab tests	-	-	-	-
Medicines	-	0.0 (0.0-1.8)	-	0.045
Total direct medical	-	0.0 (0.0-4.0)	-	0.070
Direct non-medical				
Transportation	0.0 (0.0-7.2)	0.4 (0.0-17.3)	0.0 (0.0-8.5)	0.041
Food	0.0 (0.0-6.8)	0.0 (0.0-19.5)	0.0 (0.0-7.7)	0.547

Total direct non-medical	0.0 (0.0-14.4)	1.3 (0.0-44.8)	0.0 (0.0-28.0)	0.034
Indirect costs				
Time loss[1]	29.9 (15.0-44.9)	31.0 (11.7-59.8)	29.9 (15.0-56.1)	0.816
Income loss	18.1 (0.0-49.7)	9.6 (0.0-45.2)	17.1 (0.0-45.2)	0.377
Total indirect	54.9 (29.9-95.9)	59.6 (34.9-82.7)	55.1 (29.9-90.5)	0.817
Other costs				
Nutritional supplements	13.6 (7.5-25.4)	15.5 (9.3-35.3)	14.9 (8.1-27.8)	0.404
Total costs intensive phase	84.7 (56.1-144.0)	103.7 (45.3-193.2)	96.6 (51.8-176.9)	0.557
Total cost pre-diagnosis and intensive phase				
Total direct medical costs	14.9 (4.5-46.1)	34.1 (13.1-87.5)	22.6 (6.7-63.8)	0.002
Total direct non-medical costs	29.6 (15.6-55.1)	54.0 (21.5-124.6)	37.5 (17.8-83.5)	0.022
Total direct costs	40.2 (26.1-91.7)	114.9 (45.3-250.5)	68.5 (31.7-148.6)	0.001
Total indirect costs	128.2 (34.9-357.4)	106.1 (57.8-340.9)	112.4 (52.4-343.7)	0.942
Total costs[3]	252.8 (80.9-452.8)	315.3 (125.8-543.9)	290.1 (88.7-476.7)	0.161

[1] Hourly minimum wage: USD 0.62; Daily minimum wage: USD 4.67 (http://www.pioneerlaw.com/news/minimum-wage-remuneration-2018-2075)

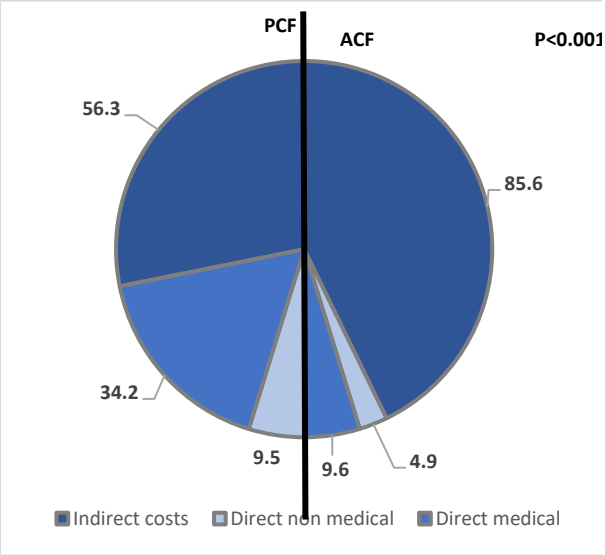
[2] Wilcoxon-Mann-Whitney

3 Total cost: from the 1st TB symptoms until the end of intensive phase

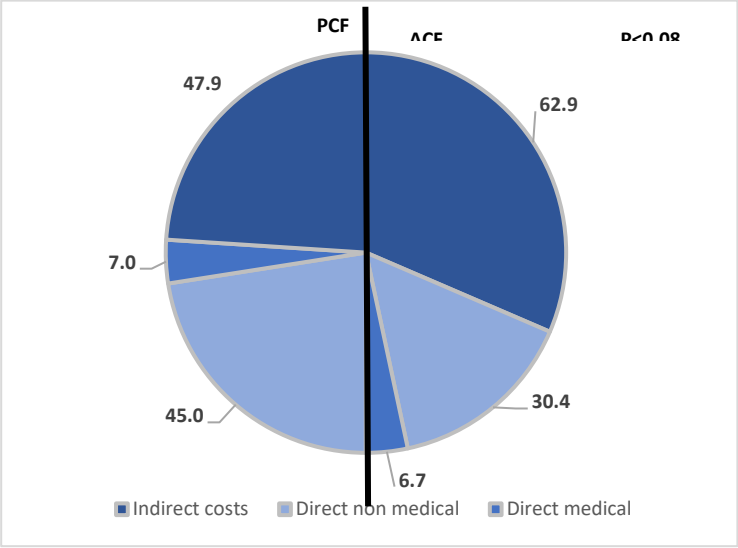
Indirect costs, particularly income loss, were the main driver of the total costs for both groups during the pre-treatment and intensive phases. However, PCF patients had higher percentages of direct medical (34% vs 10%) and non-medical (9% vs 5%, $P < 0.001$) costs during the pre-treatment period (Figure 5.2).

Figure 5.2: Proportion of indirect, medical and non-medical costs in TB patients diagnosed through ACF and PCF, Nepal, 2018

1A. Pre-diagnosis



1B. Intensive phase



P-value: Pearson's Chi-square

5.4.5 Catastrophic costs

Eighty-four patients were included in this analysis as 15 patients were unable to report the value of household income. ACF patients presented 26% lower prevalence (45% vs 61%) and 69% lower intensity (53% vs 172%) of catastrophic costs, considering direct and indirect costs (Table 5.4).

Stratified analysis (Mantel-Haenszel) used to investigate variables influencing the association of diagnostic strategy with risk of catastrophic costs showed that stratification by gender, TB relapse, poverty level, dissaving, and financial and social impacts did not change the *OR* of incurring catastrophic costs. However, stratification by age revealed significant heterogeneity in the odds of incurring catastrophic costs ($P = 0.043$), with those aged under 60 years having an *OR* of 4.6 (95% *CI*: 1.19–19.32) for catastrophic costs when diagnosed passively rather than actively, compared to an *OR* of 0.6 (95% *CI*: 0.93–3.61) in those aged over 60 years (Table 5.4).

Table 5.4: Association between catastrophic costs and PCF/ACF adjusted for each exposure variable at time, Nepal, 2018

Variable	Cases of catastrophic costs per diagnostic method n/N (%) [1]		OR (confidence interval)	
	PCF N= 45	ACF N= 39	Crude	Adjusted
Total population	24/39 (61)	20/45 (44)	2 (0.77; 5.25)	
Variables				
Gender				
Male	20/31 (65)	14/28 (50)	1.8 (0.56; 5.89)	1.8 (0.75; 4.44)
Female	4/8 (50)	6/17 (35)	1.8 (0.24; 13.84)	
Age				
≥60	4/14 (29)	6/15 (40)	0.6 (0.93; 3.61)	2.1 (0.86; 5.17)
<60	20/25 (80)	14/30 (47)	4.6 (1.19; 19.32)	
Disease category				
New case	19/33 (58)	17/38 (45)	1.7 (0.59; 4.78)	2.0 (0.83; 4.78)
Relapse	5/6 (83)	3/7 (43)	6.7 (0.34; 392.48)	
Poverty line				
Bellow	4/5 (80)	5/8 (62)	2.4 (0.11; 156.99)	2.1 (0.87; 5.19)
Above	20/34 (58)	15/37 (40)	2.1 (0.73; 6.03)	
Dissaving				
Yes	13/18 (72)	9/15 (60)	1.7 (0.32; 9.60)	1.8 (0.75; 4.49)
No	11/21 (52)	11/30 (37)	1.9 (0.53; 6.84)	
Financial impact				
Poorer /Much poorer	15/22 (68)	14/26 (54)	1.8 (0.48; 7.15)	2.1 (0.85; 5.06)
Unchanged	9/17 (53)	6/19 (31)	2.4 (0.52; 11.78)	
Social impact [2]				
Yes	10/14 (71)	14/23 (61)	1.6 (0.32; 9.13)	2.5 (0.98; 6.23)
No	14/25 (56)	6/22 (27)	3.4 (0.86; 14.08)	

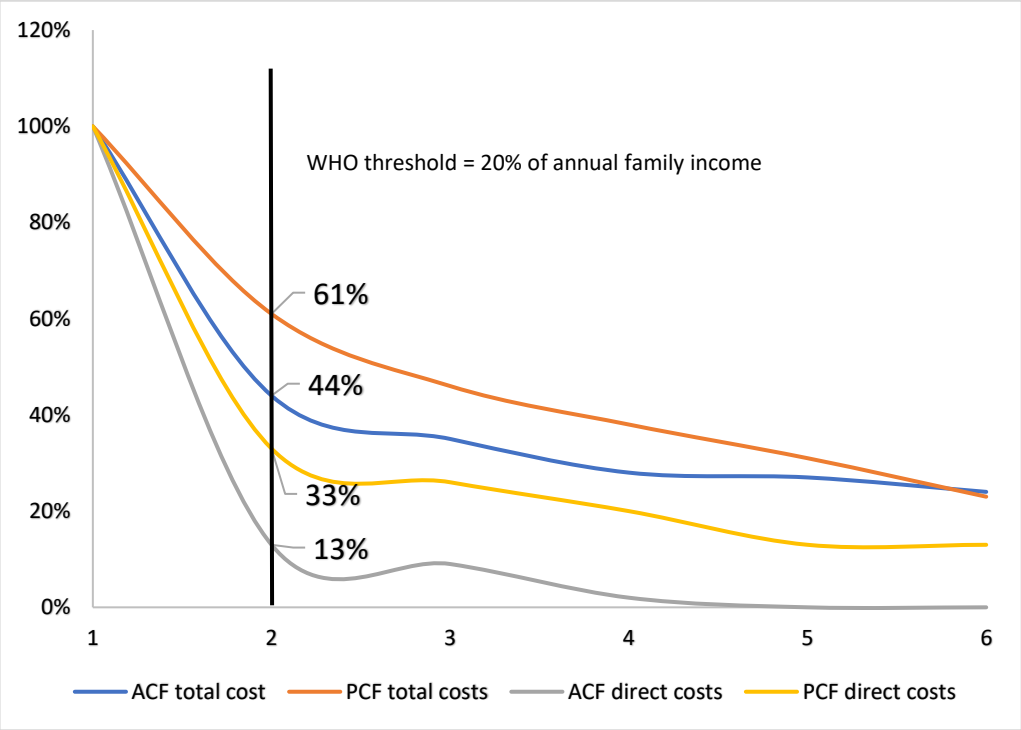
[1] Five ACF and 11 PCF patients with “zero” annual family income excluded from this analysis

4 Social impact: divorce or social exclusion or food insecurity or loss of job or Interrupted schooling

5.4.6 Sensitivity analysis

The prevalence of catastrophic costs was higher for PCF patients in all thresholds analyzed. Using the WHO threshold (that is, 20% of annual household income) and only direct costs, the prevalence of catastrophic costs was 61% lower for ACF patients when compared with PCF patients (13% vs 33%, $P = 0.029$) (Figure 5.3).

Figure 5.3: Prevalence of catastrophic costs in TB patients diagnosed through ACF and PCF during the pre-diagnosis and intensive phase, Nepal, 2018



Total costs	20%	30%	40%	50%	60%
ACF (%)	44	35	28	27	24
PCF (%)	61	46	38	31	23
P-value[1]	0.118	0.324	0.353	0.678	0.883
Direct costs					
ACF (%)	13	9	2	0	0
PCF (%)	33	26	20	5	5
P-value[1]	0.029	0.040	0.007	0.013	0.013

[1] Five ACF and 11 PCF patients with "zero" annual family income excluded from this analysis

[2] Chi Square

PCF patients were more strongly affected by recall bias and lower costs were reported for patients interviewed after one month of treatment initiation when compared with those interviewed within one month of treatment initiation. This suggests that in fact the PCF costs are more likely to be underestimated and the effect of ACF on reducing patient incurred costs is in fact greater than estimated from these self-reported data. PCF patients interviewed after one month of treatment reported lower indirect (USD 29 vs USD 282, $P < 0.001$) and total (USD 128 vs USD 366, $P = 0.007$) costs during the pre-treatment period, than PCF patients patient interviewed greater than 30 days after treatment initiation; This difference was also seen for lower direct non-medical (USD 16 vs USD 81, $P = 0.005$) and total (USD 68 vs USD 190, $P = 0.004$) costs during the intensive phase; and lower indirect (USD 76 vs USD 367, $P = 0.003$) and total (USD 232 vs USD 556, $P = 0.002$) costs during both periods combined. There was no difference in costs among ACF patients interviewed within and after one month of treatment initiation.

5.5 Discussion chapter 5

This study demonstrated that patients diagnosed through ACF incurred substantially lower costs than those diagnosed by PCF, with 65% lower direct costs and 61% lower catastrophic cost prevalence when considering only direct costs. The study also confirms the devastating financial impact of TB on poor households in Nepal and the high prevalence of catastrophic costs incurred by TB-affected households in both groups, but particularly among patients diagnosed by PCF who are aged under 60 years.

Other costing surveys conducted in Asia have also found lower costs and catastrophic costs among patients diagnosed through ACF when compared with PCF. In Cambodia, ACF patients incurred 79% lower total costs during the pre-treatment period (USD 5 vs USD 24, $P < 0.001$, costs inflated to 2018 prices (206). In India, a TB patient cost survey conducted in vulnerable populations found 75% lower total costs (USD 5 vs USD 20, $P < 0.001$, 2018 prices) and 32%

lower catastrophic costs (adjusted prevalence ratio: 0.68, 95% *CI*: [0.69–0.97]) for ACF patients (207).

The findings of this study indicate that ACF has the potential to avert a substantial portion of direct costs and catastrophic direct costs associated with TB diagnosis and care, and can thereby help reduce the broader socioeconomic consequences of TB in Nepal. Previous TB patient cost surveys conducted among PCF patients in the country have found that high direct costs (that is transportation, clinical fees and tests) pose a barrier for patients seeking TB diagnosis and treatment (114, 115). In addition, high costs have been associated with adverse TB outcomes such as a delay in seeking diagnosis and starting treatment (101, 207), death and treatment abandonment or treatment failure (120). Thus, the implementation of ACF can potentially contribute to improved treatment outcomes and reduce mortality (104). These outcomes will be analyzed in an ongoing project in Nepal (IMPACT TB).

The impact of ACF on direct costs, particularly during the pre-treatment period, is principally a consequence of savings incurred in transportation and diagnostic tests. Nepal has a poor transport infrastructure, and many patients live in areas without roads and therefore have to travel several hours or even several days to reach a health service. ACF reduces or removes the need for patients to travel long distances to reach diagnostic centers or make use of private health services and pay for laboratory tests or radiography. ACF patients receive visits from healthcare workers for TB screening, sputum collection and further referral for TB treatment for those with a positive diagnosis. Besides decreasing patient costs, ACF increases accessibility to health care.

Other community-based initiatives covering different areas of public health have been successful in improving access to health care. China's barefoot doctor system (1968–1985) expanded the coverage of healthcare services, reduced costs and provided timely treatment by training indigenous paramedics in rural areas of China (208). In Nepal, female CHVs have also improved access to health care in urban and rural areas by delivering health promotion and prevention activities at the household level (209). Furthermore, village health workers, who

were focused on immunization programs, were promoted to auxiliary health workers by the Ministry of Health in 2014–2015. The new role was expanded to provide preventive and promotive health services and basic curative services for the community (209, 210).

A difference in total income loss was not identified in this study, probably because the ACF strategy did not appear to provide an earlier TB diagnosis. Earlier diagnosis among patients diagnosed through ACF was identified in previous studies in Cambodia (211) and Viet Nam (103), however, both studies evaluated ACF among household contacts of index patients in addition to social contacts.

This study has a number of limitations. First, the calculation of catastrophic costs considered self-reported household income. This approach does not consider dissaving strategies and it is more challenging to apply in countries with strong informal economies and seasonal fluctuations in income, such as Nepal. However, the interviewers were advised to ask about and explore the average annual monthly income, regardless of seasonality of the market. In addition, this approach has been widely used (122, 206, 211, 212), which allows for comparisons to be made between our findings and other studies. Second, the calculation of catastrophic costs did not include costs incurred during the continuation phase of treatment, thus its prevalence was underestimated. Third, the analysis did not detect an association between key variables, such as poverty line, social and financial impacts, dissaving strategies, and the occurrence of catastrophic costs. A larger sample size may be required to identify these associations. Fourth, patients were recruited at different time points during the intensive phase, which influenced the degree of recall bias (213). In this study, PCF patients were more affected by recall bias than ACF patients, and may have underestimated their indirect, non-medical, and total costs as they were interviewed one month after treatment initiation. Thus, as these patients underestimated costs, the difference in costs between ACF and PCF patients may be even higher.

The study also has a number of strengths. Interviews were conducted by trained health workers who had a previous relationship with the community. The adoption

of this strategy was crucial to collect complete and accurate data because a relationship of trust between interviewer and participant is essential when asking sensitive questions about personal or household income. The present study provides important evidence to inform policy evolution for ACF scale-up in Nepal. Knowledge of the components, drivers, and distribution of costs for TB-affected households will be necessary to develop and advocate for effective interventions to mitigate costs and achieve the End TB Strategy's goal to reduce the number of TB-affected households facing catastrophic costs to zero. Our findings indicate that ACF is an important strategy to contribute to the achievement of this goal. A national TB patient cost survey for Nepal would provide comprehensive data and should be prioritized. The impact of ACF on catastrophic costs in other countries and population groups should also be robustly evaluated to inform global policy. Even though ACF reduced costs, the prevalence of catastrophic costs was still found to be very high in both groups. The expansion in coverage of social protection would play an important role in alleviating extreme poverty and, indirectly, in reducing TB incidence (214). Cash transfer programs, such as Bolsa FamÍlia in Brazil, have been successful in reducing poverty and improving TB treatment outcomes (215). In Peru, socioeconomic support for TB patients has improved TB outcomes and prevented catastrophic (122, 215). Similar interventions should be piloted, evaluated, and integrated into the NTP in Nepal.

5.6 Conclusions chapter 5

This work showed that ACF is an important strategy to avert direct costs and to reduce the proportion of TB households incurring catastrophic direct costs. The cross-sectional approach to determining patient costs recommended by WHO was applied in this first costing study. A single interview timepoint has limitations in capturing the range and depth of costs incurred by TB patients throughout the long six month treatment for TB. In the second costing study for IMPACT TB, reported in chapter 6, we therefore adapted the patient costing tool for a longitudinal design, with patient interviews at three timepoints, in an attempt to capture the changing costs incurred by TB patients during their diagnosis and treatment.

The data reported here in this first patient cost evaluation showed that ACF is not sufficient in isolation to eliminate catastrophic costs and should be implemented in tandem with other policies, such as social protection, to mitigate the financial burden of TB, particularly among the most vulnerable populations.

CHAPTER 6: Active case finding reduces household costs for people affected by tuberculosis: The IMPACT TB longitudinal costing survey in Nepal

6.1 AIMS Chapter 6

1) Conduct a longitudinal patient cost survey in four districts of Nepal implementing the IMPACT TB ACF intervention.

2) Compare the costs and socioeconomic impact of TB on patinets diagnosed via ACF or PCF.

6.2 Abstract chapter 6

Objective: The aim of this study was to compare costs and socio-economic impact of tuberculosis (TB) for patients diagnosed through active (ACF) and passive case finding (PCF) in Nepal.

Methods: A longitudinal costing survey was conducted in four districts of Nepal from April 2018 to October 2019. Costs were collected using the WHO TB Patient Costs Survey at three time points: intensive phase of treatment, continuation phase of treatment and at treatment completion. Direct and indirect costs and socio-economic impact (poverty headcount, employment status and coping strategies) were evaluated throughout the treatment. Prevalence of catastrophic costs was estimated using the WHO threshold. Logistic regression and generalized estimating equation were used to evaluate risk of incurring high costs, catastrophic costs and socio-economic impact of TB over time.

Results: A total of 111 ACF and 110 PCF patients were included. ACF patients were more likely to have no education (75% vs 57%, $P = 0.006$) and informal employment (42% vs 24%, $P = 0.005$) Compared with the PCF group, ACF patients incurred lower costs during the pretreatment period (mean total cost: US$55 vs US$87, $P < 0.001$) and during the pretreatment plus treatment periods (mean total direct costs: US$72 vs US$101, $P < 0.001$). Socio-economic impact was severe for both groups throughout the whole treatment, with 32% of

households incurring catastrophic costs. Catastrophic costs were associated with ‘no education’ status [odds ratio = 2.53(95% confidence interval = 1.16–5.50)].

Conclusion: There is a severe and sustained socio-economic impact of TB on affected households in Nepal. The community-based ACF approach mitigated costs and reached the most vulnerable patients. Alongside ACF, social protection policies must be extended to achieve the zero catastrophic costs milestone of the End TB strategy.

6.3 Background Chapter 6

Tuberculosis (TB) kills more people each year than any other single infectious disease and principally affects the most vulnerable populations in low- and middle-income countries (14). The socio-economic consequences of TB are often severe, and many TB-affected households are pushed into extreme poverty due to the high out-of-pocket expenditures and income lost during the search for TB diagnosis and treatment. Structural causes commonly found in developing countries, such as seasonal economy, poor access to healthcare facilities and low education, can also contribute to worsening the economic hardship faced by TB-affected households (213, 216). The World Health Organization’s (WHO) End TB strategy (72) has established ambitious goals to advance towards TB elimination, including zero catastrophic costs for TB affected households, to be achieved by 2020. Catastrophic TB costs are defined by WHO as total costs of TB diagnosis and care above 20% of the household’s annual income (72). The latest Global TB report published by the WHO in 2010 shows that the zero catastrophic costs milestone will not be achieved by the end of 2020. National costing surveys conducted in 12 high burden countries have shown that the percentage of TB-affected families facing catastrophic costs ranged from 27% in Kenya to 83% in Timor-Leste for all forms of TB. As catastrophic cost is an important indicator to estimate the economic burden of TB and evaluate access to healthcare, the WHO has established a monitoring framework including this indicator as essential to monitor beyond 2020. The organization has also recommended universal health coverage to improve access to high-quality TB

diagnosis and treatment and social protection schemes as priority policies to achieve the zero catastrophic costs milestone (217).

Another recommendation to monitor the progress towards the zero catastrophic costs milestone is the implementation of patient cost surveys (14). Several countries have now conducted national or local surveys by adopting cross-sectional (211) or longitudinal approaches (218); addressing costs of TB and co-morbidities such as HIV/AIDS (219, 220) and diabetes (221); and comparing active case finding (ACF) vs passive case finding (PCF) (148, 206, 217). Modelling studies have also been developed to determine the impact of specific TB interventions on patient costs (222). However, evidence regarding the impact of community-based ACF on patient costs using the more detailed longitudinal approach is still lacking.

Nepal is one of the poorest countries in Asia with 15% of the population classified as extremely poor (133). The 2018–19 national TB prevalence survey in Nepal showed an incidence rate of 245/100 000, which is much higher than previous estimates (4). This means that less than half (46%) of the incident TB cases in Nepal in 2019 (69 000) were diagnosed or notified via the government system, with approximately 40 000 ‘missing’ cases occurring annually (4). Strategies to reach these missing TB cases are urgently needed. ACF (38) reaching out into communities to actively screen and diagnose people with TB is one strategy to reduce this case notification gap, decrease morbidity and mortality and interrupt community transmission.

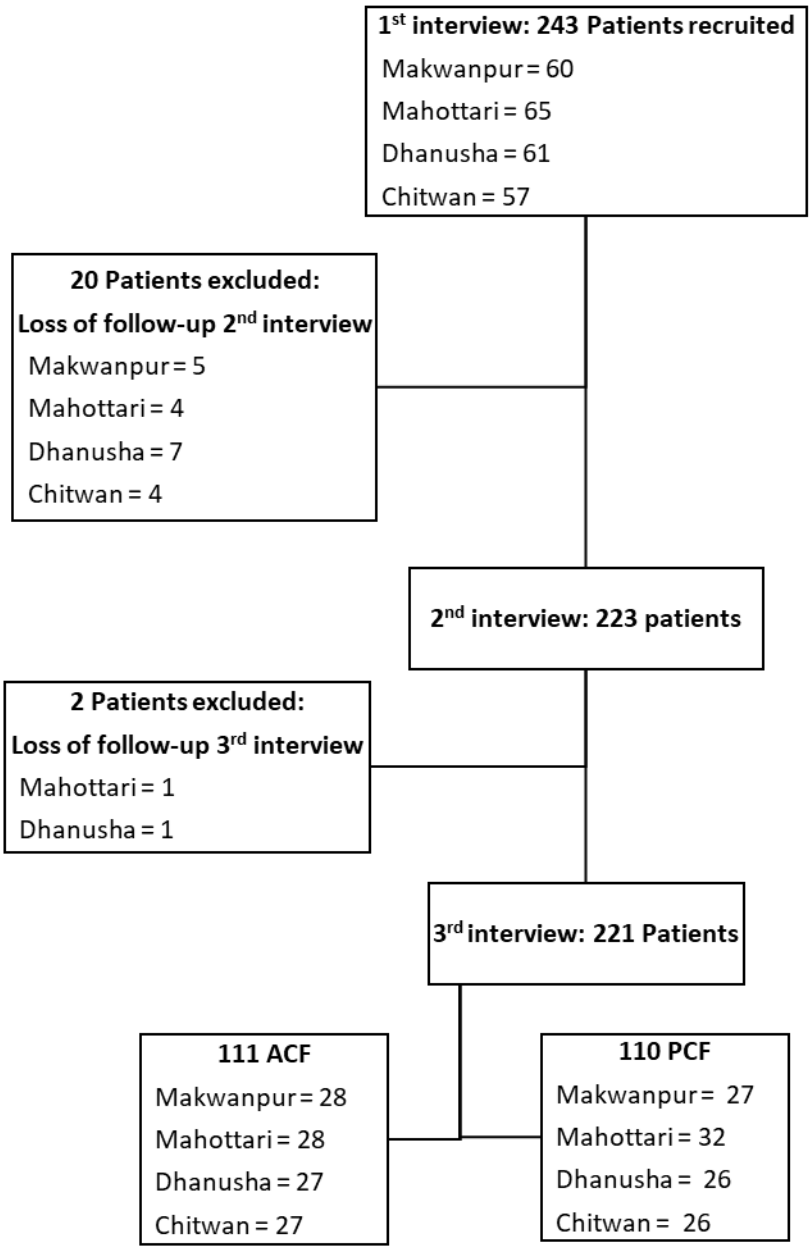
The IMPACT TB was launched in 2017 to implement a community-based ACF model in four districts of Nepal and to increase the evidence for optimal ACF scale-up policies. Here, we report the results of the cost analysis that compared costs and socio-economic impact of TB in patients diagnosed through ACF with the standard National TB Programme (NTP) PCF.

6.4 Results chapter 6

A total of 243 patients were recruited for the study. No eligible patient declined participation. Twenty-two patients (9%) were lost to follow-up, 20 patients were

not located for the second interview and two for the third interview. Therefore, 221 patients completed the three interviews and were included in the final analysis: 111 ACF and 110 PCF. No deaths occurred among the included participants. (Figure 6.1).

Figure 6.1: Study flow chart



Included and excluded patients had similar socio-economic characteristics at baseline, except for income and ownership of bicycle (Table 6.1).

Table 6.1: Baseline socio-economic characteristics of TB patients included and excluded from the study. Nepal 2019

Patient Features	Patients included N=221	Patients excluded N=22	P-value[a]
Sex, N (%)			
Male	147 (67)	12 (55)	0.260
Age, mean (SD)	48 (16)	44 (16)	0.2389
Completed education, N (%)[b]			
No education/Basic school	188 (85)	21 (95)	0.180
Secondary school	33 (15)	1 (4)	
Occupation			
Farmer	39 (18)	4 (18)	0.950
Manual labour	15 (7)	1 (5)	0.686
Unemployed	80 (36)	5 (23)	0.206
Others	87 (39)	12 (55)	0.167
Patient income, median (IQR)	45 (0-135)	110 (45-162)	0.029*
Household income, median (IQR)	153 (90-270)	184 (90-243)	0.776
Source of drinking water, N (%)			
Piped	74 (33)	8 (36)	0.785
Others	147 (67)	14 (64)	
Toilet facilities, N (%)[c]			
No toilets	41 (19)	5 (24)	0.564
Public sewage	6 (3)	0	0.443
Others	173 (79)	16 (76)	0.795
Electricity, N (%)	202 (91)	19 (86)	0.432
Assets, N (%)			
Mobile phone	200 (92)	18 (82)	0.124
Refrigerator	31 (14)	2 (9)	0.506
Television	122 (56)	10 (45)	0.345
Radio	76 (35)	7 (32)	0.775
Bicycle	144 (66)	8 (36)	0.006*
Motorbike	44 (20)	3 (13)	0.461
Livestock	156 (71)	12 (57)	0.167

6.4.1 Socio-economic profile

Most participants were male (n = 147/221; 67%), in line with the gender ratio of notified TB cases in Nepal. ACF patients were more likely than PCF patients to be manual workers (28% vs 14%, P = 0.015), have a lower level of education, with significantly more individuals in the no-education category (75% vs 57%, P = 0.013) and significantly fewer having completed secondary school (9% vs 21%, P = 0.013). Ownership of a mobile phone and television was less frequent among ACF patients compared with PCF patients (88% vs 95%, P = 0.044 and 49% vs 63%, P = 0.042, respectively). Source of drinking water, type of toilet facility and availability of electricity in the home were similar among the ACF and PCF groups. Baseline socioeconomic characteristics of patients diagnosed through ACF and PCF are shown in Table 6.2.

Table 6.2: Baseline socioeconomic characteristics of TB patients diagnosed through ACF and PCF.

Patient Features	ACF N=111	PCF N=110	Pooled sample N=221	P-value[a]
Sex, N (%)				
Male	71 (64)	76 (69)	147 (67)	0.42
Age, mean (SD)	50 (15)	46 (17)	48 (16)	0.057
Completed education, N (%)[b]				
No education	83 (75)	63 (57)	146 (66)	0.006*
Basic school	18 (16)	24 (22)	42 (19)	0.289
Secondary school	10 (9)	23 (21)	33 (15)	0.01*
Occupation, N (%)				
Farmer	23 (21)	16 (14)	39 (18)	0.23
Manual labour	31 (28)	16 (14)	47 (21)	0.01*
Unemployed	31 (28)	29 (26)	60 (27)	0.79
Others	26 (23)	49 (44)	75 (34)	0.001*
Patient income quartile				
Poorest	43 (39)	51 (46)	94 (43)	0.25
Moderately poor	13 (12)	6 (5)	19 (9)	0.10
Average	29 (26)	25 (23)	54 (24)	0.56
Wealthiest	26 (23)	28 (25)	54 (24)	0.72
Household income quartile				
Poorest	39 (35)	30 (27)	69 (31)	0.21
Moderately poor	21 (19)	23 (21)	44 (20)	0.71
Average	29 (26)	29 (26)	58 (26)	0.97
Wealthiest	22 (20)	28 (25)	50 (23)	0.32
Source of drinking water, N (%)				
Piped	34 (31)	40 (36)	74 (33)	0.37
Others	77 (69)	70 (64)	147 (67)	
Toilet facilities, N (%)[c]				
No toilets	25 (23)	16 (15)	41 (19)	0.13
Public sewage	1 (1)	5 (5)	6 (3)	0.10
Others	85 (77)	88 (81)	173 (79)	0.45
Electricity, N (%)	98 (91)	104 (94)	202 (93)	0.28
Assets, N (%)				
Mobile/Phone	95 (88)	105 (95)	200 (92)	0.044*
Refrigerator	11 (10)	20 (18)	31 (14)	0.09
Television	53 (49)	69 (63)	122 (56)	0.042*
Radio	31 (29)	45 (41)	76 (35)	0.059
Bicycle	72 (67)	72 (65)	144 (66)	0.85
Motorbike	18 (17)	26 (24)	44 (20)	0.20
Livestock	80 (74)	76 (69)	156 (71)	0.41

[a]Chi square and Fischer exact, Wilcoxon rank sum;
bBasic schools= primary level/lower secondary level (1 to 8 years of education);
[c]One missing data,
*Statistically significant

6.4.2 Treatment characteristics

Most patients included in the study were new TB cases (214/221, 97%). During the pretreatment period, ACF patients reported less hospitalization (6% vs 19%, P = 0.004) and fewer visits to health providers (median number of

visits = 2.8 vs 4.6, P < 0.001). ACF patients were less likely than PCF patients to visit public sector healthcare facilities (47% vs 55%, P = 0.026) and more likely to access other types of health providers in seeking a diagnosis, which includes local NGOs and informal providers such as pharmacists and traditional healers (25% vs 19%, P = 0.044). During the treatment period, the number of visits and type of health facilities visited were similar for both groups (Table 6.3).

Table 6.3: Treatment characteristics of TB patients diagnosed through ACF and PCF (Nepal, 2019)

Characteristics	ACF N=111	PCF N=110	Pooled sample N=221	P-value[a]
Treatment status, N (%)				
New	105 (95)	109 (99)	214 (97)	0.056
Retreatment	6 (5)	1 (1)	7 (3)	
HIV Status, N (%)				
Positive	1 (1)	1 (1)	2 (1)	0.75
Negative	76 (68)	77 (70)	153 (69)	0.80
Unknown	34 (31)	32 (29)	66 (30)	0.99
Number of weeks between onset of TB symptoms and treatment initiation[b], median (IQR)	7 (3-13)	6 (4-12)	6 (3-13)	0.87
Hospitalization pre-treatment[b], N (%)				
Yes	7 (6)	21 (19)	28 (13)	0.004*
Hospitalization treatment, N (%)				
Yes	2 (2)	1 (1)	3 (1)	0.57
Visits to health providers, pre-treatment[b]	ACF N= 300[c]	PCF N= 498[c]	Pooled sample N= 798[c]	P-value[a]
Number of visits to health providers, mean (SD)	2.8 (1.8)	4.6 (2.3)	3.7 (2.2)	<0.001 *
Type of service visited[d], N (%)				
Public health centres/hospitals	140 (47)	273 (55)	413 (52)	0.026*
Private clinics/hospitals	84 (28)	129 (26)	213 (27)	0.52
Others[e]	76 (25)	96 (19)	172 (21)	0.044*
Visits to health providers, treatment[f]	ACF N= 249[c]	PCF N= 237[c]	Pooled sample N= 486[c]	P-value[a]
Number of visits to health providers, mean (SD)	2.2 (1.2)	2.2 (1.3)	2.2 (1.3)	0.70
Type of service visited[g], N (%)				
Public health centres/hospitals	208 (86)	203 (87)	411 (87)	0.70
Private clinics/hospitals	9 (4)	17 (7)	26 (5)	0.09
Others[d]	21 (10)	12 (5)	36 (8)	0.05

[a]Chi square, Fischer exact and Wilcoxon rank sum;
[b]Six ACF and one PCF relapse cases excluded from the analysis;
[c]N is the total number of visits to health providers;
[d]One PCF visit missed;
[e]NGOs, and informal providers such as pharmacists and traditional healers;
[f]Emergency and inpatient care;
[g]13 missing data.

6.4.3 Patient incurred costs IMPACT TB study

During the pretreatment period, ACF patients incurred lower total costs (mean cost, US$56 vs US$87, P < 0.001). When analysed by cost category, ACF patients also had significantly lower direct medical (mean cost, US$41 vs US$53, P < 0.001), non-medical (mean cost, US$7 vs US$18, P < 0.001) and indirect/time loss costs (mean cost, US$8 vs US$15, P < 0.001).

During the treatment period, the costs incurred by ACF and PCF patients were similar. The total costs incurred, including both pretreatment and treatment periods, was lower for ACF patients for direct medical (mean cost, US$58 vs US$74, P = 0.009), non-medical (mean cost, US$14 vs US$28, P < 0.001) and total direct cost (mean cost, US$72 vs US$101, P < 0.001) (Table 6.4)

Table 6.4: Mean and median costs per TB patient (US$) during pretreatment and treatment period in patients diagnosed through ACF and PCF (Nepal, 2019)

Cost item	ACF N= 111		PCF N = 110		Pooled sample N = 221		P-value[a]
	Mean (95%CI)	Median (IQR)	Mean (95%CI)	Median (IQR)	Mean (95%CI)	Median (IQR)	
Pre-treatment [b]							
Direct medical	41.1 (28.7-53.6)	12.3 (0-55.8)	53.1 (41.6-64.6)	29.6 (10.2-79.2)	47.2 (38.8-55.7)	21.7 (3.5-70.3)	<0.001*
Direct non-medical	6.8 (3.7-9.9)	1.4 (0-5.8)	18.4 (11.9-24.8)	5.3 (1.8-14.1)	12.7 (9.0-16.4)	3.0 (0.4-10.8)	<0.001*
Total direct pre-treatment	47.9 (32.8-63.0)	13.3 (1.4-59.9)	71.5 (56.2-86.8)	40.9 (14.0-11.5)	59.9 (49.1-70.7)	28.4 (6.2-81.9)	<0.001*
Indirect, time loss	7.5 (5.6-9.5)	4.3 (1.9-8.7)	15.3 (11.9-18.6)	10.0 (5.6-18.0)	11.5 (9.4-13.5)	6.7 (3.3-13.6)	<0.001*
Total pre-treatment	55.5 (39.0-71.9)	20.4 (3.8-69.2)	86.7 (69.7-103.8)	58.2 (22.3-127.2)	71.4 (59.5-83.3)	33.6 (10.3-97.1)	<0.001*
Treatment							
Direct medical	19.5 (13.5-25.5)	10.8 (6.3-20.7)	21.1 (14.9-27.4)	12.2 (7.2-21.2)	20.3 (16.0-24.6)	11.8 (6.6-20.7)	0.24
Direct non-medical	7.6 (5.1-10.2)	1.9 (0.3-9.4)	9.5 (6.8-12.1)	3.4 (0.7-13.2)	8.6 (6.7-10.4)	2.7 (0.7-10.8)	0.21
Total direct treatment	27.2 (20.2-34.1)	16.2 (9.5-31.1)	30.6 (23.3-37.9)	17.9 (12.0-37.7)	28.9 (23.9-33.9)	17.9 (10.7-32.3)	0.23
Indirect, time loss	38.7 (33.2-44.1)	29.6 (21.2-50.1)	44.1 (33.4-54.8)	27.9 (17.0-51.5)	41.4 (35.4-47.3)	29.1 (19.5-50.2)	0.54
Total treatment	65.9 (55.1-76.6)	48.8 (35.4-78.5)	74.7 (60.6-88.8)	51.2 (29.9-91.7)	70.3 (61.5-79.1)	49.8 (33.2-83.4)	0.71
Total costs (pre-treatment + treatment)							
Direct medical	58.4 (45.4-71.4)	31.3 (11-73.3)	73.7 (60.0-87.5)	47.4 (21.9-102.9)	66.1 (56.6-75.5)	42.3 (18.0-87.9)	0.009*
Direct non-medical	14.1 (10.3-17.9)	6.5 (1.7-17.6)	27.7 (20.5-34.8)	15.2 (5.9-29.6)	20.8 (16.7-25.0)	10.6 (2.3-23.3)	<0.001*
Total Direct (A)	72.5 (57.2-87.8)	43.7 (21.70-92.5)	101.4 (83.6-119.2)	69.3 (39.2-136.9)	86.9 (75.1-98.7)	57.3 (27.4-112.9)	<0.001*
Income loss	114.6 (90.0-139.2)	0 (0-250.6)	119.3 (88.4-150.2)	0 (0-263.7)	116.9 (97.4-136.5)	0 (0-251.4)	0.89
Total indirect (B)	160.4 (135.8-185.1)	97.2 (42.5-286.5)	178.6 (146.4-210.7)	90.5 (46.7-302.4)	169.5 (149.3-189.6)	92.4 (42.9-296.2)	0.55
Total costs (A+B)	233.0 (204.6-261.4)	218.2 (97.1-340.6)	279.9 (244.8-315.2)	252.0 (117.9-393.3)	256.4 (233.7-278.9)	245.2 (113.1-365.6)	0.07

[a] Wilcoxon rank sum;

[b] Six ACF and one PCF relapse cases were not included in this analysis

The multiple logistic regression showed that compared with PCF patients, ACF patients were 62% less likely to incur high total costs [adjusted OR = 0.38 (95% CI = 0.19–0.77)] (Table 6.5).

Table 6.5: Association between high median costs (total costs higher than the 75th quartile) and baseline characteristics.

Baseline characteristics	Crude OR (95%CI)	Adjusted OR (95%CI)
Variables		
ACF	0.45 (0.24-0.85)*	0.38 (0.19-0.77)*
Female	0.51 (0.26-1.03)	0.99 (0.42-2.35)
Age[a]	1.64 (0.88-3.06)	1.96 (0.97-3.95)
Patient income[b]	3.57 (1.85-6.88)*	4.74 (2.09-10.76)*
No education	1.11 (0.58-2.12)	1.58 (0.73-3.41)
Manual labour	1.52 (0.75-3.08)	0.99 (0.42-2.31)

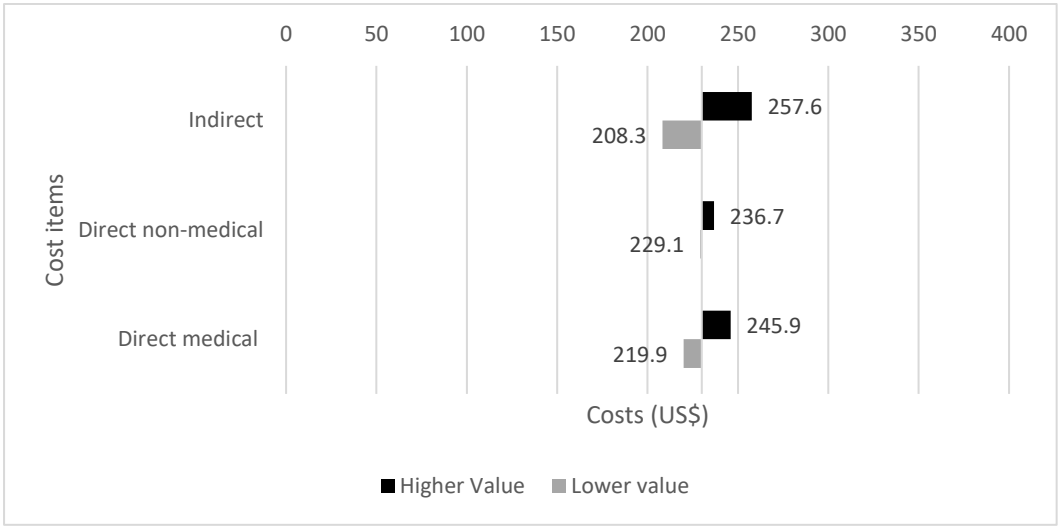
[a] Age>48 years (mean age for pooled sample)

[b] Income >US$45 (median pre-TB income for pooled sample)

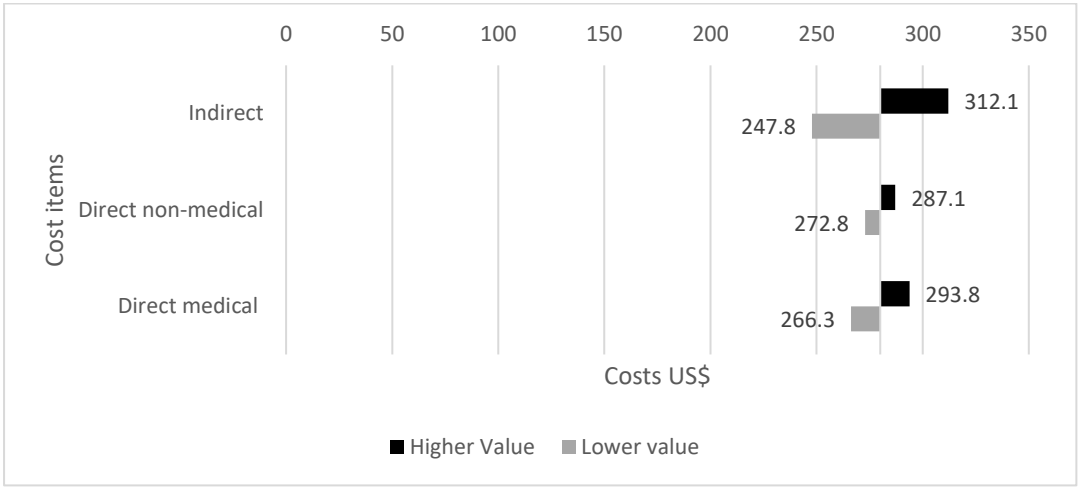
The one-way sensitivity analysis showed that in both ACF and PCF, indirect costs were the parameter with highest uncertainty. For ACF patients, the total cost varied from US$208 to US$257 and for PCF the variation was from US$248 to US$312 (Figure 6.2).

Figure 6.2: One-way sensitivity analysis varying total direct medical, non-medical and indirect, costs. Nepal, 2019.

a) Active case finding



b) Passive case finding



6.4.4 Socio-economic impact and catastrophic costs

The proportion of patients unemployed increased compared with pretreatment employment status. This was true for both ACF and PCF patients (71% increase for ACF and 75% for PCF) (Table 6.6).

ACF patients employed in formal jobs were less likely to change their employment status when compared with PCF (20% reduction in formal employment for ACF compared with 77% reduction for PCF) (Figure 6.3).

Figure 6.3: Impact of TB in employment status of patients diagnosed through ACF and PCF according to the treatment phase

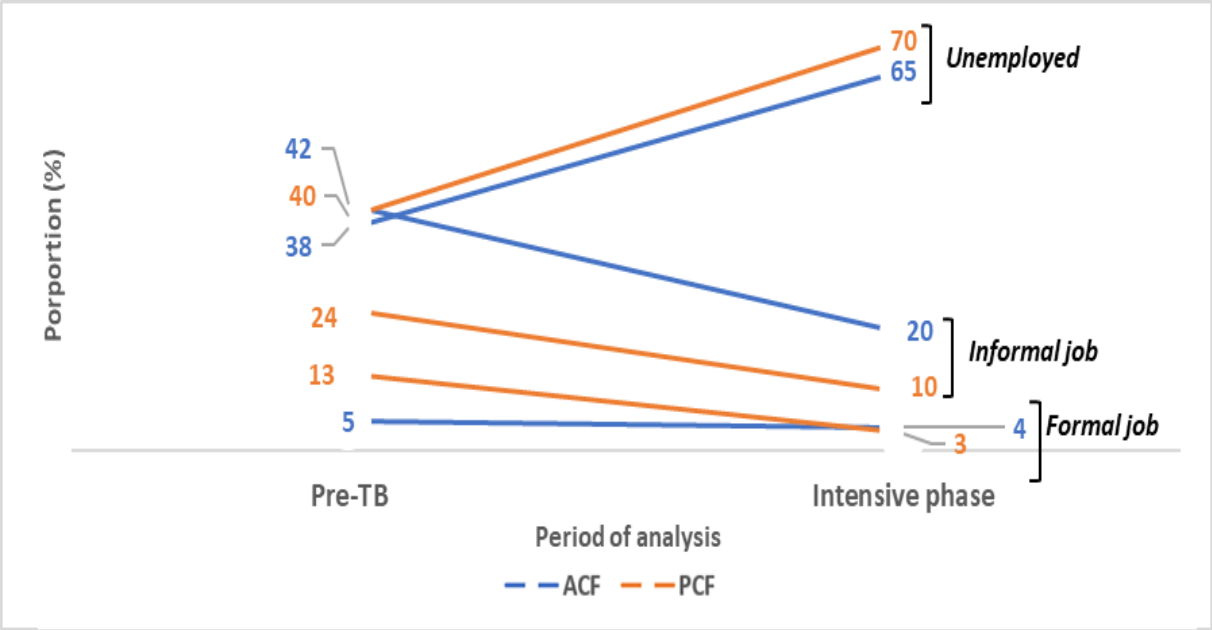


Table 6.6: Socio-economic impact in patients diagnosed through ACF and PCF at different periods of analysis (Nepal, 2019)

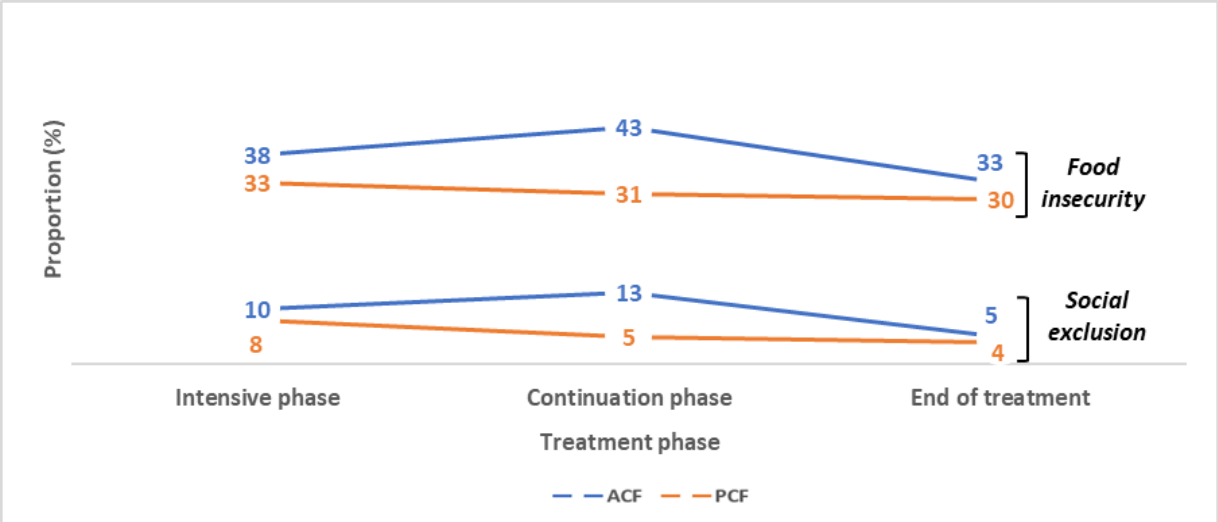
Variables	Pre-treatment N (%)		OR (95% CI)	Intensive phase N (%)		OR (95% CI)	Continuation phase N (%)		OR (95% CI)	End of treatment N (%)		OR (95% CI)
	ACF N=111	PCF N=110		ACF N=111	PCF N=110		ACF N=111	PCF N=110		ACF N=111	PCF N=110	
Unemployed	42 (38)	44 (40)	0.91 (0.53-1.57)	72 (65)	77 (70)	0.79 (0.45-1.39)	ND	ND	ND	ND	ND	ND
Food insecurity	NA	NA	NA	42 (38)	36 (33)	1.25 (0.72-2.17)	48 (43)	34 (31)	1.70 (0.98-2.95) *	37 (33)	33 (30)	1.17 (0.66-2.06)
Social exclusion	NA	NA	NA	11 (10)	9 (8)	1.23 (0.49-3.11)	15 (13)	6 (5)	2.71 (1.01-7.26) *	6 (5)	4 (4)	1.51 (0.42-5.52)
Poorer/much poorer	NA	NA	NA	58 (52)	53 (48)	1.17 (0.69-1.99)	62 (54)	53 (46)	1.36 (0.80-2.31)	53 (52)	48 (48)	1.18 (0.69-2.00)
Coping strategies	NA	NA	NA	24 (22)	27 (25)	0.85 (0.45-1.59)	15 (13)	11 (10)	1.41 (0.61-3.21)	8 (7)	10 (9)	0.78 (0.29-2.05)
Patient income> median	55 (51)	53 (49)	1.06 (0.62-1.79)	32 (56)	25 (44)	1.38 (0.75-2.52)	37 (55)	30 (45)	1.33 (0.75-2.37)	38 (53)	33 (46)	1.21 (0.69-2.14)
Household income> median	51 (47)	57 (53)	0.79 (0.46-1.34)	48 (47)	55 (53)	0.76 (0.45-1.29)	51 (47)	58 (53)	0.76 (0.45-1.29)	51 (46)	59 (54)	0.73 (0.43-1.25)
Poverty headcount[a]	44 (40)	51 (46)	0.76 (0.44-1.29)	85 (77)	87 (79)	0.86 (0.45-1.63)	76 (68)	81 (74)	0.77 (0.43-1.39)	76 (68)	78 (71)	0.89 (0.50-1.81)

NA=not applicable; ND=no data;

[a] Poverty headcount: Proportion of patients living with less than $1.9 per day, International Dollar ($) calculated applying purchase power parity (PPP), 2018 prices, conversion factor = $34.93 (https://data.worldbank.org/indicator/PA.NUS.PPP?locations=NP).

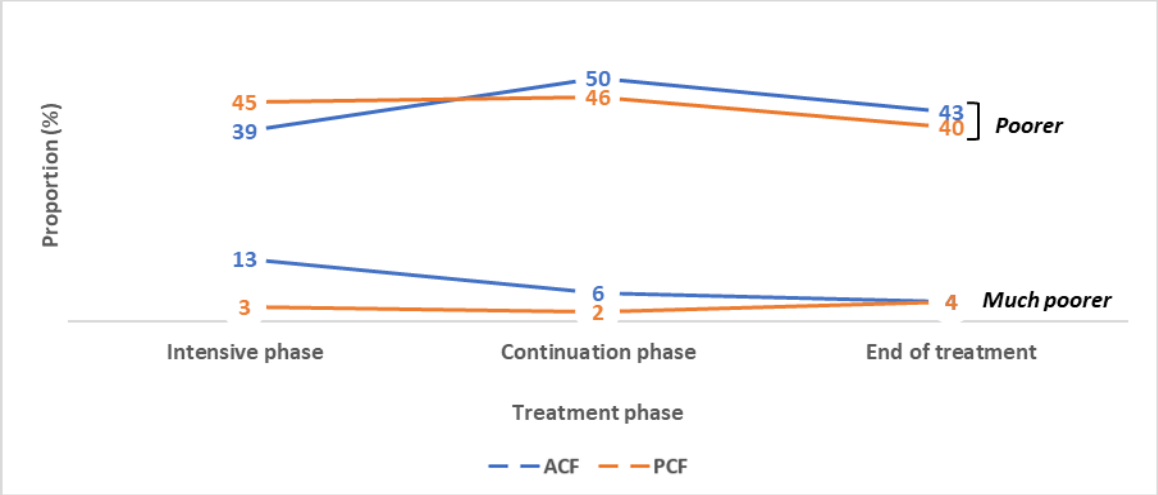
Food insecurity was reported by over a third of households and was the social impact most frequently reported at all stages of TB treatment by both ACF patients (38%, 43% and 33%) and PCF patients (33%, 31% and 30%) (Figure 6.4).

Figure 6.4: Social impact of TB in patients diagnosed through ACF and PCF according to the treatment phase.



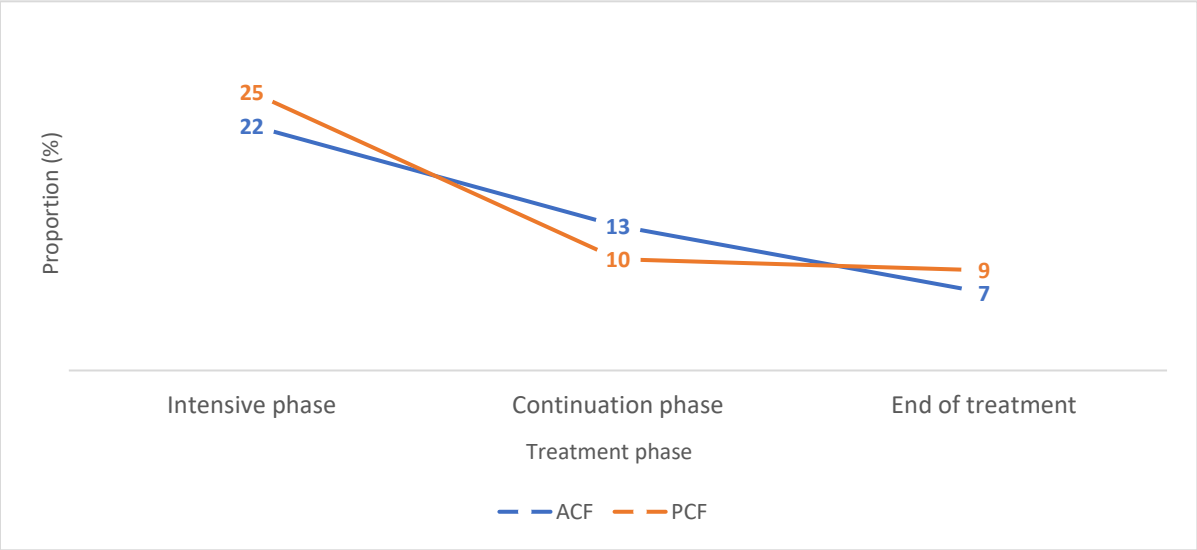
ACF patients were more likely to report food insecurity [OR = 1.70 (95% CI = 0.98–2.95)] and social exclusion [OR = 2.71 (95% CI = 1.01–7.26)] during the continuation phase when compared with PCF patients (Table 6.6). Economically, over half of all patients reported feeling ‘poorer’ or ‘much poorer’, with no patients feeling ‘richer’ (Figure 6.5).

Figure 6.5 Financial impact of TB in patients diagnosed through ACF and PCF according to the treatment phase



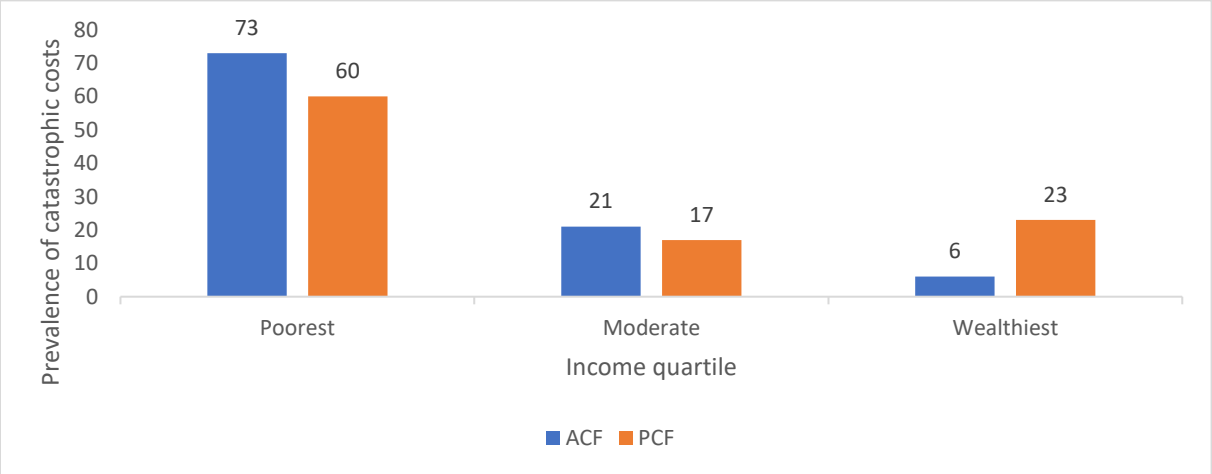
The frequency and pattern of utilization of coping strategies was similar in the two groups in all treatment phases (Table 6.6). Approximately a quarter of patients reported using coping strategies, i.e., selling essential assets or taking out loans, during the intensive phase of treatment (22% for ACF and 25% for PCF, P = 0.61) and the frequency had reduced by the continuation phase (13% for ACF and 10% for PCF, P = 0.42) and treatment completion (7% for ACF and 9% for PCF, P = 0.61) (Figure 6.6).

Figure 6.6: Coping strategies



The prevalence of catastrophic costs was similar for ACF and PCF (31% vs 32%, P = 0.91) and more frequent in the poorest households (Figure 6.7).

Figure 6.7: Prevalence of catastrophic cost according to income quartiles



'No education' was associated with catastrophic costs [adjusted OR = 2.84 (95% CI = 1.34–6.00)] (Table 6.7).

Table 6.7: Association between catastrophic costs and baseline characteristics.

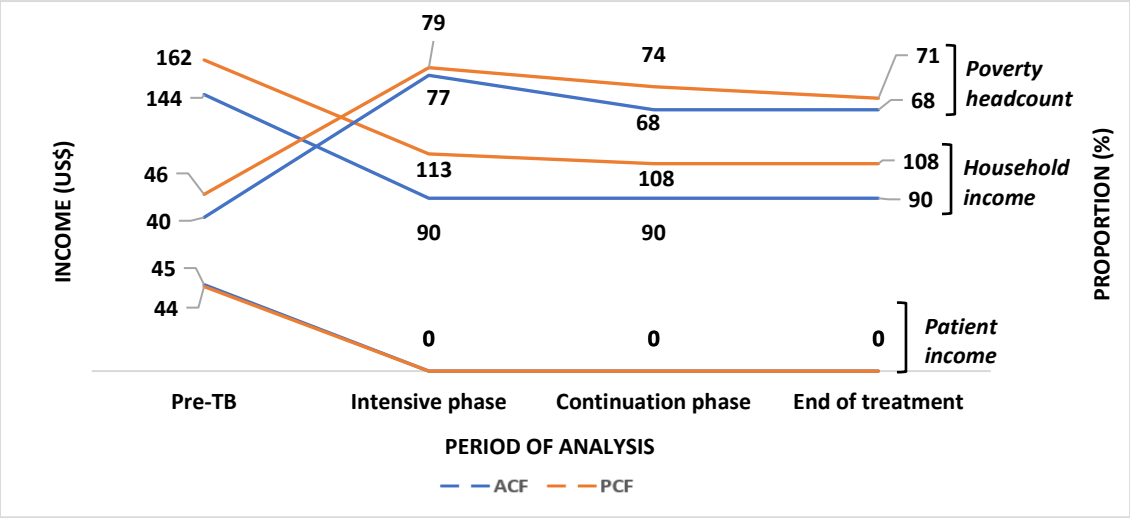
Baseline characteristics	Crude OR (95%CI)	Adjusted OR (95%CI)
Variables		
ACF	0.97 (0.54-1.72)	0.77 (0.42-1.44)
Female	0.78 (0.42-1.45)	0.72 (0.36-1.44)
Age[a]	2.10 (1.16-3.80)*	1.75 (0.92-3.32)
No education	2.87 (1.44-5.71)*	2.84 (1.34-6.0)*
Manual labour	1.53 (0.77-3.08)	1.65 (0.73-3.69)

[a] Age>48 years (mean age for pooled sample)

[b] Income >US$45 (median pre-TB income for pooled sample)

Patient income, household income and poverty headcount trends were similar for ACF and PCF throughout treatment (Table 6.6). The median patient income decreased to US$0 during the intensive phase for both groups and patients did not recover their pre-TB income by the end of treatment. The same pattern was observed for household income. In the intensive phase, the poverty headcount increased from 40% to 77% for ACF (92% increase) and from 46% to 79% for PCF (72% increase). The poverty headcount remained high until the end of treatment for both groups (Figure 6.8).

Figure 6.8: Poverty headcount (%), median, patient and household income



6.5 Discussion longitudinal patient costing study

The economic consequences of TB disease for affected families can be devastating. Our data showed that the mean total costs incurred were US$256 in a country with a Gross National Income per capita of US$970 in 2018 (133). Three quarters of TB patients experienced extreme poverty in the intensive phase of treatment. Importantly, we have shown that ACF can be an effective strategy to both reach the most vulnerable patient groups and reduce the economic impact.

ACF patients diagnosed under the community-based strategy were more likely to be those with no formal education, working in the informal sector and in the lowest socio-economic groups. These are the patients failed by the standard model of NTPs using PCF (223, 224).

These findings add to the body of evidence showing that ACF strategies can increase equity of access to TB services, particularly among the most vulnerable and disadvantaged populations, and bring us closer to achieving the Declaration of Rights for TB Patients (97, 100). Studies conducted in India and Nigeria also found higher vulnerability among ACF patients when compared with PCF, such as lower education

level, higher rates of unemployment, older patients and longer duration of symptoms (207, 225).

We also demonstrated that ACF was associated with significantly lower patient costs during the pretreatment period (mean total pretreatment costs US$56 for ACF group vs US$87 for PCF group; $P < 0.001$). Cost surveys conducted in Nepal and Cambodia found similar results as ours (148, 206). Although the number of weeks between the first TB symptoms and treatment initiation was similar between ACF and PCF, ACF patient costs were mitigated by the reduction in the number of visits to health facilities during the pretreatment period and, consequently, reduction in direct cost, such as transportation, unnecessary medication and tests in private services, and time lost waiting for appointments and traveling to and from healthcare facilities. ACF would not be expected to substantially influence the patient costs once on treatment, since both patient groups were enrolled into and treated via the government DOTS programme.

ACF was associated with lower total costs [adjusted OR = 0.38 (95% CI = 0.19–0.77)]. However, the prevalence of catastrophic costs was similar for both ACF and PCF patients, reflecting the lower initial socio-economic status of the ACF group. Also, our data showed that catastrophic costs were associated with ‘no education’ status, which was more frequent in ACF patients. Other studies have found catastrophic costs associated with number of symptoms, number of healthcare visits and use of nutritional supplements in South Africa (218); alcohol use and PCF in (217); and previous TB treatment and job loss in Indonesia (226). Our findings strengthen the evidence that while ACF may reduce household expenditure, this strategy needs to be implemented alongside social protection policies to protect TB patients from financial hardship and to achieve the zero catastrophic costs target in by the End TB strategy (72).

The longitudinal design identified a similarly severe pattern of socio-economic impact throughout the treatment for both ACF and PCF groups. The disease caused major socio-economic consequences for patients during the intensive phase. These included increased unemployment, a drastic reduction in income, high rates of food insecurity, utilization of coping strategies and falling into extreme poverty. Patients continued to

report high rates of financial and social impact at treatment completion and were not able to recover the income to the levels earned before the onset of TB symptoms. These findings indicate that TB triggered the medical poverty trap mechanism, which reinforces the poverty cycle and can persist for generations (120, 213, 216). Further studies adopting a longer follow-up are needed to evaluate the socio-economic impact post-TB treatment.

One of the limitations of our study is recall bias which may have affected the accurate estimation of costs and catastrophic cost due to the long interval between the interviews. The literature has shown that recall bias particularly affects the estimates of indirect costs, income lost in developing countries (141, 227). The same is true in Nepal, where the majority of TB patients are employed in the informal market or in seasonal jobs that do not provide regular salaries or payslips (133). Also, the prevalence of catastrophic costs by using self-reported income can be underestimated when compared with methods such as the asset linking approach or income estimated using the national average (125).

The IMPACT TB costing survey was the first longitudinal survey comparing ACF and PCF strategies in Nepal. The study design allowed the investigation of the socio-economic impact of TB throughout the whole treatment. Another advantage of this approach is the continuous collection of costing data with no extrapolation techniques (228) applied, which will increase the accuracy of estimates compared with the cross-sectional methodology. Another limitation of this study was the missing pretreatment costs for relapse and retreatment patients with possible underestimation of the total cost for ACF as this intervention had more patients in this treatment category (6 ACF vs 1 PCF). However, a cross-sectional survey conducted in Nepal indicated that PCF patients were more likely to be affected by memory bias and underestimate costs for pretreatment and intensive phase. A sensitivity analysis comparing costs reported by ACF and PCF patients interviewed within and after 1 month of treatment initiation found that PCF patients reported lower median total costs when interviewed after 1 month after starting treatment during the pretreatment period(<1 month: US$ 365.9; >1 month: US$ 128.5; P = 0.007), intensive phase of treatment (<1 month: US$ 190.4; >1 month: US$

67.6; P = 0.004) and total costs estimates (<1 month: US$ 556.3; >1 month: US$ 232.3, P = 0.002). No difference in costs was reported for ACF patients interviewed within or after 1 month of treatment initiation (148). Therefore, the missing cost in the pretreatment period for relapse and retreatment patients is unlikely to have affected the differences in total costs between ACF and PCF found in our survey.

ACF has been sporadically implemented in Nepal through several organizations and using different approaches (58, 102). However, to achieve a comprehensive and sustained implementation of efficient ACF models, some priority actions must be in place. These actions must consider the limited health system resources and the complex geographical features of Nepal. Improvements to human resource training and retention, an efficient quality control and logistics system to support diagnostic centers and reduction of import duties on advanced molecular TB diagnostic tests such as GeneXpert (220) would facilitate scale-up of ACF. The use of innovative technologies, such as drones to collect sputum sample and deliver TB medications, will be crucial to address challenges in sample transportation and comprehensively reach vulnerable communities in hard to reach areas (229, 230). Improved public–private linkages will also be essential to improve patient access to high-quality TB diagnosis and treatment and to bring ACF to the healthcare facility level (157). From the NTP perspective, an efficient allocation of human and financial resources and improvement of existing diagnostic centers are essential to successfully scale-up ACF in Nepal (66).

To break the poverty cycle among TB patients, alleviation programmes such as cash transfer, nutritional support and livelihood rehabilitation schemes must be accessible to patients from diagnosis and work in synergy with government scale-up initiatives under the SDG drive for Universal Health Coverage.

6.6 Conclusions longitudinal patient costing study

The community-based ACF model reached the most vulnerable patients and significantly reduced patient costs in the pretreatment phase. However, patients in both the ACF and PCF groups reported severe and enduring socio-economic consequences. Therefore,

policies including social protection must be evaluated and implemented to reach the End TB strategy goals. This work identifying the nature and depth of catastrophic costs faced by people affected by TB in Nepal led to and informed the design of a BNMT pilot study entitled ‘Addressing the Social Determinants and Consequences of Tuberculosis (ASCOT): A pilot implementation trial & process evaluation in Nepal’. This study was designed to evaluate the feasibility and acceptability of three different socioeconomic support models for TB patients in Nepal, with the aim to obtain funding for a fully powered intervention randomised controlled trial to test the impact of the most favourable strategies identified during the pilot. The ASCOT pilot tested small-scale intervention using three arms: social support alone, cash transfers alone, or combined socioeconomic support, alongside a control arm which received only a small food basket in addition to standard of care.

As Nepal graduates to a middle-income country, which is expected within the next five years, socioeconomic protection programmes are increasing in scope. To ensure support for families affected by TB is fully integrated into government support programmes, we must establish strong evidence for both effectiveness and feasibility.

CHAPTER 7: FINAL DISCUSSIONS AND CONCLUSIONS

7.1 Summary of Research Findings

My thesis aimed to strengthen evidence to inform policy on effective ACF strategies appropriate to be implemented by the Nepali National TB programme, embedded within the Nepali health system.

This was achieved through the two major objectives (1) determining the yields and additionality achieved using different ACF models (2) assessing the potential impact of ACF on prevalence and intensity of catastrophic costs for TB patients in Nepal.

The yield study from the TB REACH ACF project reported in chapter 3 - showed that the project identified 1,092 TB cases. Of the three case finding strategies employed, the highest yield was obtained from OPD screening at hospitals (n=566/1092; 52%). A further major finding of the project was the substantial yield of cases (n = 230) in individuals >65 years of age. This is consistent with our previous TB REACH wave 2 project which was implemented from November 2011 to June 2014. The 2019 TB prevalence survey for Nepal also shows that the elderly are among the high-risk groups unable to access existing TB diagnostic services in Nepal.

The proportion of positive tests using GeneXpert of 5.5% (n=859/15,637) was significantly higher than from microscopic testing at 2% (n=120/6309) (OR=1.4 [95% CI=1.12-1.72;'p=0.0026]). Accordingly, this study showed the increase in case diagnosis by using GeneXpert compared to traditional smear microscopy, which is consistent with other studies that have highlighted improved case detection through the use of sensitive molecular diagnostic methods.

The project contributed 22% additionality in case notifications in the intervention districts, demonstrating that GeneXpert achieved substantially higher case finding yields. Therefore, to increase national case notifications for TB, Nepal should integrate an OPD screening strategy, such as the FAST strategy(204), using GeneXpert testing in every district hospital and scale up community based ACF of TB patient contacts nationally.

NNS and NNT for hospital OPDs were lower than contact tracing and TB camps. The OPD strategy showed an NNS of 6, compared to NNS of 48 for contact tracing and NNS of 353 for TB camps. NNT was just 5 for the OPD strategy, 36 for contact tracing and 94 for TB camps. In this study, two-thirds of the TB cases among household contacts would have remained undiagnosed if GeneXpert test was not done. Hence, the contacts who harbor and discharge TB bacilli but could not be detected by conventional smear microscopy would continue suffering and transmitting the disease to their contacts unless a more sensitive test like GeneXpert is used to enable early identification of cases. Although the use of GeneXpert enabled better case detection among contacts, the wider use of GeneXpert in low-income settings needs to be evaluated in terms of its cost-effectiveness, feasibility and the priority group to be targeted by the service. WHO also recommend molecular diagnostic tests such as GeneXpert as the first line test of choice to investigate patients for TB however resource limitations are major barrier in high TB burden and low resource settings (98, 160). However, it is clear from the 2019 national TB prevalence survey in Nepal, which revealed 70% of TB cases were asymptomatic, that more sensitive screening techniques such as computer assisted chest x-ray screening should be evaluated for scale up of ACF in Nepal. Studies are needed to determine the most effective cut-off values, appropriate low-maintenance software packages, training and logistics requirements, optimal diagnostic algorithms and other implementation considerations before computer assisted chest X-ray can be effectively applied for TB screening in Nepal.

The second ACF yield study, IMPACT TB project, reported in chapter 4, showed that the project identified a total 1,133 (108%) positive TB cases. The yield rate of active case finding using GeneXpert was 5%, and with microscopy 3%. The additionality to NTP notifications in the intervention districts using GeneXpert was 13%, while the contribution of microscopy was 4%. Active Case finding should be intensified to include social contacts of index cases as well as household contacts, and this has now been proposed for integration into the Global Fund Activities for Nepal through the country proposal submitted in March 2023. Intensive ACF should be expanded to cover every district

through GeneXpert testing, to maximize case notification and close the diagnostic gap in Nepal (58).

The cross sectional costing study conducted during the TB REACH project and reported in chapter 5 showed that the prevalence of catastrophic costs was extrememly high for Nepali TB patients in the two districts evaluated, Pyuthan and Bardiya. Importantly, however, patients diagnosed through ACF incurred substantially lower costs during the pre-diagnosis period (direct medical: USD 14 *vs* USD 32, p = 0.001; direct non-medical: USD 3 *vs* USD 10, p = 0.004; time loss: USD 4 *vs* USD 13, p<0.001) and lower total costs (direct medical: USD 15 *vs* USD 34, p = 0.002; direct non-medical: USD 30 *vs* USD 54, p = 0.033). The prevalence of direct catastrophic costs was lower for ACF patients (13% *vs* 33%, p = 0.029). A lower intensity of catastrophic costs was also documented for ACF, although the difference did not reach statistical significance. Patients over 60 were particularly vulnerable to catastrophic costs when diagnosed passively rather than actively (OR: 4.6; 95% CI: 1.19; 19.3). Other costing surveys conducted in Asia such as Cambodia and India have also found lower costs and catastrophic costs among patients diagnosed through ACF when compared with PCF. ACF increases accessibility of health care where transport infrastructure is weak. Many patients live in areas without roads and therefore have to travel several hours or even several days to reach a health service in Nepal (206, 207).

These findings highlighted the important role of ACF in comprehensive patient-centric care and improving equity of access to TB diagnosis and cure.

The Longitudinal costing study conducted during the IMPACT TB project and reported in chapter 6, expanded these findings and allowed a more robust evaluation of costs incurred throughout the diagnosis and treatment phases. This is important to understand the variations in costs incurred as patients move from intensive to continuation phases, and recover the ability to earn income as they return to health.

The data showed again that the socio-economic impact was severe for both active case finding and passive case finding groups, and that this persisted throughout the whole treatment, with 32% of households incurring catastrophic costs. Catastrophic costs were

associated with ‘no education’ status. Studies conducted in India, Nigeria and Peru also found higher vulnerability among ACF patients compared with PCF, suggesting that ACF is able to reach more vulnerable, impoverished patient groups with limited mobility and without access to normal health services (120, 213, 225). An updated systematic review and meta-analysis published in 2022 regarding catastrophic costs associated with TB showed that the prevalence of catastrophic costs incurred by people with drug sensitive TB was 32%. The catastrophic costs incurred were lower among patients diagnosed via active than passive case finding (12% vs. 30%). Half (50%) of TB-affected households faced catastrophic health expenditure at 10% cut-off point (231).

ACF can contribute to reduce patient-incurred costs in the pre-diagnostic phase, but is unable to mitigate post-diagnostic costs. The prevalence and intensity of catastrophic costs remained high in the ACF group of the study. Therefore ACF is only one component of an effective strategy to achieve ‘zero catastrophic costs’ for people affected by TB. However, it is an essential component of patient centric care and should be integrated with comprehensive strategies to reduce the economic burden of TB on the most vulnerable population groups. The findings of the two patient costing surveys reported in chapters 5 and 6 have highlighted the need for a national patient costing survey to inform the effective design of socioeconomic support interventions for Nepali TB patients. A national patient costing survey in collaboration with WHO is now planned by the NTCC for 2023 and the design is being informed by the baseline data from studies in this thesis, and experience with the adaption and validation of the patient costing tools to the Nepali context.

7.3 Strengths and Limitations of Thesis

There are several strengths and limitation of my thesis. As a key strength, my thesis was not only limited to completion of a PhD academic degree but it was designed to address key policy issues of the 5 year National Strategic Plan for TB, and provide evidence to inform policy. This was achieved through the preparation of policy briefs and conducting policy dialogues with policymakers at national, provincial and district level, including the

National TB Control Centre (NTCC) and Ministry of Health and Population. These policy dialogues were designed to communicate research findings and raise awareness of the TB case detection gap, the potential of ACF, the increased yields obtained with GeneXpert testing for TB screening, the prevalence and intensity of catastrophic costs faced by TB patients, the socioeconomic impact of TB and the need for improved socioeconomic protection strategies.

The thesis findings built on substantial existing work by BNMT and others which cumulatively led to the uptake of intensified ACF policies, including social contact tracing and OPD screening (a modified strategy known as the FAST strategy within the Global Fund implementation(204)) within the national 5 year plan for TB and the national Global Fund TB application. The first longitudinal survey of the socioeconomic impacts of TB in Nepal reported in chapter 6 identified a severe pattern of socio-economic impact throughout the treatment for both ACF and PCF groups. Significant discussions are now taking place around socioeconomic protection strategies for families affected by TB in Nepal, and a national TB patient costing survey has been designed and funded to begin in 2023 in collaboration with WHO.

The ACF studies had a number of strengths, drawing on the expertise of the BNMT organization in implementing community based TB interventions in Nepal. Interviews were conducted by trained health workers who had strong established relationships of trust with the community for sensitive questions about a stigmatized disease and personal and household income. The studies provide important evidence to inform policy evolution for ACF scale up in Nepal. ACF is an important strategy to contribute to the achievement of End TB Strategy goals.

A limitation faced by all patient costing studies is recall bias, particularly around unreceipted costs such as transport and pharmacy medicines. Self-reported household income is also difficult to quantify in settings such as Nepal with a large informal economy, subsistence incomes and daily waged and seasonal labour or agriculture based incomes. These factors may have affected the accurate estimation of costs and catastrophic costs, exacerbated by the long interval between the interviews. Another limitation was the

sampling technique which was not a population based random sample. The national patient costing survey to be conducted by the NTCC and WHO in 2023 will provide a more robust estimate of patient costs and the prevalence and intensity of catastrophic costs as a baseline to measure progress nationally for the END TB strategy goal of eliminating catastrophic costs for TB affected households.

7.4 Implications, Further Research and Policy Translation

The global TB case detection gap was initially declining marginally during the early stages of this thesis. However, the Covid-19 pandemic caused severe disruption to all health interventions including TB, and tragically progess was reversed(1, 232). In 2020 deaths caused by TB increased for the first time in a decade(1). The global TB case detection gap remains at over four million in 2021, and TB incidence decline is still much slower than needed to reach the End TB targets(1).

The studies reported in chapter 3 and 4 demonstrated that substantial additionality in TB case notifications at the district level can be achieved through OPD screening and social-contact tracing strategies. Higher yields were achieved using GeneXpert than smear microscopy for active case finding. While TB camps had a relatively low yield, this strategy reaches remote populations and is an important component of comprehensive TB case finding strategy in the context of Nepal.

Household and social contact tracing of TB index cases and OPD screening should be implemented throughout Nepal within the TB FREE initiative to close the notification gap and accelerate progress towards the END TB strategy targets(163).

The WHO guidelines for systematic screening for active tuberculosis 2013 concluded that the evidence base for ACF was weak and far greater research and country experiences of implementation were needed to provide robust policy evidence. Many countries have implemented and scaled up various screening/ACF models since then. Revised

guidelines on systematic screening for TB were issued by WHO at both global and South East Asia regional level in 2020. Data and findings from the IMPACT TB project provided evidence to inform these revisions.

The majority of TB patients face catastrophic costs. The studies reported in chapter 5 and 6 show ACF is an important strategy to implement to reduce patient incurred catastrophic costs, especially in high burden LMICs, including Nepal. Chapter 6 showed Socio-economic consequences are severe and sustained for TB patients diagnosed by ACF and PCF in Nepal. ACF did however mitigate the costs in the pre-diagnotic phase. ACF has multifaceted benefits for improving patient centric care for the most vulnerable TB patients, including early detection and prompt treatment which will prevent from the suffering, death and further community transmission of TB. ACF therefore has a large role to play in achieving the WHO END TB strategy targets by 2035, including the target of eliminating catastrophic costs. Other synergetic policies for social protection, such as cash transfer in line with universal health coverage should be implemented in tandem with ACF to reduce catastrophic costs to zero among TB affected households.

The first ever prevalence survey revealed that burden of TB in Nepal is 1.6 times higher than previously estimated by WHO and about 117,000 people are living with TB disease and about 69,000 people developing TB in every year. Of those living with TB, 54% were undiagnosed while 70% of TB cases were asymptomatic (4). ACF is an essential component of a comprehensive strategy to find those “missing cases”, treat and prevent TB. ACF can help TB patients and their families to decrease costs and potentially reduce transmission. ACF increases equity of access to care and helps to find and treat TB patients earlier, reducing the long term consequences of the disease for health and socioeconomic status. Given the diverse geography and ethnic composition of Nepal, ACF is particularly important to ensure equitable access, universal health care to TB diagnosis and care among the most vulnerable populations.

In Nepal, the National Tuberculosis Control Center (NTCC), NGO partners and development organizations such as the Birat Nepal Medical Trust (BNMT), HERD,

JANTRA and Save the Children have piloted different models of ACF, but there is no complete national coverage and ACF projects have shown mixed results(102, 233-235). It is therefore key to learn lessons from failed approaches while improving and scaling up successful ones. My thesis in the BNMT Nepal project so called IMPACT TB and TB REACH Wave 5 projects evaluated the yields of ACF using GeneXpert or smear microscopy as the primary diagnostic test. The results of both projects showed strong additionality to NTP and lessons for scale-up.

Similarly, in June 2019, the WHO Joint Monitoring Mission Expert Review team recommended Nepal move towards using GeneXpert nationwide as the first diagnostic test for TB. While progress has been made, with over 100 machines now installed in country at hospitals and Primary Health Centres, coverage is incomplete. Cartridge supply via the government system is erratic and module breakdowns are frequent with long delays for servicing in remote areas. Such systemic challenges have limited the impact of GeneXpert scale-up on TB case finding. Data from the national prevalence survey provided strong evidence that chest X-ray screening to detect asymptomatic cases of TB in the community should be implemented in Nepal. Novel computer aid detection (CAD) digital screening methods, coupled with mobile chest X-ray systems could present a feasible solution for Nepal (236-238). The Japanese NGO JANTRA are currently testing such an approach in the Kathmandu valley. The case detection gap in Nepal is sizeable and a radical shift in policy will be needed to make significant progress, including all actors in the TB sector, including private providers.

The National TB Programme, known as the National TB Control Centre (NTCC), in Nepal, is responsible for delivering high quality TB service provision, including preventive and promotive services, under the guidance of the Department of Health Services (DoHS) and Ministry of Health & Population (MoHP). Proper implementation of active case finding (ACF) is challenging and needs careful context-specific design and implementation. Findings from multiple settings have shown that ACF is suitable and effective in high burden countries, particularly in areas or population subgroups with a high TB prevalence. However, significant additional human and financial resources and appropriate infrastructure and logictics capacity are needed to effectively implement

active case finding programmes. Primary health care workers are the real implementers and are key for putting ACF into practice. The long term cost-effectiveness of ACF needs to be established in further large implementation trials.

It is also recommended that further studies are conducted on strategies to reduce health system costs while maximizing additional TB case yields, as well as on costs and case yields of alternative public-private mix models for application in Nepal.

7.5 Recommendations arising from thesis findings to Nepal NTCC

A major challenge in progressing towards the TB elimination goals for Nepal established in the END TB strategy is the annual case detection gap of over 40,000 TB cases. Despite efforts in recent years to intensify case finding, the severe structural weaknesses in the underlying passive case finding system have limited the success of such efforts. To effectively increase case notification, ACF must be additional to, and not replace passive case detection mechanisms. Within fragile health systems such as Nepal, the implementation of ACF programmes can often result in a weakening of local passive case findings structures, rather than synergistic strengthening and integration of case finding approaches. For this reason ACF programmes must always be carefully designed to complement and integrate with existing diagnostic networks.

Considering the findings described in this thesis, the following ten recommendations are made to policy makers for improving patient centered TB diagnosis and care in Nepal.

The recommendations are grouped into three major themes: TB case finding scale up, application and scale-up of modern diagnostic testing methods, and social protection.

TB Case Finding Scale-up

1) Intensive ACF should be systematically sustained nationwide, potentially through the NTCC TB FREE Nepal initiative which has been started in 22/753 local palikas in 2022 (163).

2) Systematic training and mobilization of Female Community Health Volunteers (FCHV) is an effective strategy for ACF and should be applied nationally for community based contact tracing of both household and social contacts of every newly diagnosed TB index case.
3) Comprehensive OPD screening using a verbal symptom screening for triage followed by GeneXpert testing should be systematically applied in all district hospitals.

4) TB camps have comparatively low yields. However, such camps often reveal pockets of undiagnosed TB and are essential to reach remote rural populations in the challenging terrain of Nepal. TB camps may also focus on urban populations with restricted access to healthcare such as homeless or slum housing areas. TB camps are an essential component of a strategy which aims to "leave no one behind" and should be integrated into ACF strategies within the TB FREE Nepal initiative as it is scaled-up nationally.

5) Social contacts investigation has high yield in Nepal and should be implemented along with house hold contact investigation to close the notification gap.
6) Stigma reduction interventions and nutrition interventions should be the part of intersectoral TB action to encourage people to come forward for TB testing and support them through TB care. Further robust evaluation of effective stigma reduction strategies should be prioritised to identify culturally appropriate, effective interventions in the diverse communities of Nepal.

Application and scale-up of modern diagnostic testing methods

7) GeneXpert, or a comparable WHO approved, molecular diagnostic test, should be the primary diagnostic tool to detect TB as the sensitivity and ACF yield of GeneXpert is significantly higher than the ACF yield of smear microscopy. Given the substantial existing investment in GeneXpert infrastructure and training within Nepal to date, strengthening of the current

structure is likely to be the most feasible approach. Logistical supply chains and maintenance schedules for GeneXpert machines should be strengthened as a priority action.

8) GeneXpert testing of symptomatic individuals alone will not be sufficient to detect every TB case in Nepali communities, and enhanced algorithms for ACF which utilise technologies such as computer assisted chest X-ray screening should be urgently evaluated for scale-up.

Social Protection for reducing TB associated catastrophic costs

9) The planned nationwide TB-costing survey should be prioritised in 2023 to provide a robust understanding of the prevalence, intensity and category of costs faced by people affected by TB in Nepal, across the full spectrum of this diverse nation.

10) Social protection for TB patients should be prioritised utilising the evidence from the costing survey. There is an extremely high incidence and intensity of catastrophic costs, often leading to devastating long-term consequences, for people affected by TB in Nepal. My thesis studies identified severe socio-economic consequences for TB affected households which persisted throughout the whole treatment, and therefore comprehensive social protection policies should be designed and implemented as Nepal matures to a middle income country within the next five years. A task force should be established to review evidence from other settings and design an appropriate, feasible strategy for Nepal which is fully integrated with the broader social protection measures. Both TB- sensitive social protection program and TB-specific social protection program should be implemented for comprehensive coverage.

7.6 Final Conclusions

Tuberculosis remains one of the oldest pandemics and has remained stubbornly persistent despite advances in modern healthcare. Despite being a curable and

preventable disease, one quarter of the world population are infected with TB, mostly because of persistent poverty. TB is a disease of the poor, linking in poverty and stigma. WHO estimates that more than 95 percent of TB deaths occur in low- and middle-income countries where malnutrition and stigma are widespread, and access to health care is limited. There has been limited political will to address TB, and a fundamental lack of equity in access to TB services. Together, these factors have fostered the persistence of the TB epidemic among the world's poorest communities.

The thesis findings have contributed to the evidence base surrounding effective ACF policy implementation, including scale-up, in Nepal. The findings have been widely disseminated through national and international level through policy dialogue workshop, meetings and at the local level with stakeholders. The Government of Nepal has repeatedly committed to the targets enshrined in the END TB strategy, and it is hoped that political commitment will now translate to increased financial commitment and action to accelerate progress against TB.

The second UN high Level Meeting for tuberculosis will be held in New York in September 2023. It is hoped that this meeting will finally precipitate the required action by global political leaders to END TB: Every case, Everywhere.

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