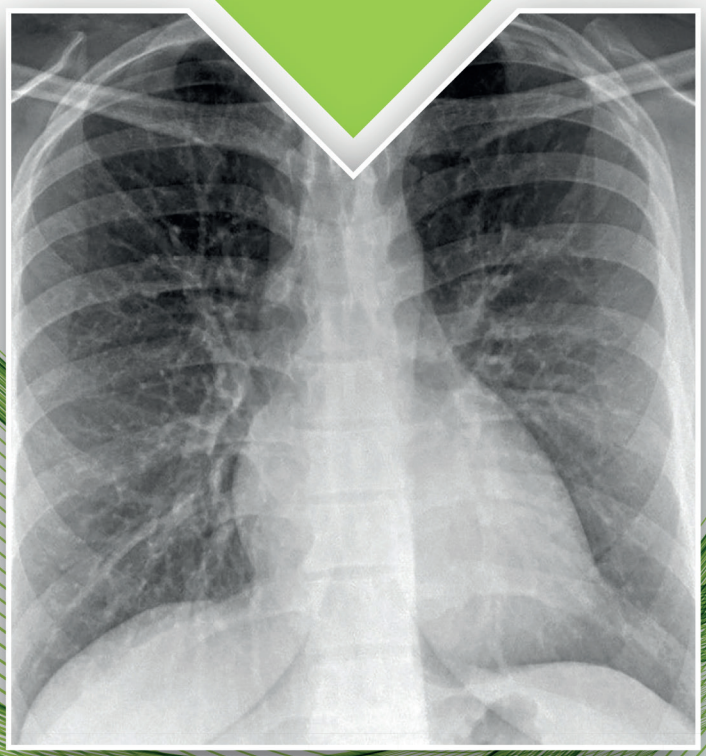
The First National TB Prevalence Survey
South Africa 2018



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EXECUTIVE SUMMARY

In the absence of a national tuberculosis (TB) prevalence survey, South Africa has used routine TB surveillance data to derive TB incidence and prevalence estimates for the country. This necessitated conducting a national TB Prevalence Survey to provide the true burden of bacteriologically-confirmed pulmonary TB disease in the country. The First National Tuberculosis Prevalence Survey, South Africa, 2018, also assessed the health care seeking behaviour among people with symptoms of TB.

Design, sample size and sampling: This nationwide cross-sectional population-based survey was designed to provide national TB prevalence estimates in the adult population (aged 15 years or above) and then extrapolated to people of all ages and all forms of TB in South Africa. The survey was conducted in accordance with World Health Organization (WHO) guidelines for national TB prevalence surveys. Given the varying burden of TB across the different provinces of the country as derived from routine data, the nine provinces were grouped into three strata of high, medium and low TB prevalence. Within each stratum a required set of clusters (geographically discrete areas) was sampled by means of a multi-stage process whereby at each stage sampling units were selected with probability proportional to population size (PPS). To meet the sample size of 55 000 individuals and a selected fixed cluster size of 500, a total of 110 clusters were sampled across the country.

Screening for TB: Individuals who met the survey inclusion criteria (15 years and older, had slept in the house for at least 10 nights of the prior two weeks) and consented to participate were screened for TB using the WHO recommended screening strategy for TB prevalence surveys. The screening strategy comprised of a symptom-based questionnaire and chest X-ray (CXR) examination. The screening questionnaire also asked about the human immunodeficiency virus (HIV) status. The participants who reported any symptoms of TB (one or more of the following: a cough of any duration, unexplained loss of weight, night sweats, unexplained fever), and/or an abnormal CXR that was suggestive of TB, were requested to produce two sputum specimens. The first specimen was tested for TB using Xpert® MTB/RIF Ultra (Xpert Ultra), and the second one which was taken at least an hour after the first underwent liquid culture for *Mycobacterium tuberculosis* on the BACTEC* MGIT 960 (Becton-Dickinson, Sparks, MD, USA) system.

Profile of survey participants: A total of 68,771 individuals were enumerated in the households within the selected clusters. Of these, 53,250 met the inclusion criteria, from which 35,191 (66.1%) consented and participated in the survey. Survey participation was lower in males than in females and was lowest among the youth (15-24 years) but improved with increasing age. Participation was higher in rural areas than in urban areas. Among the participants, 9,066 (25.8%) were eligible to submit a sputum specimen. One hundred and seventy-eight (178/9066) participants reported that they were on TB treatment at the time of their enrolment into the survey.

Definition of a Survey TB case: The criteria for defining a case in this survey were:

1) A positive culture for *Mycobacterium tuberculosis*, or, in the absence of a positive culture,

2) A positive Xpert Ultra result without a history of previous TB, PLUS CXR findings suggestive of active TB.

Two-hundred and thirty-four (234) participants met the Survey TB case definition. This included 220 who were culture positive (144 of these also Xpert Ultra positive), and 14 who were Xpert Ultra positive and culture negative, with no history of TB and had CXR findings suggestive of active TB.

HIV status among survey TB cases: As part of the interview process participants were asked about their HIV status. Those who were eligible for sputum samples were also offered optional HIV testing on a dried blood spot (DBS) sample. The HIV status in the survey was determined using results from the DBS sample if available, or by self-reported status where there was no DBS result. HIV status was classified as an unknown where there was no self-reported status and no DBS result. HIV status was known or established in 191 of the survey TB cases, and 55 (28.8%) of these were HIV-infected.

Health care seeking among participants with symptoms of TB: Among the 5,168 survey participants who reported at least one TB symptom, 3,442 (66.6%) reported not having sought care for the symptoms at the time of the survey. Proportionately more males (71.3%) than females (63.4%) did not seek care. The proportion of symptomatic participants who did not seek care was highest (82.3%) in the youngest age group (15-24 years) and decreased with age, reaching 62.9% in those aged 45-54 years old, and 54.8% in those 65 years and older. Most (2,071/3,442 [60.2%]) of those who had not sought care indicated they were planning to seek care; just over a quarter (917 [26.6%]) felt their symptoms were not sufficiently serious for them to seek care, 223 (6.5%) reported not having sufficient money to travel to a health facility, and 189 (5.5%) reported that the nearest health care facility was too far away. Among those who had sought care most had attended a government facility.

The key survey findings:

- ***The burden of tuberculosis***
  The prevalence of pulmonary TB in the population aged 15 years and older in 2018 was estimated at 852 per 100,000 population (95% CI 679-1,026). Men had a 1.6 times higher prevalence than women (1,094 per100,000 [95% CI 835–1,352] compared to 675 per 100,000 (95% CI 494–855]). TB prevalence was highest in those aged 35-44 years (1107 per 100,000, [95% CI 703–1,511]) and those 65 years and older ((1,104/100,000 [95% CI 680–1,528]) and lowest in the 15-24 year age group 432 per 100,000 (95% CI 232-632). The prevalence of TB (all forms, all ages) in South Africa in 2018 was 737 per 100,000 population (95% CI 580-890).

- ***Prevalence and notifications***
  The estimated number of TB cases was more than the cases that were notified in 2018, with a Prevalence: Notification (P:N) ratio of 1.75. The gap was largest in those aged 15-24 years (P:N ratio 2.91) and those 65 years and older (P:N ratio 2.88).

- ***Subclinical tuberculosis***
  A high proportion (57.8%) of the bacteriologically confirmed TB cases did not report any TB symptoms at the time of the survey. These individuals were considered to have subclinical TB. They represent a phase in the continuum of TB disease and may in time develop symptoms and have the propensity to transmit TB.

- ***Tuberculosis and HIV***
  The percentage of survey TB cases with HIV (28.8%) was half that reported for TB cases on treatment within the national TB management programme (58.0%) in 2018. This finding is consistent with reports in the literature of a higher community burden of HIV-uninfected TB when active case finding efforts are undertaken. Among TB cases with a known HIV status, the majority who did not report symptoms were HIV-uninfected (83/107 [77.6%])

- ***Health care seeking for TB symptoms***
  Health care seeking among participants with symptoms suggestive of TB was delayed with almost two-thirds not having sought care at the time of their participation in the survey. Among them, 60.2% reported they were still planning to seek care, and a further 26.6% regarded the symptoms as not serious. A fifth (19.5%) of survey TB cases who were symptomatic and had sought care had been diagnosed and started on treatment.

- ***Summary and key programmatic implications***
  The survey was a nationally representative population-based survey that has, for the first time, provided a national estimate of the true burden of TB in South Africa. The prevalence estimates were derived following WHO standardized methodology ensuring the robustness of estimates and allowing for comparisons with other countries and regions. Important issues that will help in formulating future strategies to effectively address the TB epidemic were uncovered. The survey findings revealed that:

  (i) South Africa has a high TB burden including many people with undetected TB in the community;

  (ii) Subclinical TB contributes to the TB burden in the country;

  (iii) TB in HIV-negative individuals is common at the community level; and

  (iv) Individuals with symptoms suggestive of TB delay seeking care

Based on these findings, the key programmatic recommendations are to:

- Strengthen and design TB interventions targeted towards men, young people, and the elderly to increase TB case detection.
- Use technology and mHealth solutions to widen the reach and facilitate entry into the cascade of care.
- Carefully consider the role and use of CXRs in case finding among patients who do not report symptoms and would be otherwise missed.
- Increase awareness of the significance of TB symptoms to prompt early care seeking.
- Increase and sustain heightened vigilance by healthcare professionals in assessing TB symptoms among those who attend health care facilities to promote early identification of presumptive TB and elicit diagnosis.
- Undertake research to better understand subclinical TB and approaches for its detection and management.

Conclusion

The First National Tuberculosis Prevalence Survey, South Africa, 2018, identified a high TB burden, higher in males (1,094/100,000) than in females (675/100,000), and highest among individuals aged 35-44 years and the elderly aged 65 years and older. The largest prevalence to notification gap was in the youth aged 15-24 years and those 65 years and older. A higher proportion of TB was detected among HIV-uninfected individuals, with most reporting no symptoms. HIV-infected participants identified as TB cases were more likely to report symptoms and hence are more likely to report and be treated in contrast to those who are HIV-uninfected who are less likely to report symptoms and seek care and therefore potentially contribute to ongoing community transmission of TB. Subclinical TB has emerged as another area that requires further research and will be important for long-term disease control efforts. Although TB symptoms at first may be perceived to be benign leading to delays in health care seeking, this perception needs to be corrected as TB remains the number one infectious disease cause of mortality in South Africa. In addition, a high index of suspicion, evaluation and follow-up of people presenting with TB-related symptoms by health care providers, is needed to improve case detection.

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ART	Antiretroviral Treatment
CHIVSTI	Centre for HIV and STIs
CI	Confidence Interval
CTB	Centre for Tuberculosis
Cult	Culture
CXR	Chest X-ray
DBS	Dried blood spot
DMC	Data management committee
DOTS	Directly observed treatment, short-course
EA	Enumeration area
EC	Eastern Cape
ELISA	Enzyme-linked immunosorbent assay
FS	Free State
GDP	Gross domestic product
GP	Gauteng
HCW	Health Care Worker
HDI	Human development index
HIV	Human immunodeficiency virus
HSRC	Human Sciences Research Council
HTS	HIV testing services
ID	Identification
IEC	Information, Education, Communication
IPW	Inverse probability weighting
IT	Information Technology
IQR	Interquartile range
ISO	International Organization for Standardization
KZN	KwaZulu-Natal
LIS	Laboratory information system
LP	Limpopo
MDG	Millennium Development Goals
MDR	Multidrug resistant
MGIT	Mycobacteria Growth inhibitor tube
MI	Multiple value imputation
MO	Medical officer
MoS	Measure of size
MP	Mpumalanga
MTB	Mycobacterium tuberculosis complex
MTR	Midterm review
NALC	N-acetyl-L-cysteine
NaOH	Sodium Hydroxide
NC	Northern Cape
NDOH	National Department of Health
NDP	National Development Plan (of South Africa)
NICD	National Institute for Communicable Diseases
NSP	National Strategic Plan on HIV, TB and STIs
NTM	Non-tuberculous mycobacteria
NTCP	National TB Control Programme
NW	North-West
OHS Care	Occupational Health Services
PA	Posterior-Anterior
PFMA	Public Finance Management Act
PIN	Personal Identification Number
PLWH	People living with HIV
P:N ratio	Prevalence: Notification ratio
PPS	Probability proportional to population size
PST	Pre-Survey Team
PSU	Primary sampling unit
PTB	Pulmonary Tuberculosis
QC	Quality control
REDCap	Research Electronic Data Capture
Rif	Rifampicin
RR	Rifampicin resistant
SA	South Africa
SAL	Small area layers
SAMRC	South African Medical Research Council
SANAS	South African National Accreditation System
SAPS	South Africa Police Service
SC	Steering Committee
SDG	Sustainable Development Goals
SOP	Standard operating procedure
SFS	Survey Field Site
SP	Service Provider
SR buffer	Sample reagent buffer
STIs	Sexually Transmitted Infections
TB	Tuberculosis
TBc	Tuberculosis Complex
VPs	Visiting Points
WC	Western Cape
WHO	World Health Organization
Xpert Ultra	Xpert MTB/RIF Ultra®
USA	United States of America
USD	United States Dollar
ZAR	South African Rand
ZN	Ziehl Neelsen

1. INTRODUCTION

1.1 The tuberculosis (TB) epidemic in South Africa

South Africa is one of the 30 high burden tuberculosis (TB) countries that collectively contributed to 87% of the estimated incident cases worldwide in 2017 (1). It accounted for 3% of TB cases globally and adjusting for population size, it is often ranked the highest in terms of incidence rate for TB.

The estimated incidence has however been declining gradually and is estimated to have fallen by 7% between 2010 and 2017 (322/100,000) (2). Evidence of declines of the rate of microbiologically confirmed pulmonary TB (PTB) dates back to 2008 (3) and the decline in estimated TB incidence has been consistent between the laboratory confirmed PTB incidence rates and notification data reported by the National Department of Health (NDOH). HIV has had a devastating impact on TB in South Africa and is a key driver of the TB burden in the country. While the aggressive scale up of antiretroviral treatment (ART) has curbed and reversed the rapid increase of TB, the country's TB epidemic remains typified by high HIV-coinfection rates, estimated at 60% in 2017 and in 2019 (1, 4). In addition, there are high rates of drug-resistant TB, with the estimated incidence of multi drug resistant/rifampicin resistant (MDR/RR) TB at 7,700 cases in 2017 and 14,000 cases in 2019 (1, 4).

TB has maintained its rank as the leading cause of death although the proportion of deaths due to TB has decreased significantly since 2007 when it peaked at 12.7% (5) decreasing to 6.4% in 2017 (1). In 2017, there were an estimated 22,000 deaths from TB (excluding HIV co-infected patients), with another 56,000 deaths in people co-infected with HIV.

1.2 The national response to TB

The national TB response is guided by the goals and activities detailed in the National Strategic Plan (NSP) on HIV, TB and sexually transmitted infections (STIs) (6). The NSP is closely aligned with the country's National Development Plan (NDP), (7) locating the "struggle against HIV, TB and STIs within the broader framework for economic and social development" (6). The vision of the NSP is a South Africa free from the burden of HIV, TB and STIs, and the goals of the 2017-2022 NSP (the country's 4th NSP) include among others i) accelerating prevention to reduce new HIV and TB infections and STIs, ii) reducing morbidity and mortality by providing HIV, TB and STI treatment, care and adherence support for all, and iii) strengthening strategic information to drive progress towards achievement of the NSP goals. The specific objectives and subobjectives related to TB within the NSP include reducing TB incidence by at least 30%, and implementing the 90-90-90 strategy for TB where the first 90 aims to find 90% of all TB cases and place them on appropriate treatment (6).

1.3 Surveillance of tuberculosis and the need for the prevalence survey

The South African National TB Control programme (NTCP) uses an electronic TB register, TIER.Net (8) as a surveillance system. TIER.Net captures TB data at the sub-district level from paper-based registers completed at facility level by nurses. Although the system has many benefits, it however has some limitations. These limitations include incomplete data and duplication of records when persons accessing TB services do so in more than one facility, or when patients use different names, or the same names spelled differently. The incidence and prevalence calculations derived from TIER.Net are therefore based on notifications and represent an estimate of TB cases in South Africa. The 2019 Global TB report showed a large difference between the modelled estimates of the burden of disease and the notified cases (4). While both notification and modelled estimates have limitations, the difference is still large and would impact efforts aimed at ending TB by 2035.

Although several efforts aimed at finding additional cases of TB have been initiated (9), these have not provided much additional benefit and have raised uncertainty around the accuracy of the modelled estimates which are

based on TB notifications. Primary transmission of PTB is a major driver of the epidemic and any missed cases are missed opportunities with long-term consequences. Resolving the uncertainty of the true burden of TB disease through the implementation of a national survey was necessary. The survey would also assist in providing information about possible population groups in which TB is under-diagnosed or missed. The NTCP, therefore, commissioned a nationwide TB prevalence survey to establish the true burden of PTB disease in South Africa. South Africa had never previously conducted a national TB prevalence survey and therefore was overdue for implementing a formal systematic study to describe the TB burden.

At the global level, since 2007, more than 33 national TB prevalence surveys have been conducted in 31 countries, following standardized World Health Organization (WHO) methodologies (10-12). These surveys provide population-level TB estimates using a community-level active case finding strategy as opposed to passive case identification that is routinely practiced. Furthermore, since notification data only account for patients started on treatment, and previous studies have highlighted inaccuracies and under reporting within these data (13, 14), the TB prevalence surveys conducted thus far in other countries have provided important insights to guide programmes to develop effective strategic plans aimed at Ending TB by 2035. The prevalence survey data from these countries have also been incorporated into the global TB models to improve the accuracy of the country and WHO estimates reported annually.

2. AIM AND OBJECTIVES

The aim of the national TB prevalence survey was to enhance TB control in South Africa by informing the NTCP about the epidemiological situation of active PTB and offering insight on ways in which TB control can be improved.

2.1 Primary objective

To estimate the nationwide prevalence of bacteriologically (Xpert Ultra and/or culture) confirmed PTB disease among the adult (≥15 years) population of the Republic of South Africa.

2.2 Secondary objective

To identify the extent to which people with pre-existing TB or with symptoms suggestive of PTB seek care, and if so, from which type of health service provider.

3. METHODS

3.1 Survey design

This was a cross-sectional nationwide, multistage cluster-based survey that was conducted following the WHO standardized methodology for national TB prevalence surveys (15). Population proportionate cluster sampling was performed, and targeted individuals aged 15 years and older. Given the varying burden of TB across the different provinces of the country as derived from routine data, the nine provinces were grouped into three strata of high, medium and low TB prevalence. Within each stratum, the required number of clusters (geographically discrete areas) were sampled, employing a multi-stage process, whereby at each stage (province, district, and sub-district/municipality level) sampling units were selected with probability proportional to their population size (PPS). At the final stage, where a single cluster was selected from a sub-district/municipality, all clusters in the sub-district were listed and one cluster was randomly selected. If the clusters varied considerably in their population, then the cluster was selected with PPS. This stratified design increased the precision and representativeness of the overall national estimate of TB prevalence.

The 2011 South African census defined small area layers (SALs), which were used as the building blocks for defining the clusters sampled at the first stage. The SAL is the new classification of the lowest geographical area by Statistics South Africa replacing the Enumeration areas (EAs) (16). A SAL consists of approximately 180 households in urban areas, and 80 to 120 households in deep rural areas. SALs exist at a level higher than EAs. EAs having relatively few visiting points (VPs) were merged to form a SAL. A VP is defined as a stand or an address that may include one or more households. A household is defined as a group of people who live and eat together from the same pot. For example, individuals in a hostel who eat together are considered a single household; alternatively, they may, if not sharing a single pot, be classified as separate households within a single VP (16).

A selected fixed cluster size of 500 individuals eligible to attend the survey was used, with a resulting design effect of 1.44 (coefficient of variation k=0.5), based on previously calculated prevalence from notifications in 2013 (17). Allowing for a participation rate of 85%, the required sample size was estimated at 54,873 individuals aged 15 years and above from these 110 clusters. Ultimately, 110 clusters were selected and were distributed as shown in Figure 1.

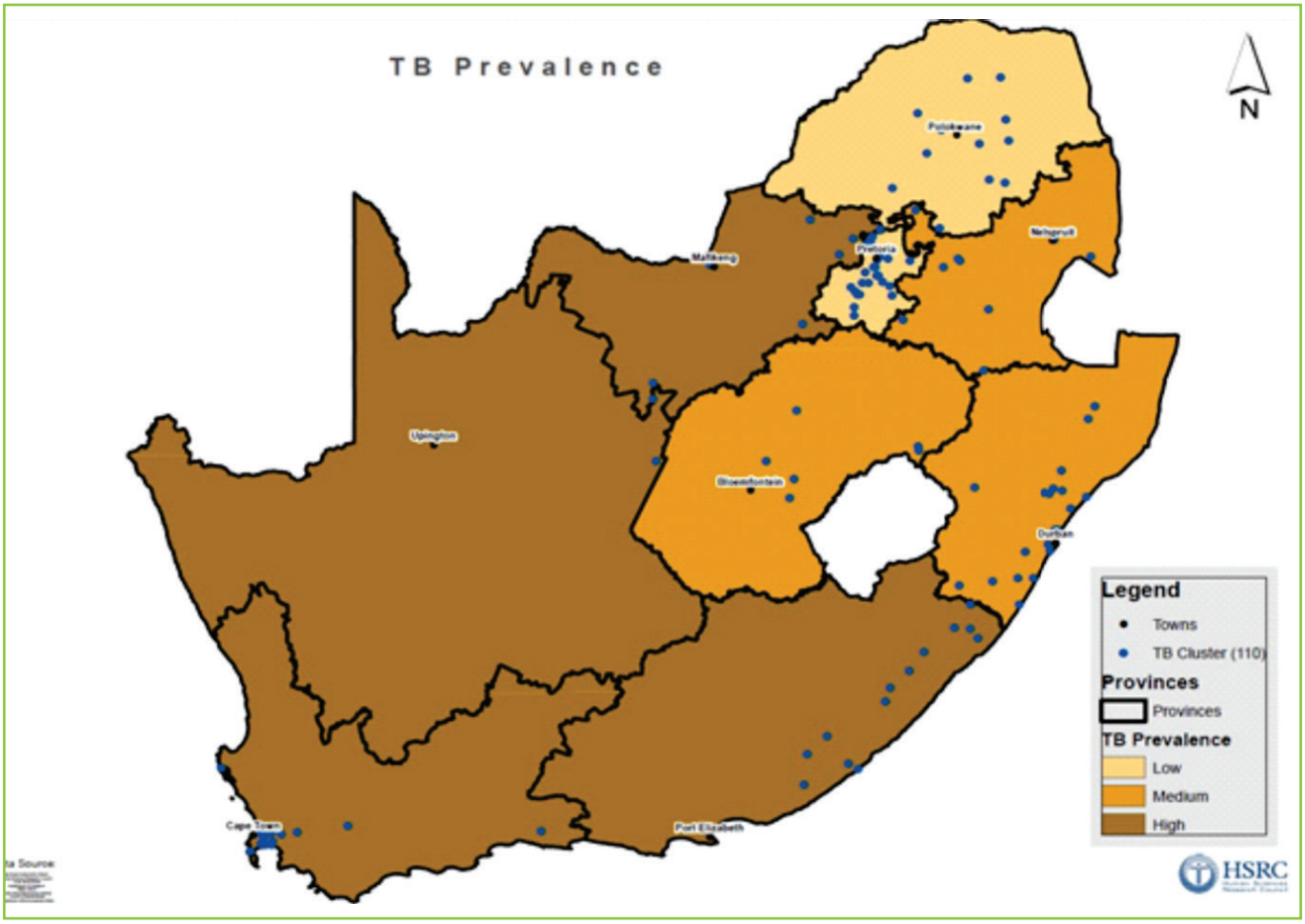

Figure 1. Map of South Africa showing provinces, selected major towns (black dots) and the clusters (blue dots) sampled for the survey

3.2 Survey inclusion and exclusion criteria

The inclusion criteria for survey participation were as follows:

- persons aged 15 years and older
- persons who had slept in the house for at least 10 nights of the prior two weeks
- persons who could provide informed consent (assent and parental or guardian consent was required for those aged younger than 18 years).

The exclusion criteria were as follows:

- persons under the age of 15 years
- persons living in congregate settings, including prisons, hospitals, hotels, offices, diplomatic compounds, schools, universities, dormitories and student hostels
- persons who could not provide informed consent (or for those younger than 18 years, where their assent and/or their parents'/guardians' consent could not be secured)
- persons who were visiting the area and had not slept in the house for at least 10 nights in the prior two weeks.

3.3 Screening strategy to identify participants with active TB

The screening algorithm to identify participants with active TB was optimised between available resources and test sensitivity. The eligible participants were screened using a TB symptom screening questionnaire for one or more of the following symptoms:

(i) cough of any duration

(ii) unexplained weight loss

(iii) drenching night sweats

(iv) unexplained fever

as recommended in the South African National TB programme guidelines (18), and aligned to WHO recommended screening strategy for TB prevalence surveys (15). Chest X-rays (CXRs) were included as part of the screening algorithm and they were read on site in the field by trained Medical Officers (MOs) as described below (see Section 3.11.7). Information on HIV status and previous/current TB history was also collected during the screening interview.

The participants who screened positive on symptoms and/or on CXR (had radiological abnormalities suggestive of TB) were eligible for sputum examination for TB and were requested to provide two sputum specimens, the first one immediately and the second specimen an hour later.

The first sputum specimen was tested with Xpert Ultra (Xpert Ultra, Cepheid, USA) and the second specimen underwent liquid culture on the BACTEC MGIT 960 (Becton Dickinson, USA) with further speciation to confirm the presence of *Mycobacterium tuberculosis complex (MTB)* in positive cultures. Those participants who declined or could not undergo CXR were eligible for sputum specimen examination, regardless of the symptom screen outcome. Sputum specimens were couriered under cold-chain conditions and tested at the Centre for Tuberculosis (CTB), of the National Institute for Communicable Diseases (NICD), in Johannesburg. Figure 2 summarizes the screening and testing strategy that was used to identify participants with active TB.

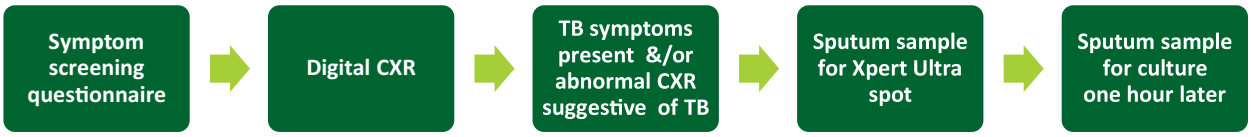

Figure 2. Summary of screening strategy and testing for survey

3.4 HIV testing

Participants who were eligible for sputum examination were also offered an HIV test by means of a dried blood spot (DBS) sample. HIV testing was performed by the Centre for HIV and STIs (CHIVSTI) at the NICD. To maintain anonymity, the DBS cards were barcoded, and the participant received a barcoded voucher that they could use to retrieve the results at their local clinic. In accordance with guidelines in the country, the clinics would repeat the HIV test and give pre- and post-test counselling (19).

3.5 Definitions

3.5.1 TB survey case

Due to concerns related to possible false-positive results from Xpert Ultra in low pre-test probability settings such as surveys, the final case definition aimed to be conservative but robust and was finalised with input from the WHO technical support team and during several workshops on the topic. A TB case in this survey was defined as any MTB culture positive case irrespective of Xpert Ultra results. In addition, for individuals where the culture

was not positive for MTB (this included negative cultures, contaminated cultures, and individuals where culture was not done because there was no sample), a survey case was defined when:

(i) The Xpert Ultra was positive (excluding trace results),

(ii) The participant did not acknowledge a history of a previous TB episode (i.e., no history of TB past or current), and

(iii) The CXR findings were suggestive of active TB as confirmed by an external CXR reading panel.

3.5.2 HIV status

The final HIV status for this survey was determined using the DBS result where this was available, or by self-reported status where there was no DBS result. Where both the DBS result and the self-reported status were available the DBS result was regarded as the final result. HIV status was regarded as unknown where there was no self-reported status and no DBS result.

3.6 Survey preparation

3.6.1. Procurement of equipment and supplies

Survey equipment and supplies were procured by the collaborating partners, following their roles and responsibilities in the survey, including inviting tenders for the provision of mobile digital X-ray equipment with radiographers and specimen courier services, in compliance with the Public Finance Management Act (PFMA) of South Africa (20). The survey required that screening sites be set up in areas that were convenient to each cluster across the country. In areas where there were no buildings or where there were inadequate amenities for these sites, items such as tents, tables, chairs, and mobile ablution facilities were procured from the nearest provider or from local suppliers in the area in accordance with PFMA requirements (Figure 3).

Figure 3. Survey field activities: A survey screening site with tents and mobile X-ray equipment in a rural area

3.6.2. Survey data collection

The survey data were collected electronically, using web-based questionnaires and survey forms on the Research Electronic Data Capture system (REDCap) (21). The data was downloaded onto servers that were hosted at the HSRC and backed up in daily, weekly and monthly cycles. Each participant was assigned a unique barcoded survey identifier (survey ID number) which was scanned into the system at every stage of the survey.

3.6.2.1 Questionnaires and registers

Two main questionnaires were used: the household questionnaire, which included the household census form, and the individual questionnaire, which included symptom screening questions for TB.

Paper-based registers were also used to capture some of the survey information to track each participant during and after screening. This information was also used to verify and confirm data on REDCap. These registers contained identifiers namely, the unique survey ID number, names, address (where available or a physical description of the household where an address was not available), telephone number (where available) and other demographic characteristics of the participants. The registers were kept securely under strict access control to ensure the privacy and confidentiality of the information of survey participants. Identifiers such as names and contact details were collected to facilitate tracing individuals if their sputum specimens tested positive for TB and the participant therefore had to be placed on TB treatment.

CXR registers

The radiographer maintained a register of all participants attending the CXR van (CXR services were provided through a mobile system in a van), noting those who had a CXR done and those who did not, and the reasons thereof. A separate CXR register was used by the MO to complete information on the number of participants who had a CXR taken and to document the CXR findings for each participant.

Specimens registers for sputum and DBS specimens

The sputum specimen register maintained by the survey nurses (see Section 3.6.3) captured information on sputum specimens collected from participants. It also provided information about the quality and quantity (volume) of the sputum specimen, and whether the sputum sample was a first or second specimen for each participant. This register also summarized the number of sputum specimens collected daily and at the end of each activity in each cluster. Information on the number of DBS specimens that were collected and the barcode for each DBS card was also included in the register.

3.6.3 Training of survey field staff

The fieldwork was implemented by four field teams, each comprised of a core of 14 individuals termed the fixed field team. Each team included a MO, a team leader, a professional (registered) nurse, two nurse assistants, four interviewers, an Information Technology (IT/data) technician, a data checker, a security officer (an individual assigned to oversee and ensure the security of all survey materials and equipment in the field), a radiographer, and a driver who drove the survey van with the survey equipment (i.e. survey materials and supplies including printers, tablets, cooler bags, and sputum sample cups).

Training of the field teams was conducted from 3 to 12 July 2017, before piloting the survey. Training sessions were either combined sessions where all team members participated so that all team members understood all the processes of the survey, or breakaway sessions for smaller groups where training focused on the roles assigned to particular team members.

Staff from the NICD's CTB and CHIVSTI provided training on sputum sample collection and handling, and on DBS sample collection and handling, respectively.

A radiologist trained the MOs on the reading and interpretation of CXR images for the survey. Given the role of the CXR in the screening process the MOs were trained to over-read the CXR changes so as to increase the survey CXR screening sensitivity and to minimize missing any potential TB cases.

Subsequent shorter and in-the-field training was conducted as required to address deficient areas identified by the survey investigators or requested by teams, and also after the mid-term review (mid-way through the implementation of survey when external reviewers visited the survey to assess and monitor implementation). Training was also provided whenever a new person joined a team. The training was based on a field operations manual and standard operating procedures (SOPs) for all procedures. The field operations manual and the SOPs were based on the survey protocol and the TB prevalence survey handbook (15).

3.7 Implementation of field activities

3.7.1 Organization of fieldwork

The main activities in each cluster were conducted over 7 days. Each team undertook work in three clusters consecutively (with a two-day break in between the clusters for rest and travel to the next cluster), after which the team took a week of rest away from the field. Fieldwork was undertaken in one province at a time.

3.7.2 Field teams

In each field team, there were permanent members (see section 3.6.3 and Annexure ii for field team composition and list of field survey staff), and these were joined by flexible team members in each cluster. Flexible team members comprised six community volunteers, the local TB focal person, the district TB coordinator (and other provincial DOH representatives when they were available) and local leaders. Community volunteers, being from the area, were familiar with the particular cluster and were well known in the cluster, and this facilitated communication about the survey as well as community support for the survey and participant recruitment. The local leaders also facilitated community entry into each cluster, communication about the survey and community support. The TB focal person facilitated communication with the local clinics about the survey and the delivery of HIV DBS results to the clinic.

3.8 Cluster activities

The survey activity flow is summarised in Figure 4.

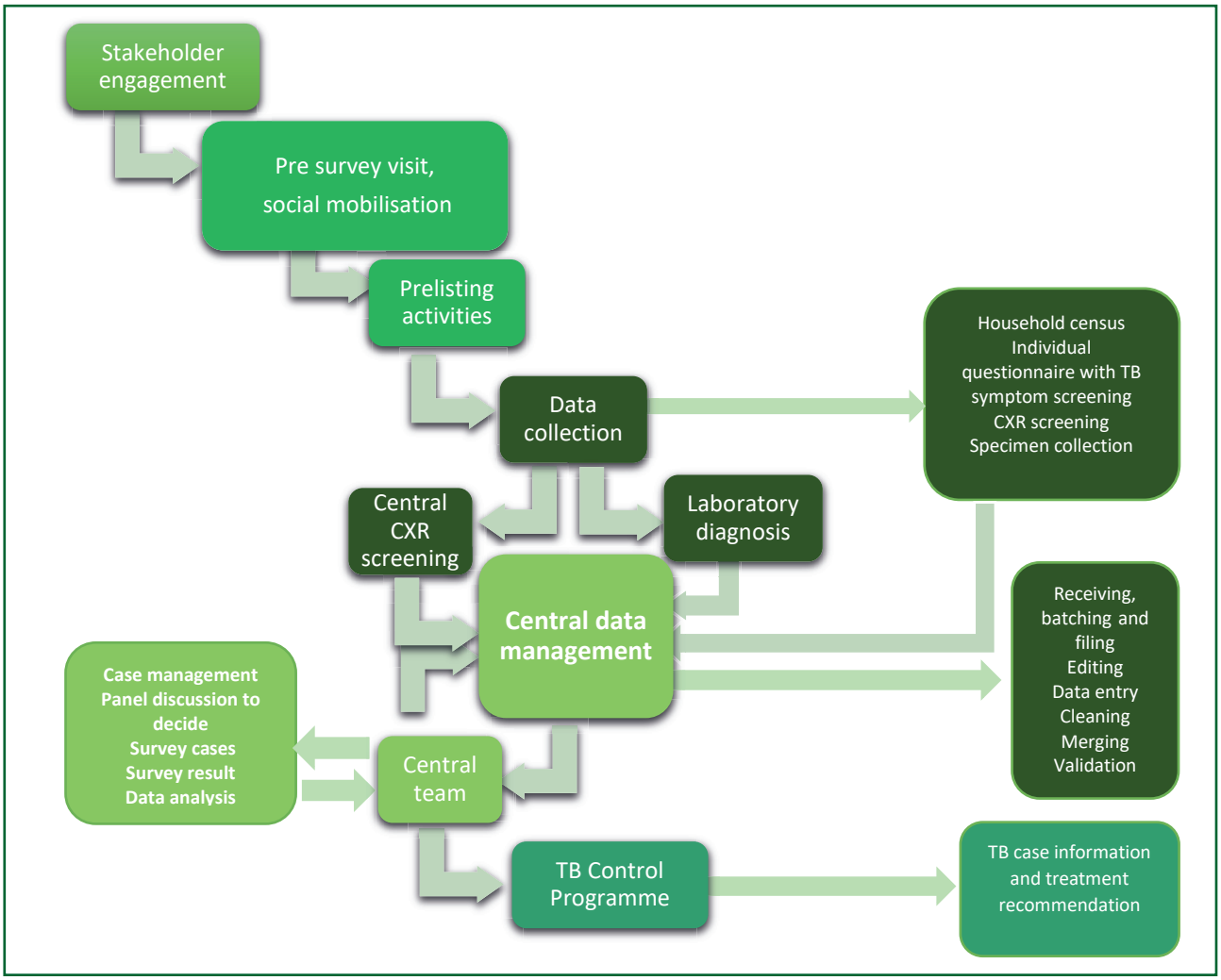

Figure 4. Survey flow diagram

3.8.1 Stakeholder engagement, pre-survey visits and social mobilization

The pre-survey Team (PST) consisting of members of the survey team and wherever possible DOH officials, visited each cluster prior to commencement of survey activities. These pre-survey visits were generally completed 1-3 weeks prior to commencement of field activities in a cluster. The visits were for preliminary assessments of selected clusters, including obtaining information about the facilities and amenities available to inform decisions about requirements for the screening site, the security situation in the area, network connectivity, the type of terrain (to inform the type of vehicles needed to move within clusters) and accessibility of the community (e.g. the best time to conduct survey activities, whether most people would require transport to the screening site, etc.) (Figure 4).

Figure 5. Survey site visit: Representatives from WHO country office and NDOH with a representative from the Global Fund standing in front of the survey banner in a rural cluster in the KwaZulu-Natal province

The visits also helped establish contact and build rapport with the local leaders and community "gate-keepers" (including political, religious and traditional leaders, local associations and organizations with influence in the area, and police and other security structures), and in sensitizing these leaders and "gate-keepers" about the survey. The PST assessed the feasibility of the field operations in each cluster and gathered any information that could influence cluster survey activities. The PST also briefed the community leaders about the need for volunteers and the nature of support that would be required from them and the volunteers before and during the survey activities.

In addition to meeting with local leaders and community "gate-keepers", social mobilization and engagement activities were undertaken to inform all other stakeholders about the survey and to obtain their support. A variety of social mobilization and engagement strategies and activities were used to introduce the survey and encourage participation. These strategies and activities were guided by the local community leaders and the type of area in which the cluster was located. In most clusters (both rural and urban), door-to-door visits, posters with survey information in the dominant local language (Figure 6), survey pamphlets, media messages on local radio stations and newspapers (where these were available), and loud hailing (using a loud-speaker to share information about the survey, while the announcer was in a vehicle that travelled across the cluster) were adopted. In urban clusters, phone calls and text messages were also used where such details could be obtained from Neighbourhood Watch committees or other local structures that permitted these actions.

Figure 6. A poster advertising the survey in IsiZulu in a rural area of South Africa

Social media communications were also used in some clusters: these included messages to the community or Neighbourhood Watch Facebook pages, community forum text messages, in addition to distribution of pamphlets at central points such as shops and malls (Figure 7).

Figure 7. Community engagements: Pre-survey visit in a suburban area - a field team supplying information and brochures outside a shopping mall

3.8.2 Pre-survey listing

Pre-survey listing activities were conducted over 2-3 days and involved volunteers visiting each household in the selected clusters and listing all household occupants (including children and temporary visitors) prior to the arrival of the main survey team. The volunteers were trained to record this information on a simple paper-based form. Pre-survey listing helped to delineate the geographical boundary of each cluster and to generate updated information regarding the number of households and the population size in the selected cluster.

3.8.3 Participant screening, and specimen collection

After the pre-survey visit and pre-survey listing the activities in a cluster unfolded as follows:

- *Days 1-2:* Household interviews, with household survey census (enumeration), and distribution of the invitations to participate in the survey screening activities for those who were eligible.
- *Days 3-6:* Individual interviews, including the TB screening questionnaire, CXR screening, collection of specimens, and courier of specimens to the laboratory.
- *Day 7:* Close out of cluster. To maximize participation, the duration of activities in each cluster could be extended at the discretion of the team leader after consultation with the survey leaders.

3.8.4 Survey census and household questionnaire

The survey census was conducted in the first two days of the main survey field activities in each cluster. The survey team visited all households in the cluster and provided further information about the survey and obtained consent from the head of the house to administer the household questionnaire which included the household survey census. This questionnaire collected basic socio-demographic data of all individuals in the household (including children and temporary residents). Eligible household members were issued barcoded invitation slips which contained information on place (location), date and time for screening at the survey field site (SFS). Pamphlets with details of the survey team were left at the households where there was no one at home, or where the head of the household was not at home at the time of the visit.

3.8.5 Individuals reporting at the survey field site

The standard procedure entailed individuals with the barcoded survey invitation slips presenting for screening at the SFS on Day 3 of field activities in each cluster. In a few cases where the household-based activities were completed earlier e.g., on Day 1 in the cluster, the screening could also start earlier such as on Day 2. The fieldworker stationed at the SFS entrance (referred to as the receptionist) validated the invitation slip by using the barcode to retrieve the individual's data (collected during the household-based activities), and match the reported demographic data with that already in the household database. After validation, the individual was then given a site tracking sheet to track their movement through the different survey stations while undergoing the various survey procedures at the SFS. The tracking sheet also helped to ensure that participants completed all SFS procedures for which they were eligible.

3.8.6 Group information session, informed consent and individual interview

From the receptionist, the individual then attended a group information session where further details about the survey were shared with several potential participants at the same time. Thereafter, signed informed consent for participation in the survey was obtained from each individual who agreed to take part. Individuals were considered enrolled (therefore survey participants) once consent was signed. Persons under the age of 18 years (legal minors) were asked to give assent and sign an assent form. Parental/guardian consent was also required for legal minors to be enrolled in the survey. After consent and assent were obtained, the individual interview was then administered by survey staff. The individual participant interviews collected individual demographic information, information about current and past TB treatment, and HIV status. Participants could decline to disclose their HIV status. A TB symptom screen was also completed during the interview and those with any one or more of the following symptoms were eligible for sputum examination:

(i) Cough of any duration
(ii) Unexplained weight loss
(iii) Drenching night sweats
(iv) Unexplained fever

Those who reported these symptoms were asked about health care seeking for the symptoms.

Figure 8. A survey field site: Enrolled participants await individual interviews

3.8.7 Chest X-ray procedures

All participants were requested to undergo CXR screening, and digital posterior-anterior (PA) CXR images were taken. The participants were offered a lead apron for protection against radiation. Radiation procedures were explained to the pregnant women, and they could decline the CXR if they wished to do so. As a further safety measure, the radiographers enquired about the date of the last menstrual period to determine pregnancy status in women of reproductive age. Additionally, participants with physical disabilities which prevented a CXR being taken, those who declined CXR and those who could not come to the SFS even when transport was offered, such as the very elderly and those with severe physical disabilities, did not undergo CXR screening.

Each CXR had the participant's survey ID as well as names and surname. The CXR images were read and interpreted on site by MOs who were blinded to the symptom screening outcome. CXRs were scored as normal or abnormal using a standardised method as shown below:

- Normal CXR: Clear lung fields and no abnormality detected.
- Abnormal CXR: Suggestive of TB. Any lung abnormality (including pleura) detected (e.g. opacities, cavitation, fibrosis, pleural effusion, calcification(s), or any unexplained or suspicious shadow which on interpretation by the MO could be related to TB.
- Abnormal CXR: Not TB-related. Any lung abnormality (including pleura) detected that on interpretation by the MO is not related to TB.

Radiologist CXR reading

All CXRs that were reported to have abnormalities by the MOs were also reviewed by a central radiologist. The radiologist reading was to further classify the abnormality based on the extent and localisation. The radiologist also reread 20% of all CXRs that were reported as normal by the MOs, as a quality assurance process. An external CXR reading panel also read the CXRs of participants who had Xpert Ultra positive and/or culture positive results.

3.8.8 Sputum collection

Participants who screened positive by one or both screening modalities (TB symptoms and/or CXR changes suggestive of TB) were eligible for sputum examination. Participants who did not undergo a CXR for any reason (as described above) were eligible for sputum examination, regardless of the symptom findings. Participants eligible for sputum examination were asked to produce two sputum samples as previously described, one specimen immediately and the second an hour later. The sputum collection process was supervised by a nurse. Participants who were unable to provide one or both sputum specimens on site were provided with sputum containers and requested either to produce the sputum specimens the following day at home, or to return to the SFS to produce and submit the specimens. The survey team followed up on those who did not return the specimens by sending text messages, making telephone calls or visiting them at home. Sputum specimens were kept between 2°C and 8°C in a cooler bag with ice packs, or in refrigerator (in the survey van) whilst on site. A dedicated courier company transported specimens from each SFS to the CTB at the NICD. All specimens were triple packaged on site with ice packs also placed in the courier boxes to maintain the cold chain during transportation. Every specimen had its specific laboratory request form. Specimen logs were provided with all specimen boxes to ensure the chain of custody.

3.8.9 Dried blood spot (DBS) collection

DBS samples for HIV testing were collected from those who were eligible for sputum sample collection and consented to HIV testing. Blood was collected by finger prick and spotted onto Whatman® filter paper as three discrete spots. The filter papers were left to dry before being packed individually and transported to the CHIVSTI at the NICD for testing. To maintain anonymity, the DBS cards were barcoded. Participants also received a barcoded voucher that they could use to retrieve the HIV test results at a clinic in the cluster if they wished to do so.

3.8.10 Sputum and DBS specimen transportation

Sputum and DBS samples were transported to the NICD two to three times a week. Digital thermometers were used to ensure that specimens were maintained within the specified temperature range. For each batch of specimens couriered to the laboratory, dispatch notes, indicating the date and time of departure and arrival, were included. These notes were signed at the time of dispatch and at the time of specimen receipt.

3.8.11 Mop-up operations (Follow-up of participants)

To increase participation, 'mop-up operations' (following up of individuals in a cluster using phone calls, text messages using phone numbers obtained during household enumeration), and door-to-door re-visits to remind and encourage those invited to attend survey screening) were conducted to reach individuals who had not attended the SFS 24 hours after the date and time stated on their invitation slips. These individuals were identified by comparing the SFS and the survey household invitation databases at the end of each day of SFS activities.

3.8.12 Reimbursements for participation

Participant reimbursements for time spent on survey activities were introduced to enhance enrolments from the 10th cluster onwards. These were valued at USD5, approximately R50 (ZAR) at the time of the survey. Participants could choose from a mix of mobile phone airtime vouchers, grocery vouchers and parcels that contained a selection of household items such as laundry powder, bath soap, and non-perishable food items (Figure 9). The items for reimbursement were chosen on the advice of the community volunteers.

Figure 9. Reimbursements for survey participants: Parcels with food items ready for transportation to a survey cluster

3.9 Laboratory Methods

3.9.1 Specimen reception and registration

Two sputum specimens (one for Xpert Ultra, one for MGIT culture), and one DBS for HIV testing were expected to be received by the TB laboratory for each survey participant eligible for sputum collection. At unpacking, the two sputum specimens from each participant were matched using the unique barcoded identification number. The specimens were then registered on the laboratory information system (LIS) with each being allocated a new unique laboratory number. DBS specimens were referred to CHIVSTI for further processing. The shipping logs received from the individual SFSs were used in conjunction with the specimen request forms for specimen

tracking. Any missing or leaked samples were reported to the team leader for another sample to be collected if the team was still in the cluster.

3.9.2 Processing of specimens

Specimens received in the laboratory were verified against the laboratory worksheet and the specimen log sheet. Processing of each specimen was done following the manufacturer's instructions and standard operating procedures. Figure 10 shows the laboratory workflow for the processing of Xpert Ultra, TB culture and DBS specimens.

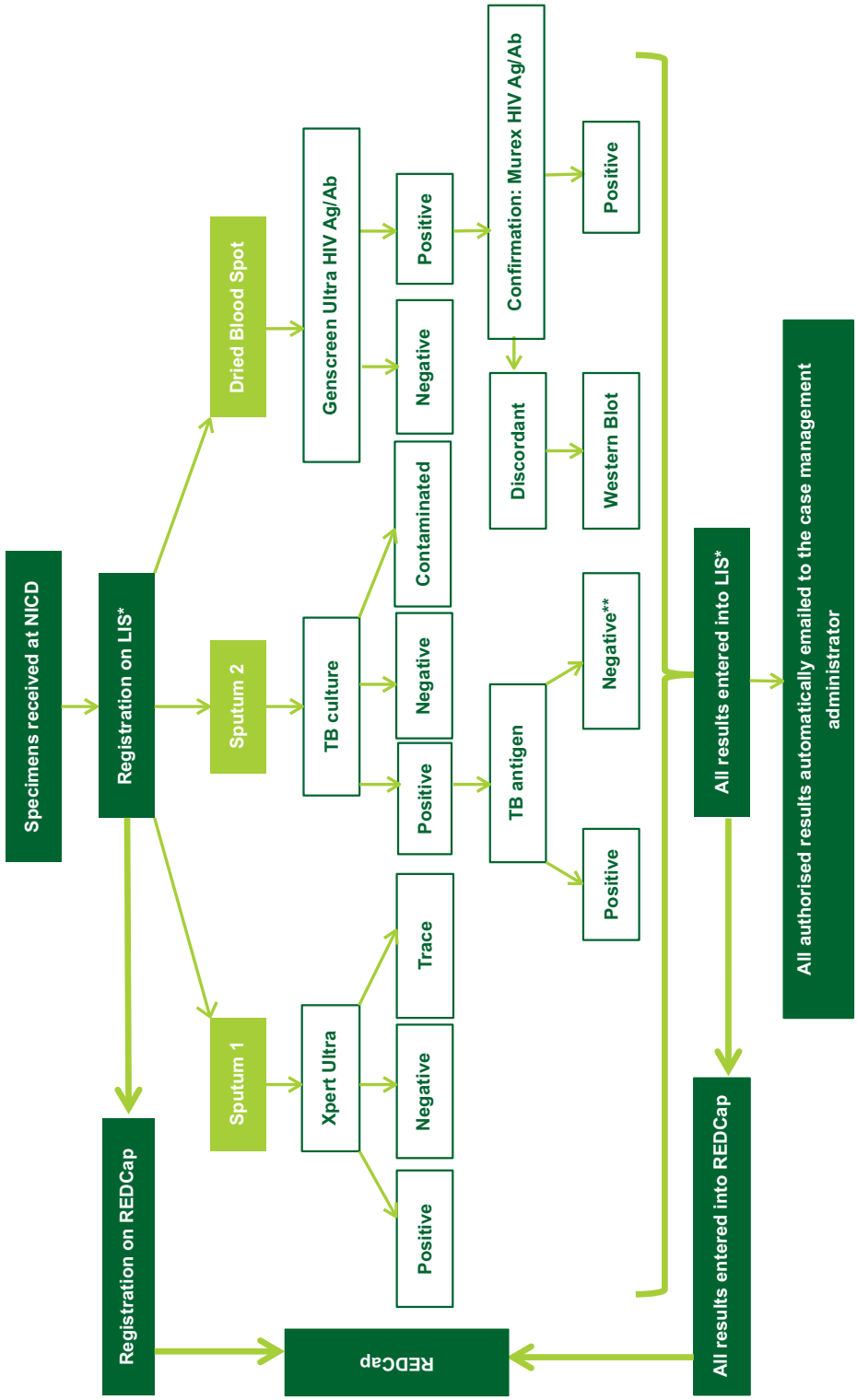

Figure 10. Laboratory work-flow for the processing of Xpert Ultra, TB culture and dried blood spot specimens

3.9.3 Xpert® MTB/RIF Ultra

The Xpert MTB/RIF Ultra (Xpert Ultra) (Cepheid, Sunnyvale, USA) was used according to WHO recommendations at the time of the survey (Textbox 1). The raw sputum specimens for Xpert Ultra testing were processed according to the manufacturer's instructions. In brief, the sample reagent (SR) buffer was added to the specimen in a 2:1 ratio (SR buffer: specimen), and this mixture was then vortexed and incubated for 15 min at room temperature. Two milliliters of this solution were transferred to the Xpert Ultra cartridge, which was then loaded into the appropriate module. Results were recorded as positive, negative or indeterminate/trace (Figure 10). If an invalid result occurred or the test was unsuccessful, the specimen was re-tested to obtain a final valid result. This was done from the SR Buffer mixture if <4 hours, or from the matched culture sediment, if available. An Xpert Ultra 'trace' result was considered as negative for MTB.

Textbox 1. *Use of Xpert® MTB/RIF Ultra in diagnosis of TB*

The use of Xpert® MTB/RIF Ultra in all settings was recommended by the WHO in 2017, due to the increased sensitivity of the Xpert Ultra cartridge compared with the previous Xpert® MTB/RIF cartridge (G4) for the detection of Mycobacterium tuberculosis in specimens with low numbers of bacilli, especially in smear-negative cases, and amongst people living with HIV. The increase in sensitivity is attributed to the low limit of detection (16 bacilli/ml of sputum) and the inclusion of two additional molecular targets (IS6110 and IS1081) (22).

3.9.4 Culture of Mycobacterium tuberculosis

The sputum samples submitted for culture were decontaminated using the NAC-PAC®RED (AlphaTec, Vancouver, Washington, USA) TB digestion and decontamination system containing pre-packed N-acetyl-L-cysteine (NALC) and sodium hydroxide (NaOH)/sodium citrate solution, to provide an end concentration of 1.5%. The decontaminated sediments were then inoculated into a MGIT containing 7 ml liquid medium used for the detection of mycobacterial growth using BACTEC™ MGIT 960 System (Becton-Dickinson, Sparks, MD, USA).

Specimens that were positive following incubation in the BACTEC™ System were examined for acid-fast bacilli and for purity, using the Ziehl Neelsen (ZN) staining method and by inoculation onto blood agar, according to standard operating procedures. MTB on culture positive specimens was confirmed by testing for the presence of the MPT64 antigen, using the MGIT TBc (Becton- Dickinson, USA) identification test (Figure 10). The MGITs were incubated for a maximum of 42 days before no growth was reported.

3.9.5 HIV testing

DBS specimens were first tested on the Genscreen Ultra HIV Ag/Ab (BioRad, Hercules, California, USA), which was used as the primary screening assay. All specimens that tested negative were reported as negative. Those that were positive were then tested on the Murex HIV Ag/Ab Combination (Diasorin, Saluggia, Italy), which served as the confirmatory assay. All specimens that tested positive on the confirmatory assay were reported as positive. If the confirmatory assay was negative (discrepant result), then the screening test was repeated. If the results were still discrepant, then the GS HIV-1 Western Blot (Bio-Rad Laboratories) assay was performed to confirm the final result (Figure 10).

3.9.6 Laboratory results entry and reporting

Xpert Ultra and culture results were interfaced from the respective instruments to the LIS. Results were also directly entered into the RedCap system. All positive Xpert Ultra, culture and HIV results were immediately emailed to the case management team and for relay to the TB coordinators in the case of TB results. HIV results were not shared with the TB coordinators. Hard copies of all the laboratory results were also filed and stored securely as source documents for the survey.

3.10 Case management

The survey case management team comprising of a microbiologist, a radiologist, a MO and an administrator reviewed all the survey data of participants with positive sputum results. The purpose was to examine and verify all the results and survey data and to determine if the participant met the criteria for classification as a survey TB case or not. The case management team met bi-weekly or monthly, depending on the number of bacteriologically positive results received. This meeting reviewed the laboratory results, the information from the screening questions on TB symptoms, history of prior TB from the individual interview data, HIV status (self-reported status or DBS result), CXR field reading and the radiologist's report. All the data was extracted from REDCap. The team made consensus decisions on each participant's results and determined those that were survey cases and those that were not, based on the survey case definition. If the Xpert Ultra result was positive but there was no positive culture result and there was previous or current TB episode, an external expert panel reviewed the CXR for final case determination.

The case management team also ensured that the positive sputum results were sent to the TB coordinator in each area. The information shared with the TB coordinator included a copy of the microbiology laboratory result, the participant's survey ID, address, telephone number and the TB history as reported in the survey questionnaire. For Xpert Ultra positive results, the result for rifampicin resistance was included. The culture results were also shared once they became available. The TB programme was responsible for ensuring that all participants with positive sputum results were tracked, notified and received treatment through the TB coordinator in each cluster.

The HIV results were available within 10 days of DBS collection and participants who wished to know the test result could use the barcoded voucher they had to retrieve the results at a clinic in the cluster. The clinics would repeat the HIV test with pre- and post-test counselling in accordance with the HIV testing guidelines in the country (19).

3.11 Data management

The survey data were handled and managed as outlined in the survey data management plan. The survey information was captured in real-time into the REDCap data system. The data capture forms in REDCap had logic and range checks. Data were synchronized from the different database sections: the household census database, the individual questionnaire database, the CXR database (both field and central CXR data) and the laboratory (sputum and DBS results) database. The data manager worked with the data team and the field team in ensuring all the survey data requirements were incorporated in the REDCap system designed for the survey. In addition, the data manager worked with the data team to obtain daily updates of the data collection from the field, and also had oversight of any data corrections or edits on the REDCap system.

3.12 Quality assurance, monitoring and evaluation

3.12.1 Quality control of the field work

The survey investigators and other senior members of the central survey team conducted regular field visits to observe the survey procedures and to support the field teams. In addition, one central survey member would periodically follow the survey processes to observe the activities of all the field personnel and give feedback on areas that were to be corrected whenever necessary. Each team leader, supported by the field-based IT/data technician and data checker, was responsible for ensuring the quality of the data collected in each cluster. The field-based data checks were conducted as described in a field data SOP. The data checkers checked for inconsistencies and missing information in real-time. This information was communicated to the team leader to expedite correction in the field.

3.12.2 Quality assurance of the chest X-ray images and interpretation

In addition to reporting on the radiological findings, the MOs also reported on the quality of digital CXR images. If the quality was suboptimal, they would request a repeat CXR. The central radiologist also reported on image quality and consulted with the field-based radiographer to address the quality of the CXR images when necessary.

As described above, to maintain the CXR survey threshold for detection of participants with possible TB, all the abnormal CXRs, as determined by the MOs, were read by an off-site central radiologist as soon as was possible. The radiologist also read 20% of those CXRs identified as normal by the MOs for a further quality check. If there were discrepancies in interpretation of the CXR results, this would be communicated to the MO, so that the reading could be reviewed. If the survey team was still operating in that cluster, and the MO agreed with the revised reading by the radiologist for images determined to be suggestive of TB, the participant would be recalled to give sputum specimens. Otherwise, the feedback from the radiologist was used to guide future readings by the MOs.

3.12.3 Quality assurance in the laboratory

The CTB at the NICD is a WHO endorsed supranational TB Reference Laboratory,(23) and both CTB and CHIVSTIs are accredited by South African National Accreditation System (SANAS) to ISO 15189:2012.(24) All laboratory procedures are quality controlled to ensure accuracy and reproducibility of results. The laboratories have SOPs relating to all procedures of specimen receipt, processing and reporting.

For positive TB culture and/or Xpert Ultra results, manual capture of participants' laboratory results into REDCap was cross-checked with the printed result, and a proportion (10%) of those participants whose sputa tested bacteriologically negative, was also checked for the correct entry.

3.12.4 Quality control of data

The data manager was responsible for ensuring survey data quality and was supported through regular data management meetings. The database was designed to flag data entry errors with logic and range checks as per field instruments. The data checkers in the field were responsible for real-time data checking. System reports using STATA version 15 (Stata Corporation, College Station, Texas, USA) were generated to help the data checkers flag missing data, and the system was frequently checked for errors that were corrected in real-time. Team leaders in the field helped with tracing participants who had missing or erroneous data. Once this information was collected it was provided to the data checker who worked with the data team and the data manager to capture or correct information in the database. Weekly summary statistics reports were generated for monitoring and were discussed by the data management committee. The data in the survey database were verified using source documents from the field, including the CXR registers, and sputum and DBS specimen logs.

3.13 Ethical considerations

The survey protocol was approved by the SAMRC research ethics committee (Reference EC001 2/2012). Amendments to the protocol were submitted and approved by the ethics committee. Approval was updated annually until survey completion. Participants were provided with reimbursements for their time spent on the survey as described above. The survey databases were password-protected to ensure confidentiality of survey data. While all efforts were made to locate each SFS within walking distance of community members, transport was provided for those who needed assistance to attend the SFS.

3.14 Fieldwork timeframe

Data collection was undertaken over 23 months, from August 2017 to July 2019. One hundred-and-eight of the 110 clusters were completed within 20 months of survey inception (end of April 2019). The survey operations were paused between May and June 2019 because the national general elections that took place in May 2019. There was an extremely low participation rate in cluster seven in KwaZulu-Natal province, and this was replaced with a similar cluster (similar location in an urban formal area) in the same province. Five other clusters across the country were replaced due to safety and security concerns, and a further two clusters were replaced because the community stakeholders did not grant entry into the community.

3.15 Statistical analysis

Data analysis was done using STATA® statistical software (STATA version 15, College Station, Texas, USA). Data were summarized by frequencies and percentages, and by medians as appropriate. Following the recommendations by WHO for estimating prevalence of bacteriologically confirmed tuberculosis through TB prevalence surveys, primary sampling unit (PSU) i.e. cluster-level analysis and individual-level analysis were considered, using recommended methods (15, 25). The primary analysis for reporting the overall, sex-specific and age-specific results of the survey was set at the individual level.

Binary logistic regression models were applied for the individual-level analysis to account for:

(i) The clustered design of the survey (using robust standard errors)

(ii) Missing TB status results among sputum eligible participants using multiple imputation techniques and

(iii) Non-participation by inverse probability weighting methods.

For the TB status imputation model, age group, CXR panel reading, cough of more than two weeks, HIV status, sex, TB burden strata, and race were included. Using *ice* and *mi* commands in STATA, 20 datasets were imputed, and the respective TB prevalence estimates were combined to provide final TB estimates, which are reported below. The TB estimates are reported per 100,000 population with 95% CI. To calculate the ratio of prevalent to notified cases (Prevalence: Notification, [P:N] ratio) we used notifications for "new and relapse notified cases" that are broken down by age group and sex for 2018 (4), and the 2018 population estimates for South Africa (26).

3.16 Field management of participants needing urgent health attention

Although the survey did not target acutely ill individuals, in certain instances while in the field, MOs encountered participants who required urgent health interventions based on their symptoms, physical presentation or CXR findings. The MOs referred these participants to the nearest health facility or hospital, using a letter of referral from the survey.

4. RESULTS

4.1 Enumerated population by eligibility and ineligibility characteristics

A total population of 68,771 people was enumerated from 19,969 households in survey clusters (Table 1). Figure 11 compares the age and sex distribution of the enumerated population with that from the 2011 National Census (16), extrapolated to 2018. While the general structure of the population is the same, there were some differences between the populations including:

(i) A lower percentage of children aged 0-14 years (both males and females) enumerated compared to the national population (6.9% compared to 10.9% among those 0-4 years, 21.7% compared to 30.1% overall for 10-14 years),

(ii) Higher proportions of females in the survey population when compared to the national population (19.5% compared to 17.8% in those aged 15-24 years, and 11.0% compared to 9.4% in those aged 45-54 years), and

(iii) A higher proportion of older males enumerated compared to the national population, 6.3% compared to 4.1%.

Among those who were enumerated 53,250 (77.4%) were eligible to participate in the survey. More females (55.8%) than males were enumerated, while the ineligible proportion per survey protocol comprised 14,913 children under the age of 15 years and 504 non-resident adults (Table 1).

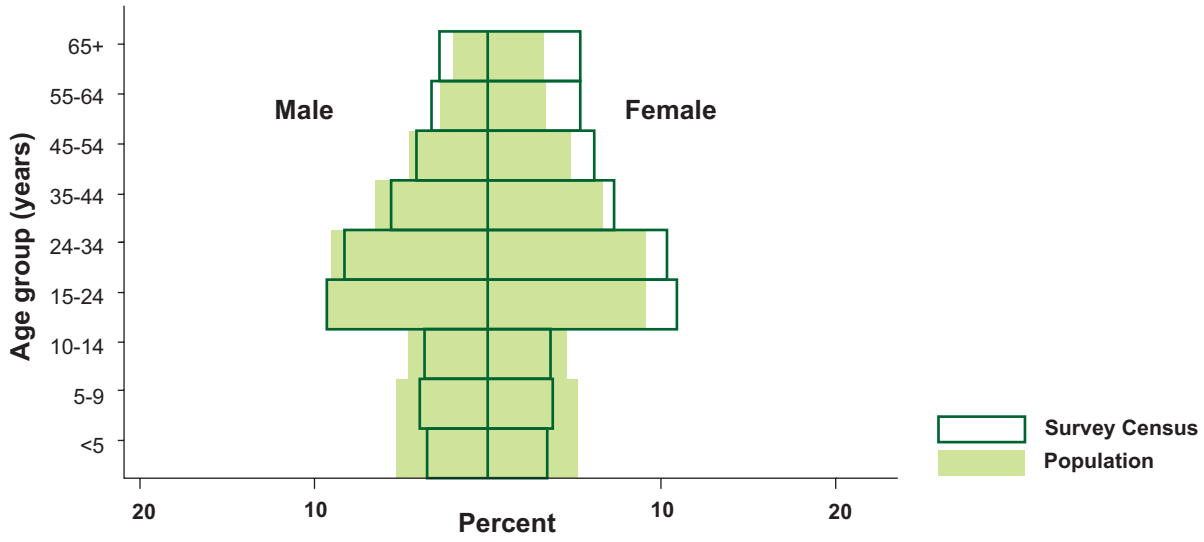

Figure 11. Age and sex pyramid of the 2018 survey enumerated population compared with the 2011 South African census population, extrapolated to 2018

Table 1 shows the enumerated population by eligibility and selected demographic characteristics. Of the 68,771 people enumerated, 58.9% were in the urban areas. A total of 14,913 were children less than 15 years old and were therefore ineligible to participate in the survey. An additional 395 people were visitors to the clusters at the time of the survey and were also not eligible to participate. Just over half of these non-residents were male. Among those who were eligible to participate, approximately 50% were under the age of 35 years.

Table 1. Enumerated population by eligibility criteria and selected demographic characteristics (N=68,771)

Characteristics	Ineligible to participate				Eligible to participate		Missing eligibility information		Total	
	<15 yrs		Not residents							
	n	%	n	%	n	%	n	%	n	%
Total	**14,913**		**395**		**53,250**		**213**		**68,771**	
Age group (years)										
0-4	4,748	31.8	0	0	N/A	N/A	N/A	N/A	4,748	6.9
5-9	5,261	35.3	0	0	N/A	N/A	N/A	N/A	5,261	7.7
10-14	4,904	32.9	0	0	N/A	N/A	N/A	N/A	4,904	7.1
15-24	0	0	120	30.4	13,700	25.7	47	22.1	13,867	20.2
25-34	0	0	107	27.1	12,636	23.7	41	19.2	12,784	18.6
35-44	0	0	77	19.5	8,724	16.4	31	14.6	8.832	12.8
45-54	0	0	41	10.4	6,984	13.1	29	13.6	7,054	10.3
55-64	0	0	32	8.1	5,733	10.8	22	10.3	5,787	8.4
65+	0	0	18	4.6	5,473	10.3	27	12.7	5,518	8
Unknown	0	0	0	0	0	0	16	7.5	16	0
Sex										
Male	7,522	50.4	202	51.1	22,561	42.4	84	39.4	30,369	44.2
Female	7,390	49.6	193	48.9	30,689	57.6	126	59.2	38,398	55.8
Unknown	1	0	0	0	0	0	3	1.4	4	0
Geotype										
Urban	8,691	58.3	240	60.8	31,481	59.1	103	48.4	40,515	58.9
Rural	6,222	41.7	155	39.3	21,769	40.8	110	51.6	28,256	41.1

4.2 Survey participation

Among the 68,771 enumerated people 53,250 (77.4%) met the survey inclusion criteria and 35,191 (66.1%) participated. Survey participation varied across clusters and was generally lower in clusters that were in urban areas when compared to those in rural areas (Figure 12). Following very low participation rates in the first 10 clusters, a decision was made to provide reimbursements to participants for their time spent on survey activities. This had a positive effect in most rural communities, but this was not the case in urban settings. In addition, tailored messaging about the survey in the local media was increased. The net effect was an improvement in the average participation rate after the interventions. However, despite these efforts, the overall participation rate was 66.1%, which was lower than the target of 85%.

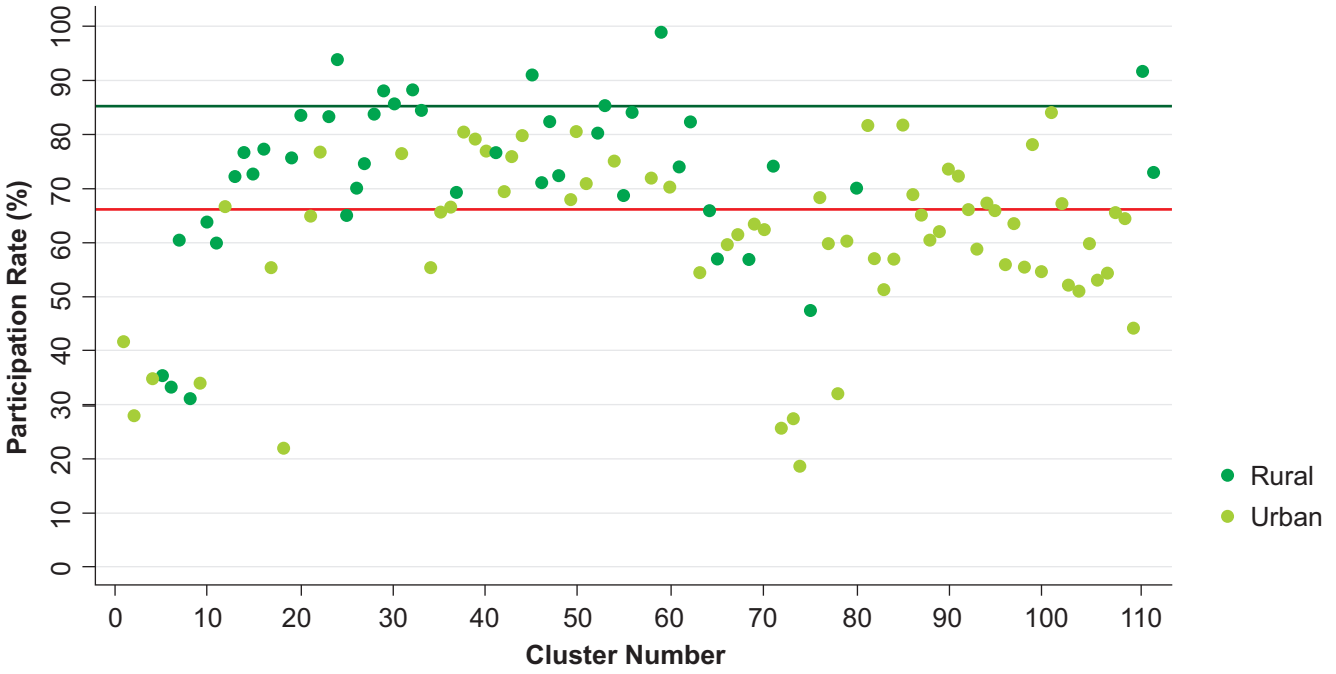

Figure 12. Participation rate per cluster (in chronological order) stratified by cluster geotype and target participation rate (green line: 85%), average survey participation rate (red line: 66.1%)

In all age groups a notable percentage of the eligible population did not participate in the survey and more females than males participated across all age groups (Table 2 and Figure 13). Table 2 shows the distribution of eligible individuals and those who participated by selected demographic characteristics. Forty-five percent (16,002) of all participants were younger than 35 years old and 62.0% of participants were female. The median age of participants was 37 years; interquartile range (IQR) 25-55 years. Although participation was higher in rural clusters, more than half (59.1%) of all participants were from urban areas.

Table 2. Eligible individuals and survey participants by demographic characteristics (N=53,250)

	Total eligible (N=53,250)		Participants (N=35,191)		Non-Participants (N=18,059)	
	n	%	n	%	n	%
Total	**53,250**		**35,191**		**18,059**	
Age group (years)						
15-24	13,700	25.7	8,477	24.1	5,223	28.9
25-34	12,636	23.7	7,525	21.4	5,111	28.3
35-44	8,724	16.4	5,479	15.6	3,245	18.0
45-54	6,984	13.1	4,888	13.9	2,096	11.6
55-64	5,733	10.8	4,373	12.4	1,360	7.5
65+	5,473	10.3	4,449	12.6	1,024	5.7
Sex						
Male	22,561	42.4	13,388	38.0	9,173	50.8
Female	30,689	57.6	21,803	62.0	8,886	49.2

	Total eligible (N=53,250)		Participants (N=35,191)		Non-Participants (N=18,059)	
	n	%	n	%	n	%
Race						
Black African	31,020	58.3	31,019	88.1	0	0.0
Indian/White	972	1.8	972	2.8	0	0.0
Coloured	3,199	6	3,199	9.1	0	0.0
Unknown	18,059	33.9	1	0.0	18,059	100
Geotype						
Urban	31,481	59.1	19,483	55.4	11,998	66.4
Rural	21,769	40.8	15,708	44.7	6,061	33.5

Participation was lowest among the youth but improved with increasing age (Figure 14); among the youth 61,9% of those who were eligible participated, compared to 81.3% in those aged 65 years and older. By sex 59.3% (13,388/22,561) of eligible males participated while 71.0% (21,803/30,689) of eligible females participated. The lowest participation rate was observed in men aged 25-34 years while the highest was among females older than 55 years.

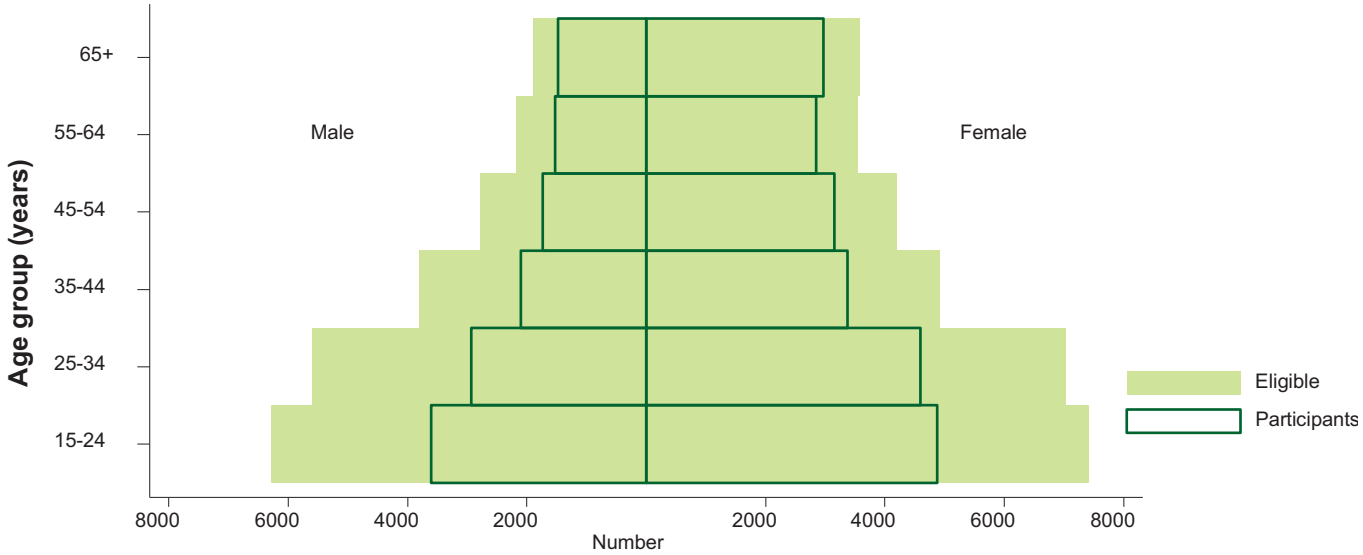

Figure 13. Population pyramid showing participation by age and sex compared to the eligible population enumerated at household level

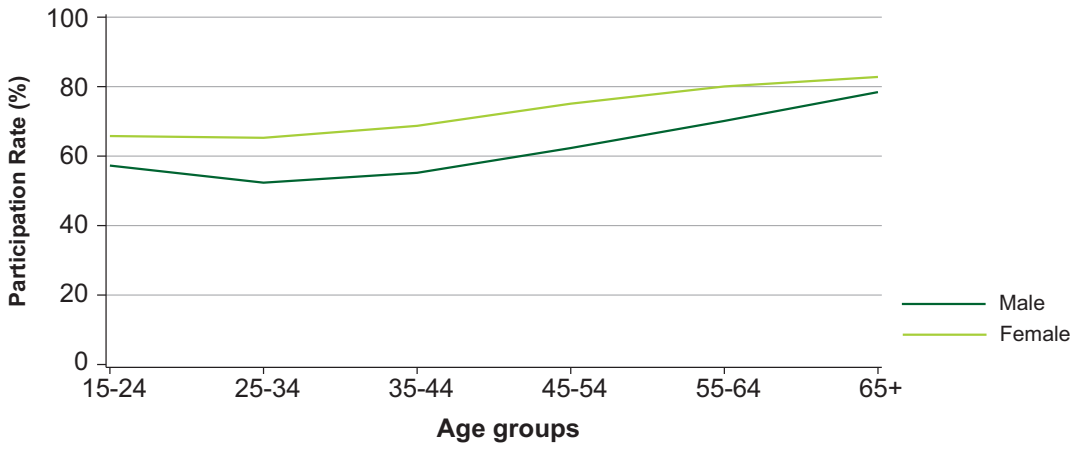

Figure 14. Participation by age and sex compared to the eligible population as enumerated at household level

Figure 15 shows the survey flow from the survey census, indicating final numbers of participants included and screened, those who screened positive, those who provided sputum, and DBS samples and the test results.

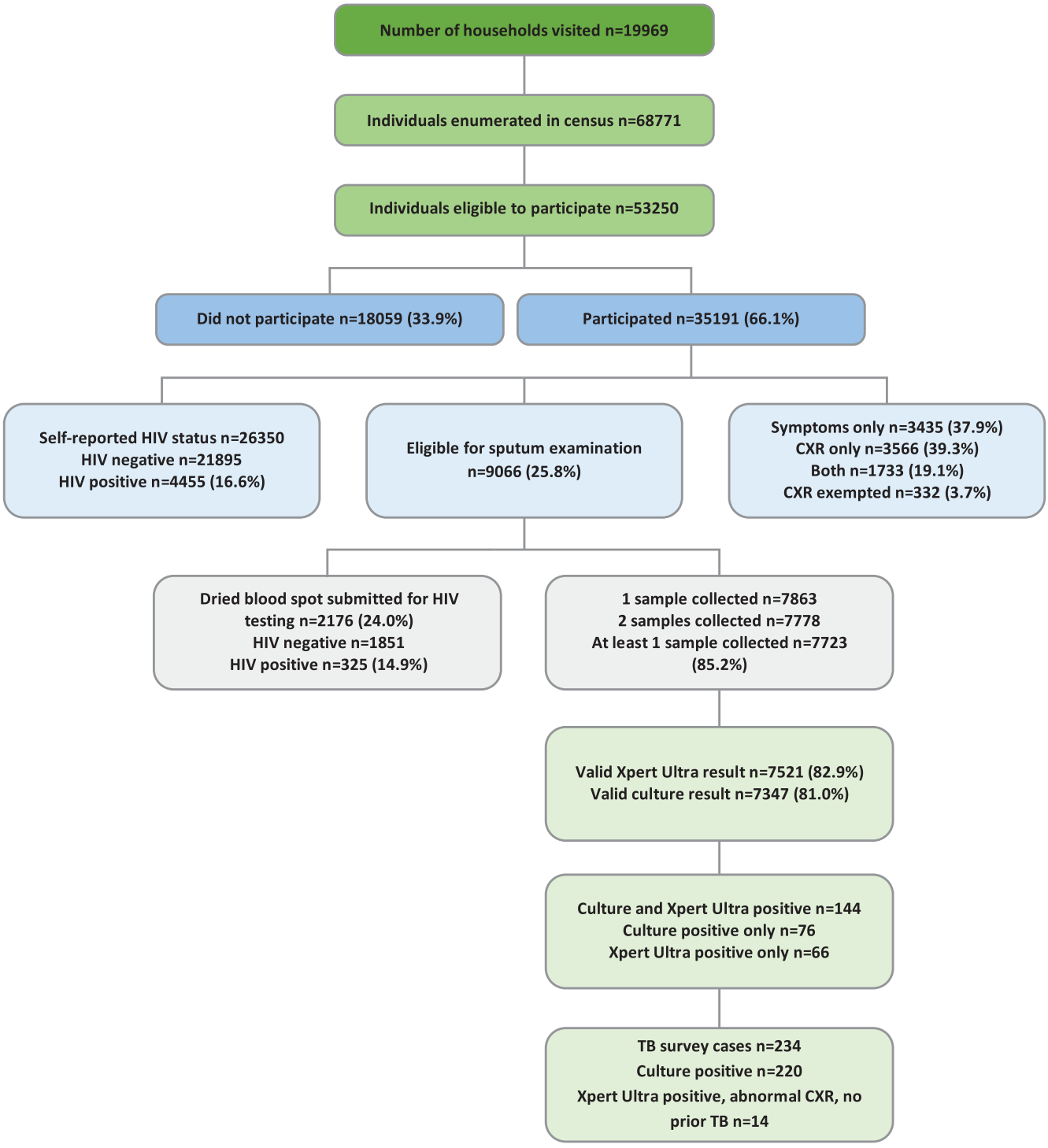

Figure 15. Consort diagram of survey population, screening and laboratory test results
**Denominator for participation: - those who are eligible to participate, N=53,250.*

4.3 Screening

4.3.1 Symptom screening

As shown in Table 3, of the 35,191 participants enrolled into the survey 8.5% reported cough (defined as a persistent cough of any duration), 4.2% reported an unexplained fever of 2 weeks or more, 4.7% reported unexplained weight loss and 6.0% reported drenching night sweats. Participants reporting any one of the symptoms increased with age.

Among males, 9.6% reported a cough, with 5.6% reporting a cough of at least 2 weeks duration, and 7.2% reported night sweats. Among females, 7.8% reported a cough with 3.7% reporting a cough of at least 2 weeks duration, and 5.3% of females reported night sweats. Across geotypes, 7.5% of participants in urban areas and 9.7% in rural areas reported a cough of any duration. More participants in rural areas than in urban areas reported fever, weight loss and night sweats (Table 3). A total of 2964 (8.2%) participants reported to have been on TB treatment before the survey, while 178 (0.5%) reported that they were on TB treatment at the time of the survey and were thus TB programme cases. Of these 178, 88 (49.4%) also reported to have been previously treated for TB.

Table 3. Demographic characteristics of survey participants reporting TB-related symptoms

Number of participants		Persistent cough of any duration		Cough for at least 2 weeks		Fever		Weight Loss		Night Sweats	
	N	n	%	n	%	n	%	n	%	n	%
Total	**35,191**	**2,994**	**8.5**	**1,554**	**4.4**	**1,482**	**4.2**	**1,647**	**4.7**	**2,119**	**6.0**
Age group (years)											
15-24	8,477	400	4.7	150	1.8	195	2.3	184	2.2	177	2.1
25-34	7,525	425	5.6	219	2.9	216	2.9	330	4.4	343	4.6
35-44	5,479	474	8.7	253	4.6	230	4.2	313	5.7	391	7.1
45-54	4,888	510	10.4	283	5.8	253	5.2	275	5.6	392	8.0
55-64	4,373	513	11.7	272	6.2	283	6.5	277	6.3	401	9.2
65+	4,449	672	15.1	377	8.5	305	6.9	268	6.0	415	9.3
Sex											
Male	13,388	1,286	9.6	749	5.6	541	4.0	642	4.8	965	7.2
Female	21,803	1,708	7.8	805	3.7	941	4.3	1,005	4.6	1,154	5.3
Race											
African	31,019	2,550	8.2	1,281	4.1	1,365	4.4	1,440	4.6	1,898	6.1
Indian/ White	972	82	8.4	59	6.1	20	2.1	26	2.7	31	3.2
Coloured	3,199	362	11.3	214	6.7	97	3.0	181	5.7	190	5.9
Unknown	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Geotype											
Urban	19,483	1,465	7.5	801	4.1	655	3.4	750	3.8	931	4.8
Rural	15,708	1,529	9.7	753	4.8	827	5.3	897	5.7	1,188	7.6

4.3.2 Chest X-ray screening

A total of 34,746 (98.7% of participants) CXRs were taken CXR uptake was equally high by sex, age group and geotype (Table 4). CXRs were not taken when participants declined the CXR, were pregnant females, were bedridden and could not attend the SFS even when transport was provided, were disabled such that the survey CXR equipment could not take the images from them, and when there was a breakdown of the CXR equipment.

Of those participants who had CXRs taken 15% had abnormalities suggestive of TB. Most CXR abnormalities in field readings were observed in those 65 and older. Those who did not have CXR taken were eligible for sputum investigation irrespective of symptom screen findings.

Table 4. CXR screening among survey participants by demographic characteristics

Field CXR Findings											
Number of Participants		CXR taken		Normal		Abnormal Suggestive of TB		Abnormal Not TB related		No CXR	
	N	n	%	n	%	n	%	n	%	n	%
Total	**35,191**	**34,746**	**98.7**	**28,886**	**83.1**	**5,299**	**15.3**	**561**	**1.5**	**445**	**0.1**
Age group (years)											
15-24	8,477	8,382	98.9	7,953	93.8	385	4.5	44	0.5	95	1.1
25-34	7,525	7,401	98.4	6,786	90.2	570	7.6	45	0.6	124	1.6
35-44	5,479	5,423	99.0	4,611	84.2	768	14.0	44	0.8	56	1.0
45-54	4,888	4,851	99.2	3,835	78.5	941	19.3	75	1.5	37	0.8
55-64	4,373	4,341	99.3	3,118	71.3	1,096	25.1	127	2.9	32	0.7
65+	4,449	4,348	97.7	2,583	58.1	1,539	34.6	226	5.1	101	2.3
Sex											
Male	13,388	13,298	99.3	10,627	79.4	2,517	18.8	154	1.2	90	0.7
Female	21,803	21,448	98.4	18,259	83.7	2,782	12.8	407	1.9	355	1.6
Race											
African	31,019	30,631	98.7	25,590	82.5	4,602	14.8	439	1.4	388	1.3
Indian/ White	972	954	98.1	754	77.6	168	17.3	32	3.3	18	1.9
Coloured	3,199	3,160	98.8	2,541	79.4	529	16.5	90	2.8	39	1.2
Unknown	1	1	100.0	1	100.0	0	0.0	0	0.0	0	0.0
Geotype											
Urban	19,483	19,225	98.7	16,602	85.2	2,304	11.8	319	1.6	258	1.3
Rural	15,708	15,521	98.8	12,284	78.2	2,995	19.1	24	0.2	187	1.2

4.4 Sputum examination eligibility and results

Approximately a quarter of participants 25.8% (9,066) were positive on screening based on symptoms and/or CXRs; median age 49 years (IQR 33-63); and 3,849 (42.5%) were males. Figure 16 shows eligibility for sputum examination by symptom and by CXR findings. Among sputum eligible subjects, 3,435 (37.3%) screened positive by symptoms only, 3,566 (39.3%) by CXR abnormalities only and 1,733 (19.1%) by symptoms and CXR. A further 332 (3.7%) were exempted from or could not have a CXR taken and were thus eligible for sputum examination as per the survey protocol. Those who did not have a CXR done were mainly females, 86%.

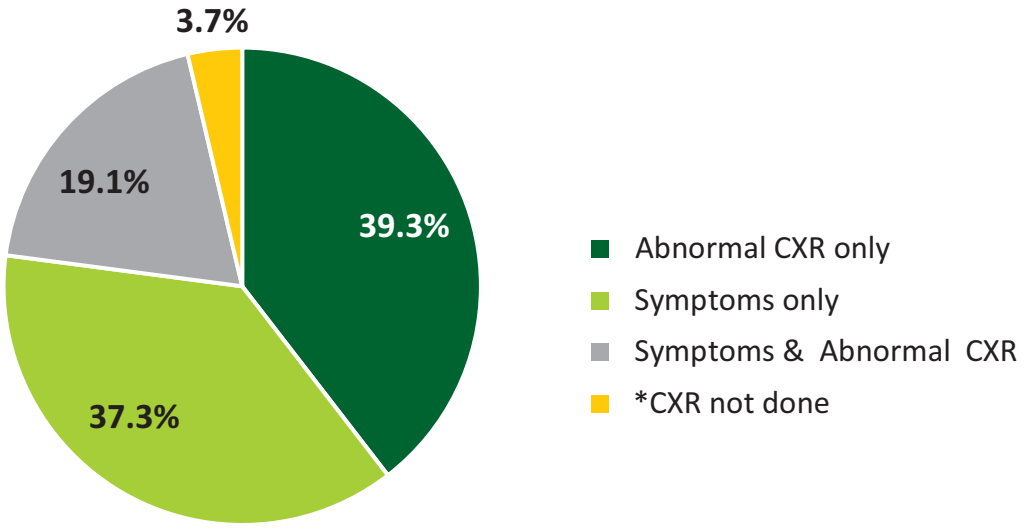

Figure 16. Eligibility for sputum examination by symptoms and CXR findings (N=9,066)

**CXR was not done because the participant declined to consent, or was pregnant, or had disabilities that made it impossible to take the CXR or was bedridden and not able to attend the screening site.*

Among those who were sputum eligible by symptoms only, 20.7% were aged 25-34 years. Of those who were sputum eligible, 1,710 (19%) reported a history of previous TB, and 140 (1.5%) reported that they were on TB treatment at the time of the survey (Table 5). Among those with a history of TB, more than half (51.5%) were eligible for sputum investigation by CXR abnormality only.

Table 5. Eligibility for sputum examination by age, sex, geotype and TB treatment history

	Total sputum eligible		Symptom only		Both symptom and field CXR		Field CXR only		CXR exempted	
	n	%	n	%	n	%	n	%	n	%
Total (N)	**9,066**	**100.0%**	**3,435**	**37.9%**	**1,733**	**19.1%**	**3,566**	**39.3%**	**332**	**3.7%**
Age group (years)										
15-24	1,064	11.7	603	17.6	75	4.3	310	8.7	76	22.9
25-34	1,381	15.2	710	20.7	159	9.2	411	11.5	101	30.4
35-44	1,393	15.4	582	16.9	268	15.5	500	14.0	43	13.0
45-54	1,499	16.5	540	15.7	319	18.4	622	17.4	18	5.4
55-64	1,625	17.9	506	14.7	390	22.5	706	19.8	23	6.9
65+	2,104	23.2	494	14.4	522	30.1	1,017	28.5	71	21.4
Sex										
Male	3,849	42.5	1,286	37.4	818	47.2	1,699	47.6	46	13.9
Female	5,217	57.5	2,149	62.6	915	52.8	1,867	52.4	286	86.1
Race										
African	7,894	87.1	2,997	87.2	1,512	87.2	3,090	86.7	295	88.9
Indian/ White	258	2.8	79	2.3	39	2.3	129	3.6	11	3.3
Coloured	914	10.1	359	10.5	182	10.5	347	9.7	26	7.8
Unknown	0	0	0	0	0	0	0	0	0	0

	Total sputum eligible		Symptom only		Both symptom and field CXR		Field CXR only		CXR exempted	
	n	%	n	%	n	%	n	%	n	%
Strata										
Low	1,931	21.3	1,637	47.7	667	38.5	1,637	45.9	196	59.0
Medium	1,882	20.8	1,616	47.0	946	54.6	1,616	45.3	116	34.9
High	5,253	57.9	313	9.1	120	6.9	313	8.8	20	6.0
Geotype										
Urban	4,214	46.5	1,714	49.9	667	38.5	1,637	45.9	196	59.0
Rural	4,852	53.5	1,721	50.1	1,066	61.5	1,929	54.1	136	41.0
Past history of TB										
Yes	1,710	18.9	303	8.8	507	29.3	881	24.7	19	5.7
No	7,307	80.6	3,118	90.8	1,209	69.8	2,669	74.8	311	93.7
Missing	49	0.5	14	0.4	17	1.0	16	0.4	2	0.6
Current TB										
Yes	140	1.5	26	0.8	67	3.9	45	1.3	2	0.6
No	8,902	98.2	3,399	99.0	1,663	96.0	3,511	98.5	329	99.1
Missing	24	0.3	10	0.3	3	0.2	10	0.3	1	0.3
Total	**9,066**	**100.0**	**3,435**	**100.0**	**1,733**	**100.0**	**3,566**	**100.0**	**332**	**100.0**

Of the 9,066 sputum-eligible participants, 7,521 (83.0%) submitted the first specimen for Xpert Ultra testing and 7,347 (81.0%) submitted the second specimen for culture (Table 6).

Table 6. Distribution of specimen collection and testing by demographic characteristics

	Total participants eligible for sputum collection		Xpert Ultra sputum sample received and tested		Culture sputum sample received	
	N	%	n	%	n	%
Total (N)	**9,066**		**7,521**	**82.9**	**7,347**	**81.0**
Age group (years)						
15-24	1,064	11.7	769	10.2	757	10.3
25-34	1,381	15.2	1,122	14.9	1,098	14.9
35-44	1,393	15.4	1,170	15.6	1,138	15.5
45-54	1,499	16.5	1,290	17.2	1,254	17.1
55-64	1,625	17.9	1,415	18.8	1,371	18.7
65+	2,104	23.2	1,755	23.3	1,729	23.5
Sex						
Male	3,849	42.5	3,301	43.9	3,250	44.2
Female	5,217	57.5	4,220	56.1	4,097	55.8
Geotype						
Urban	4,214	46.5	3,651	48.5	667	9.1
Rural	4,852	53.5	3,870	51.5	1,066	14.5

Total population enumerated at household level	**68,771**
Individuals eligible to participate at household level	**53,250** (77.4%) of those enumerated
Eligible individuals who participated	**35,191** (66.1%) of all eligible = participation rate
Participants eligible for sputum collection	**9,066** (25.8%) of participants
Valid Xpert Ultra result	**7,521** (82.9%) of sputum collection eligible
Valid culture results	**7,347** (81,0%) of sputum collection eligible

Figure 17. Summary of the enumerated population and survey participants

A valid Xpert Ultra sputum result was obtained for 7,521 individuals (82.9%), 7,347 (81.0%) had a valid culture result available (Figure 17), and 7,292 (80.4%) had both a valid Xpert Ultra and culture result. Among these, 198 (2.6%) and 288 (3.9%) specimens were rejected due to leakage or low volume for Xpert Ultra testing and culture, respectively.

4.5 Xpert Ultra and culture results

Among the 9,066 participants eligible for sputum examination there were 220 with culture positive results and 223 with Xpert Ultra positive results (Table 7). Among the 223 participants with Xpert Ultra positive results, 144 also had positive culture results for M. tuberculosis. The other 79 included 66 with negative culture results, and 13 without a conclusive culture result (nine had contaminated cultures and four were not processed for culture as the samples were rejected due to either having leaked in transit, or specimen volume being below the required volume for processing). Culture detected 76 cases, of which 74 were negative for Xpert Ultra and two were not processed for Xpert Ultra.

Of the 223 Xpert Ultra positive participants, there were seven rifampicin resistant individuals, four males and three females, three were culture negative and four culture positive. The three culture negative participants had a past history of TB. Of the four culture positive participants, two were currently on TB treatment. The rest were all rifampicin susceptible.

Table 7. Culture and Xpert Ultra results among participants eligible for sputum examination (N=9,066)

Culture result	Xpert MTB/RIF Ultra result				Total
	Positive	Negative*	Invalid	Sputum not collected /Rejected	
Total	**223**	**7,286**	**12**	**1,545**	**9,066**
MTB positive	144	74	0	2	220
MTB negative	66	6,460	11	49	6,586
Contaminated	9	383	0	4	396
NTM**	0	145	0	0	145
Rejected/ Sputum not collected	4	224	1	1,490	1,719

** The Xpert Ultra Negative results include 71 participants with Xpert Ultra trace results (see below).*

***NTM-Non-tuberculous mycobacteria*

The distribution of Xpert Ultra and TB culture results by demographic characteristics is shown in Tables 8 and 9 respectively.

Table 8. Distribution of Xpert Ultra results by demographic characteristics

Variable	Total sputum eligible	MTB detected		MTB not detected		Trace		Invalid		Not collected	
	N	n	%	n	%	n	%	n	%	n	%
Total	**9,066**	**223**	**2.5**	**7,215**	**79.6**	**71**	**0.8**	**12**	**0.1**	**1,545**	**17.0**
Age group (years)											
15-24	1,064	19	1.8	741	69.6	9	0.8	0	0.0	295	27.7
25-34	1,381	48	3.5	1,059	76.7	14	1.0	1	0.1	259	18.8
35-44	1,393	51	3.7	1,102	79.1	14	1.0	3	0.2	223	16.0
45-54	1,499	51	3.4	1,224	81.7	11	0.7	4	0.3	209	13.9
55-64	1,625	28	1.7	1,379	84.9	6	0.4	2	0.1	210	12.9
65+	2,104	26	1.2	1,710	81.3	17	0.8	2	0.1	349	16.6
Sex											
Male	3,849	123	3.2	3,138	81.5	37	1.0	3	0.1	548	14.2
Female	5,217	100	1.9	4,077	78.1	34	0.7	9	0.2	997	19.1
Race											
African	7,894	165	2.1	6,214	78.7	57	0.7	10	0.1	1,448	18.3
Indian/ White	258	3	1.2	216	83.7	4	1.6	0	0.0	35	13.6
Coloured	914	55	6.0	785	85.9	10	1.1	2	0.2	62	6.8
Geotype											
Urban	4,214	129	3.1	3,483	82.7	34	0.8	5	0.1	563	13.4
Rural	4,852	94	1.9	3,732	76.9	37	0.8	7	0.1	982	20.2

Table 9. Distribution of culture results by demographic characteristics

	Total sputum eligible	Positive for MTB		Negative for MTB		Contaminated		NTM		Not collected	
	N	n	%	n	%	n	%	n	%	n	%
Total	**9,066**	**220**	**2.4**	**6,586**	**72.6**	**396**	**4.4**	**145**	**1.6**	**1,719**	**19.0**
Age group (years)											
15-24	1,064	22	2.1	692	65.0	31	2.9	12	1.1	307	28.9
25-34	1,381	51	3.7	979	70.9	49	3.5	19	1.4	283	20.5
35-44	1,393	43	3.1	1,027	73.7	49	3.5	19	1.4	255	18.3
45-54	1,499	35	2.3	1,119	74.6	76	5.1	24	1.6	245	16.3
55-64	1,625	29	1.8	1,234	75.9	76	4.7	32	2.0	254	15.6
65+	2,104	40	1.9	1,535	73.0	115	5.5	39	1.9	375	17.8
Sex											
Male	3,849	123	3.2	2,906	75.5	162	4.2	66	1.7	599	15.6
Female	5,217	100	1.9	3,680	70.5	234	4.5	79	1.5	1,120	21.5

	Total sputum eligible	Positive for MTB		Negative for MTB		Contaminated		NTM		Not collected	
	N	n	%	n	%	n	%	n	%	n	%
Race											
African	7,894	165	2.1	5,623	71.2	359	4.5	138	1.7	1,609	20.4
Indian/ White	258	3	1.2	208	80.6	9	3.5	0	0.0	38	14.7
Coloured	914	52	5.7	755	82.6	28	3.1	7	0.8	72	7.9
Geotype											
Urban	4,214	133	3.2	3,238	76.8	138	3.3	56	1.3	649	15.4
Rural	4,852	87	1.8	3,348	69.0	258	5.3	89	1.8	1,070	22.1

*NTM: Non-tuberculous Mycobacteria

By age group, most of the microbiologically positive results were in ages 25-34 years and 35-44 years at 3.5% and 3.7% respectively for Xpert Ultra; and 3.7% and 3.1% respectively for culture. By sex, there were more males with both Xpert Ultra positive and culture positive results (3.2% in males and 1.9% in females for both Xpert Ultra and culture).

Table 10 shows culture and Xpert Ultra results by history of TB treatment (current and previous) and CXR findings. Of the 144 participants with positive Xpert Ultra and culture results, 6.9% were on treatment for TB at the time of the survey and 25.0% had a history of previous TB. Among participants with a culture positive result and an Xpert Ultra negative result (n=48), 11 (22.9%), reported having a history of previous TB and none were on TB treatment at the time of the survey. Sixty-six participants had culture negative and Xpert Ultra positive results. Among these participants 18 (27.3%) were currently on TB treatment and more than half (34; 51.5%), had a previous history of TB. In addition, CXR abnormalities were observed in almost all (98.5%) of participants in this group.

Among participants with Xpert Ultra trace results (n=71), 29 (40.8%) reported having previous TB and two were currently on TB treatment. Of the 71, only 26 (36.6%) had a culture positive result, 38 (53.5%) had culture negative results, four samples had contaminated cultures, and three were not processed for culture as the samples were rejected due to insufficient specimen volume. Among the 26 with culture positive results, five participants had a history of previous TB, none were currently on TB treatment, and all had abnormal CXRs suggestive of TB. There were more participants with a previous history of TB in those with culture negative results (60.5%) compared to those with culture positive results (19.2%) (Table 10). CXR abnormalities were observed in 84.2% of the participants with a culture negative result and a previous history of TB.

For the seven samples where culture results were not available, one participant was currently on TB treatment, one had prior TB treatment, and five did not report a history of previous TB treatment, all 7 had abnormal CXRs.

Table 10. Comparison of Xpert Ultra and culture results by TB treatment history and CXR findings

Xpert Ultra and Culture result		Currently on TB treatment		History of past treatment		No history of past treatment		Central CXR reading abnormal suggestive of TB*		CXR not done	
	N	n	%	n	%	n	%	n	%	n	%
Total (N)	**7,181**	**116**		**1,472**		**5,655**		**3,216**		**259**	
Cult+/Xpert +	144	10	6.9	36	25.0	103	71.5	141	97.9	2	1.4
Cult+/Xpert -	48	0	0	11	22.9	37	77.1	45	93.8	0	0
Cult-/Xpert +	66	18	27.3	34	51.5	21	31.8	65	98.5	0	0
Cult-/Xpert -	6,422	80	1.2	1,278	19.9	5,110	79.6	2,725	42.4	240	3.7
Cult not done/ Xpert +	4	1	25	0	0	3	75	4	100	0	0
Cult not done/ Xpert -	221	2	0.9	49	22.2	171	77.4	78	35.3	7	3.2
Cult+/Xpert not done	2	0	0	0	0	2	100	2	100	0	0
Cult-/Xpert not done	49	1	2	4	8.2	45	91.8	17	34.7	0	0
Xpert Trace/cult +	26	0	0	5	19.2	21	80.8	26	100	0	0
Xpert Trace/cult -	38	1	2.6	23	60.5	15	39.5	32	84.2	1	2.6
Xpert Trace/Cult not done	3	0	0	1	33.3	2	66.7	3	100	0	0
Xpert Trace/Cult Contaminated	4	1	25	0	0	3	75	4	100	0	0
Xpert+/Cult Contaminated	9	0	0	3	33.3	6	66.7	8	88.9	0	0
Xpert-/NTM	145	2	1.4	28	19.3	116	80	66	45.5	9	6.2

** CXRs of all participants with bacteriologically confirmed results were read by a radiologist for final interpretation.*

4.6 Survey TB cases

A total of 234 TB survey cases, 124 (53.0%) males, 110 females, 54 (23.1%) aged 25-34 years and 48 (20.5%) aged 35-44 years (Table 11), were identified comprising of 220 culture positive participants of which 144 were Xpert Ultra positive, 74 were Xpert Ultra negative and two were not tested by Xpert Ultra. An additional 14 cases that were classified as TB survey cases were Xpert Ultra positive, culture was not positive for MTB, did not have a history of TB, and had CXR findings that were suggestive of active TB as confirmed by an external CXR reading panel (Figure 18).

Table 11. Demographic characteristics of Survey TB Cases

Categories	Survey TB Cases	
	N	%
	234	
Age		
15-24	23	9.8
25-34	54	23.1
35-44	48	20.5
45-54	38	16.2
55-64	30	12.8
65+	41	17.5
Sex		
Male	124	53
Female	110	47
Race		
African	175	74.8
Indian/White	4	1.7
Coloured	55	23.5
Geotype		
Urban	141	60.3
Rural	93	39.8

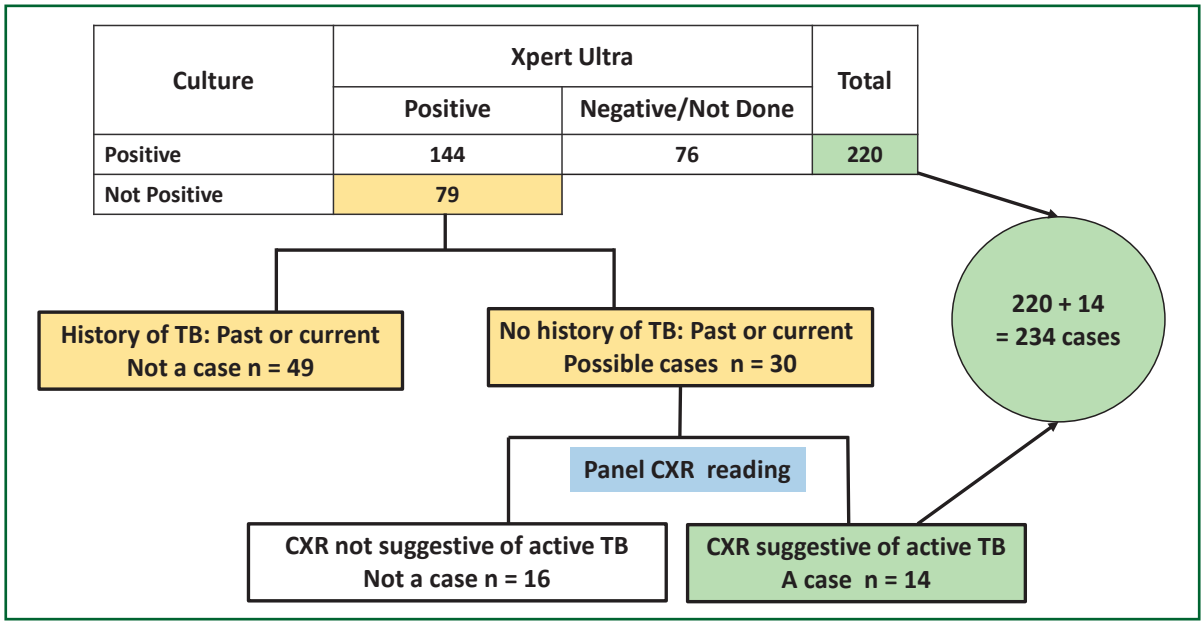

Figure 18. Survey TB cases by culture and Xpert Ultra (N=234)

* *Xpert Ultra trace results were regarded as negative.*

4.7 Estimated prevalence of TB in South Africa, 2018

4.7.1 Estimated prevalence of TB in adults ≥15 years in South Africa, 2018

The survey estimated the prevalence of bacteriologically confirmed PTB in South Africa at 852 (95% CI 679-1,026) per 100,000 population among individuals 15 years and older (Table 12). The estimated prevalence of PTB in males 15 years and older was more than 1,000 per 100,000 population and was approximately 1.6 times that of women. Prevalence peaked in those aged 35-44 years and in those aged 65 years and older and was lowest among those aged 15-24 years.

Table 12. Estimated prevalence of bacteriologically confirmed pulmonary TB (≥15 years), by sex and by age group, South Africa (Method: IPW+MI)

Prevalence per 100,000 population		95% CI
Overall	**852**	**679-1,026**
Sex		
Male	1,094	835-1,352
Female	675	494-855
Age group (years)		
15-24	432	232-632
25-34	902	583-1,221
35-44	1,107	703-1,511
45-54	1,063	682-1,443
55-64	845	505-1,186
≥65	1,104	680-1,528

4.7.2 Estimated TB prevalence in South Africa, all ages and all forms, 2018

Using this survey estimate, the prevalence of TB for all forms of TB and ages in South Africa were calculated adjusting for individuals less than 15 years (29%), a rate ratio of child to adult TB (0.6) and the proportion of notified cases that are extra-pulmonary TB (9.7%). This was performed by the WHO using standard methods. The estimated prevalence of TB (all ages, all forms) in South Africa in 2018 was 737 (95% CI 580-890) per 100,000 population.

Figure 19 shows the estimated number of TB cases in the community for 2018 using the point estimate data from Table 12 and stratified by age. The highest estimated number of cases was among those aged 25-34 years. Although the estimated number of cases in those aged 65 years and older was lower than for other age groups, the prevalence was above 1%.

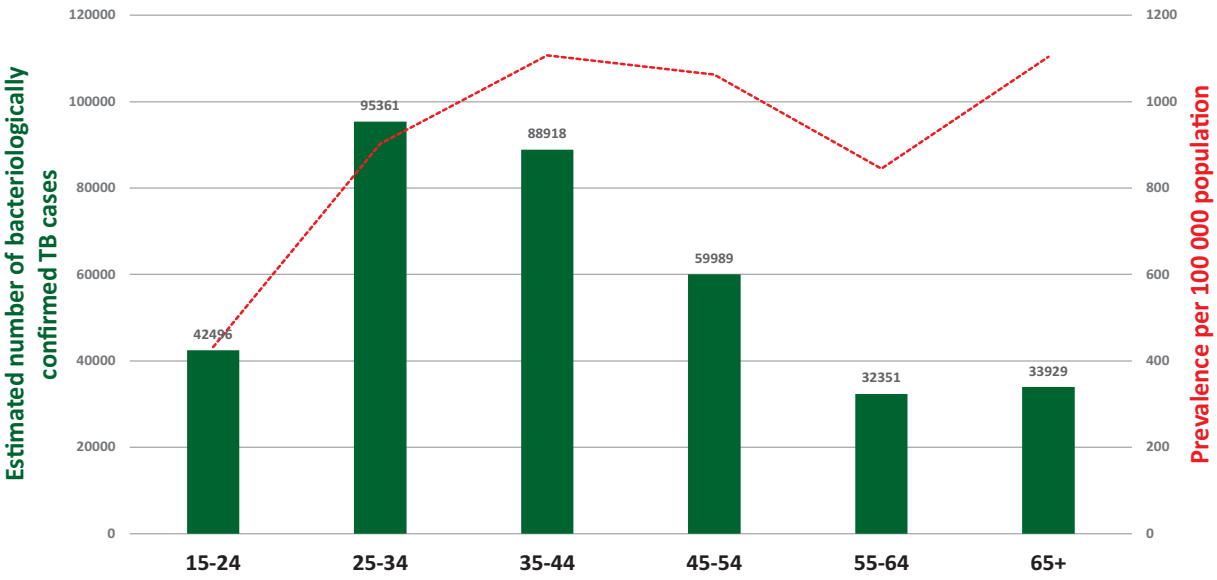

Figure 19. Comparison of the estimated number of bacteriologically confirmed TB cases (green bar) with prevalence (red line) by age group (≥15 years), South Africa, 2018

4.8 The gap between TB prevalence and notification

The ratio of the bacteriologically confirmed pulmonary TB cases to the case notification rate (2018) (P:N ratio) is shown in Table 13. Across all age groups and in both males and females more prevalent cases were estimated than were notified. The largest gap was in those aged 15-24 years and the elderly 65 years and older where the P:N ratios were 2.91 and 2.88 respectively. The ratios for males and females were 1.89 and 1.70 respectively.

Table 13. Ratio of prevalence (P) to notification (N) for pulmonary TB ≥15 years, South Africa, 2018

Category	P:N ratio
Total	**1.75**
Male	1.89
Female	1.70
Age group (years)	
15-24 years	2.91
25-34 years	1.61
35-44 years	1.55
45-54 years	1.66
55-64 years	1.63
≥65 years	2.88

4.9 Characteristics of survey TB cases

More than half (57.8%) of the survey cases had CXR abnormalities suggestive of TB only without reported symptoms of TB; 82 (35.0%) were symptomatic with CXR abnormalities suggestive of TB, 16 (6.8%) were symptomatic only and one (0.4%) did not report symptoms and had not undergone CXR (Figure 20 and Table 14). If only symptoms had been used to screen for survey cases without CXR, 135 (57.7%) of the survey TB cases would have been missed. Overall CXR screening detected 217 (92.7%) of the survey cases.

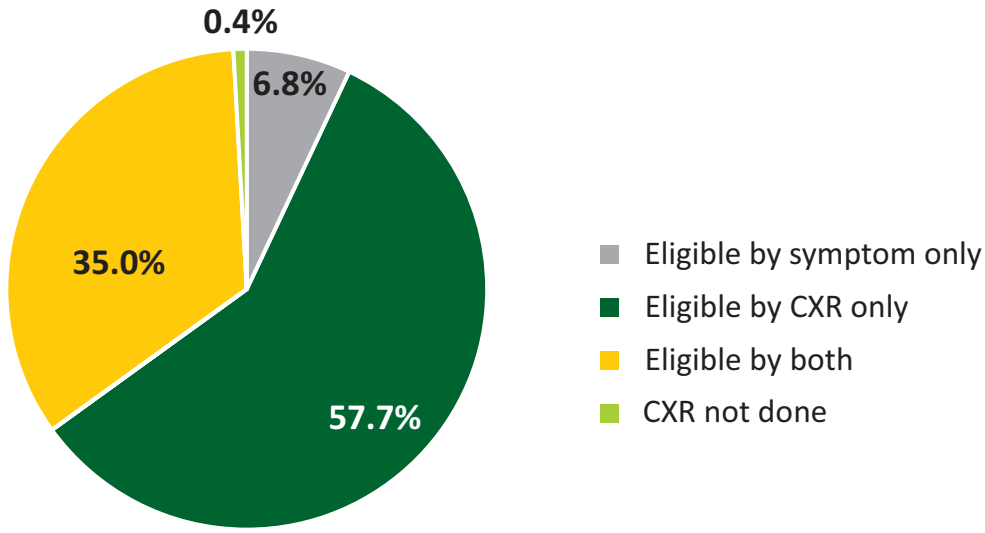

Figure 20. Symptoms and/or abnormal CXR among survey TB cases (N=234)

**CXR was not done because the participant declined to consent, or was pregnant, or had disabilities that made it impossible to take the CXR or was bedridden and not able to attend the screening site.*

Table 14. History of TB treatment among Survey TB cases (N=234)

Total	234	100
History of past TB treatment		
Yes	52	22.2
No	182	77.8
Currently on TB treatment		
Yes	10	4.3
No	223	95.3
Missing	1	0.4

Fifty-two (22.2%) of the survey TB cases were previously treated for TB and 10 (4.3%) were on treatment at the time of the survey (Table 14). A total of 69 (29.5%) of the survey TB cases reported a cough (any duration), while 44 (18.8%) reported cough of longer than two weeks (Table 15).

Table 15. Survey TB cases by symptoms and history of TB treatment (N=234)

Characteristic	n	%
Cough of any duration		
Yes	69	29.5
No	164	70.1
Missing	1	0.4
Cough ≥2 weeks		
Yes	44	18.8
No	189	80.8
Missing	1	0.4
Fever		
Yes	29	12.4
No	204	87.2
Missing	1	0.4
Loss of weight		
Yes	43	18.4
No	189	80.8
Missing	2	0.9
Night Sweats		
Yes	51	21.8
No	181	77.4
Missing	2	0.9
CXR Findings		
Normal	15	6.4
Abnormal suggestive of TB	217	92.7
Missing/not done	2	0.9

Table 16 describes the concordance level of results between Xpert Ultra and culture methods. Of the 234 survey TB cases, 144 (61.5%) were detected by both methods. A total of 14 cases (6.0%) were diagnosed by Xpert Ultra but were missed by culture, while 48 (32.5%) were diagnosed by culture but missed by Xpert Ultra.

Table 16. Culture and Xpert Ultra results for Survey TB cases (N=220)

		Culture Result									
Xpert Ultra Result		Positive for MTB		Negative for MTB		Contaminated		Not done		Total	
		n	%	n	%	n	%	n	%	N	%
	Total	**220**	**94.0**	**7**	**3.0**	**6**	**2.6**	**1**	**0.4**	**234**	**100.0**
	MTB detected	144	61.5	7	3.0	6	2.6	1	0.4	158	67.5
	MTB not detected	48	20.5	0	0.0	0	0.0	0	0.0	48	20.5
	Trace	26	11.1	0	0.0	0	0.0	0	0.0	26	11.1
	Not done	2	0.9	0	0.0	0	0.0	0	0.0	2	0.9

4.10 HIV infection

Tables 17 and 18 provide information about the HIV status of survey participants as determined by self-reported status from the individual questionnaire and by testing for HIV antibodies among those who were eligible for sputum examination and consented to give a DBS specimen for HIV testing. Overall, the HIV status from self-reporting and from DBS testing in the survey was known for 26,877 (76.4%) and 4,588 (17.1%) were HIV positive. Among the 9,066 sputum eligible participants 6,543 (72.1%) knew and reported their HIV status and 1,517 (23.2%) self-reported to be HIV-infected. Among these 9,066 sputum eligible participants who were offered HIV testing by DBS 2,176 (24.0%) provided a DBS specimen and had a valid HIV test result, and 325/2,176 (14.9%) tested positive. Therefore, among the 9,066 sputum eligible participants, HIV status from self-reporting and from DBS testing in the survey was known for 7,061 participants, and 1,647 (23.3%) were HIV positive.

Among those with a known HIV status, there was a sequential increase in the percentage of participants with HIV starting with all participants (17.1%), followed by screen positive participants (23.3%), then survey TB cases (28.8%) and finally programme cases (58.0%) (Table 17). TB programme cases were those participants who were already on treatment at the time of survey participation.

Table 17. HIV status of Survey participants (N=35,191)

Category	Participants with a known HIV status			HIV prevalence among participants with a known HIV status		
	Total	Known HIV status	%	HIV-uninfected	HIV-infected	% HIV-infected
All participants	35,191	26,877	76.4	22,289	4,588	17.1
All screen-positive participants	9,066	7,061	77.8	5,414	1,647	23.3
Screen-positive participants by symptoms only	5,168	4,173	80.7	3,156	1,017	24.4
Screen-positive participants by CXR only	3,566	2,641	74.1	2,060	581	22.0
Survey cases	234	191	81.6	136	55	28.8
*Programme cases	178	162	91.0	68	94	58.0

HIV status determined by a DBS result and in its absence the self-reported status. *Programme cases: individuals already on treatment through the NTCP prior to enrolment into the survey.

Among the 234 survey cases, 191 (81.6%) had a known HIV status, and 107 (56.0%) of these 191 survey cases did not report any symptoms of TB. The majority of cases who did not report symptoms, 77.6% (83/107) were HIV-uninfected. The percentage of participants with HIV increased as the number of symptoms increased starting from 22.4% among those with no symptoms, to 41.6% among those with two TB symptoms and was 45.4% among those who reported four symptoms (Table 18).

Table 18. The correlation of HIV status and symptoms among Survey TB cases (N=191)

Number of TB Symptoms	Survey TB Cases with a known HIV status (N =191)			
	HIV-infected	HIV-uninfected	Total	% HIV co-infection
0	24	83	107	22.4
1	10	24	34	29.4
2	10	14	24	41.6
3	6	9	15	40.0
4	5	6	11	45.4
Total	**55**	**136**	**191**	**28.8**

4.11 Health care seeking behaviour for participants with TB symptoms

Among the 5,168 survey participants who reported at least one TB symptom, two-thirds (3,442) reported not having sought care for the symptoms at the time of their participation in the survey. More males (71.3%) than females (63.4%) did not seek care (Table 19).

Table 19. Sex and age of symptomatic participants who did not seek care (N=5,168)

Category	Number of symptomatic participants	Number of participants that did not seek care	% of participants that did not seek care
Sex			
Male	2,104	1,500	71.3
Female	3,064	1,942	63.4
Age group			
15-24 years	678	558	82.3
25-34 years	869	688	79.2
35-44 years	850	573	67.4
45-54 years	859	540	62.9
55-64 years	897	526	58.7
≥65 years	1,016	557	54.8
HIV status			
HIV-uninfected	3,156	2,164	68.6
HIV-infected	1,017	574	56.4

The percentage of symptomatic participants who did not seek care was highest in younger participants and decreased with increasing age starting at 82.3% in those aged 15-24 years, then 62.9% in those 45-54 years old and 54.8% in those 65 years and older. Fifty-six percent (56.4%) of HIV-infected participants had not sought care for their symptoms compared to 68.8% of those who were HIV-uninfected. Among the 3,442 participants with symptoms who had not sought care, the majority 2,071 (60.2%), indicated that they were planning to seek care. A further 917 (26.6%) felt their symptoms were not serious enough for them to seek care, 223 (6.5%) reported not having sufficient money to travel to a health care facility, and 189 (5.5%) reported that the health care facility was too far away for them to attend (Figure 21).

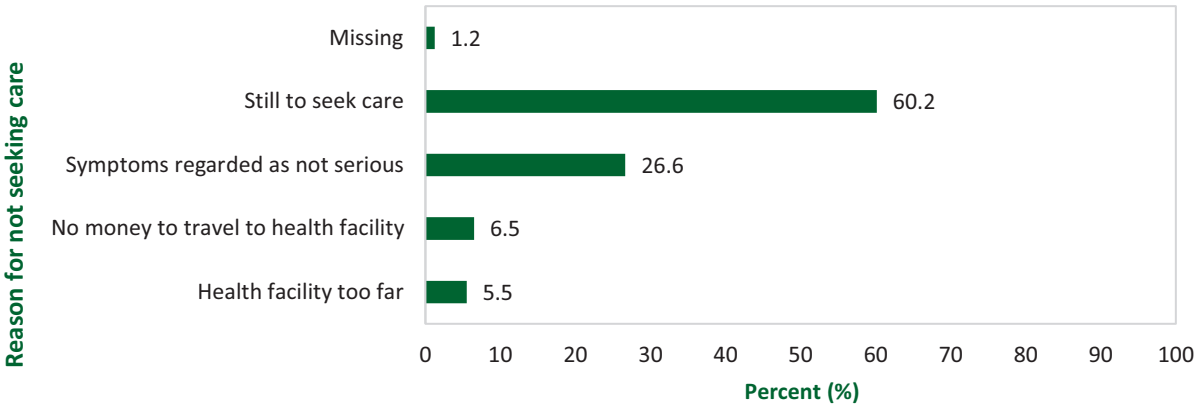

Figure 21. Multiple reasons allowed for not seeking care by symptomatic participants (N=3,442)

Among the 1,726 participants with symptoms who had sought care, more than 90% had attended a public healthcare facility, with the majority attending a clinic (1,497; 86.7%) and 139 (8.0%) seeking care from the private sector (Figure 22). Among the 234 survey TB cases, 41 that were symptomatic had sought care for their symptoms before the survey: 31 attended a community clinic, four attended a government hospital and 6 attended a private sector facility. Among these 41 participants eight (19.5%) were on treatment for TB at the time of enrolment into the survey. Therefore 33 (34%) symptomatic TB cases had not yet been diagnosed or started on treatment prior to the survey.

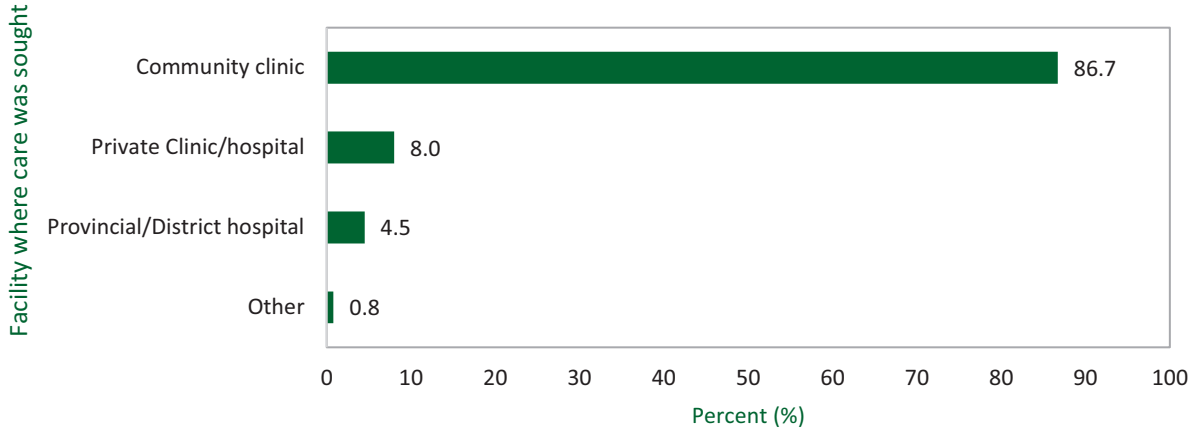

Figure 22. Facility where care was sought by symptomatic patients (N=1,726)

5. DISCUSSION AND PROGRAMMATIC IMPLICATIONS

This survey, conducted from 2017-2019, is the first ever national population-based survey of TB in South Africa. It provides information on the epidemiology of TB and unique information on the true burden of bacteriologically confirmed PTB in South Africa.

5.1 Major findings

South Africa has a high TB burden, including many people with undetected TB in the community. The prevalence of TB (all forms, all ages) in South Africa in 2018 was 737 (95% CI 580-890) per 100,000 population. Restricting this analysis to PTB and based on the survey findings (bacteriologically confirmed TB), prevalence was 852 per 100,000 population and was lowest in the youth (15-24 years) and peaked in those aged 35-44 years and in the elderly aged 65 years and older. In these latter age groups, the prevalence exceeded 1% (1,107/100,000 (95% CI 703-1,511), and 1,104/100,000 (95% CI 680-1,528), respectively. The percentage of survey participants with HIV infection among programme cases was very similar to the notification data (58.0%)(17), and was lower in those that were detected in the survey.

Based on the survey results, the estimated number of TB cases (390,000) was more than the cases notified in 2018 (235,652) and this translates to a prevalence to notification ratio of 1.75. The largest prevalence to notification gap was in the youth aged 15-24 years and in those 65 years and older. The gap between the cases that were notified and those detected in the survey is an important finding indicating missed cases by the TB programme and it implies risk for ongoing transmission in the community.

To effectively deal with the TB epidemic, this gap needs to be narrowed down and closed. This requires strengthening and more efficient implementation of current interventions, and introduction of new interventions where this is needed. There is need for improved notification of TB cases especially among those that are laboratory diagnosed and data quality improvement may also narrow the notification gap. Targeting the TB cases missed in young people for example could leverage on efforts and actions in the National Adolescent and Youth Health Policy (27), which advocates for adolescent and youth friendly health services. The six objectives of this policy include two objectives that could support narrowing of the prevalence notification gap specifically: (i)The use of innovative, youth-oriented programmes and technologies to promote the health and wellbeing of adolescents and youth which can incorporate cell phone-based screening, and (ii) The provision of comprehensive, integrated sexual and reproductive health and rights services integrated with HIV/AIDS and TB, which can provide TB screening and testing services when the youth attend facilities for other services.

These measures are notable given that the survey showed that young people were least likely to seek care for TB symptoms.

The high TB prevalence in those 65 years and older could be due to ageing and other chronic diseases that increase the risk of TB. Nonetheless, the high prevalence to notification gap in this age group indicates missed opportunities for case detection, given that most participants in this age group reported TB symptoms and some (45%) had sought care for their symptoms. Screening for TB in the elderly should be increased and this can be achieved by increasing the index of suspicion for TB in the elderly and through improved integration of healthcare services by incorporating TB screening into care for other chronic conditions that are prevalent in older people.

The other major findings from this survey were that i) Men often have TB and are undetected or not reported to the NTCP; ii) Subclinical TB is underestimated as a contribution to the TB burden; iii) TB in HIV-negative individuals is also common, and iv) Health care seeking for individuals who report TB symptoms is delayed. We further discuss these major findings below.

5.1.1 Men often have TB and are undetected or not reported to the NTCP

In this survey, the TB burden was higher in males, with a prevalence almost 1.6 times that of females. This finding is consistent with findings from other TB prevalence surveys in Africa and Asia (10, 28). In addition, the prevalence to notification gap in males was 1.89, which is higher than that in women (1.70). The disproportionately higher TB prevalence, and the higher prevalence to notification ratio in men has previously been associated with delays in seeking care and access barriers in high TB burden settings. Studies in the region have found that healthcare services may be organized and operate in inconvenient ways for men, such as having operating times that conflict with men's schedules, and being projected as spaces geared for and mainly frequented by women and children (29). The literature also indicates that pressures to uphold images of strength and perfect health may result in delayed care seeking for TB symptoms by men (30). There is therefore a need to specifically address the higher TB disease burden in men through interventions that will effectively reach them, and this can be through men's social networks, using technology to facilitate screening and through other men's health programmes such as the voluntary medical male circumcision programme as part of an integrated health care system.

5.1.2 Subclinical TB is underestimated as a contribution to the TB burden

Another important finding in this survey was a very high proportion (57.8%) of TB cases among participants who did not report any TB symptoms and yet had bacteriological confirmation of TB. These cases of subclinical TB were detected through CXR screening and would have otherwise been missed by symptom-based screening, and therefore CXR played a key role in detecting TB cases in this survey. This highlights the significant role of CXR in such surveys and also suggests that CXR should be given greater consideration in TB case finding in community screening in high risk populations. A review of literature from Asia reported a range between 40% and 79% of TB cases without symptoms, hence while this finding is not new, it however partly explains undetected TB where case finding is largely passive and dependent on care seeking for TB symptoms (31).

Subclinical TB is an emerging area that requires further research both in terms of tools for detection, and appropriate treatment regimens and management (32). Individuals with subclinical TB, though not "overtly suffering" from TB when they present, represent a phase in the continuum of TB disease and may in time develop symptoms and present to care. They do however have the propensity to infect others (33) even at this early stage and efforts to address this issue will be important if the long term goals to of the End TB strategy are to be realized (34).

5.1.3 TB prevalence among HIV-uninfected individuals is also high

The percentage of survey cases with HIV (28.8%) was half of that reported for TB cases enrolled in the TB programme (58.0%) in 2018 (17). This finding indicates the success of the investment of the HIV programme to find and treat TB/HIV cases in the community. The lower HIV coinfection rate is consistent with information reported in the literature of a higher burden of HIV-uninfected TB when active case finding efforts are undertaken (35). Interestingly, among TB cases who did not report symptoms, the majority were HIV-uninfected (78%). Thus, the higher than expected prevalence of TB in this survey was in part driven by undetected TB among HIV-uninfected individuals. It is however important to note that HIV-infected TB cases were more likely to be symptomatic. These symptomatic individuals therefore would have a greater likelihood of being detected through the HIV programme as the current screening approach is based on symptoms and TB screening is part of integrated HIV and TB services in the country. In addition, more than two-thirds of HIV-uninfected symptomatic participants had not sought care for their symptoms. Thus, strategies to detect HIV-uninfected cases earlier are needed and should include patient and healthcare provider education and awareness about TB also occurring in HIV-uninfected people.

5.1.4 Care seeking for TB symptoms is delayed

Care seeking among participants with symptoms suggestive of TB was delayed with almost two-thirds having not sought care at the time of their participation in the survey, and 60.2% of these reporting that they were still planning to seek care. A further 26.6% regarded the symptoms as not serious and thus did not seek care. Fewer men, younger people and those who were HIV-uninfected sought care for their symptoms. In-depth qualitative research is needed to better understand the reasons for delayed care seeking so as to inform interventions to address this gap overall and for specific population groups in particular men and the youth where the prevalence to notification gap is larger as has been described above. In addition, interventions to increase knowledge of TB and awareness of TB symptoms and their importance are still needed. Further work is also needed to better implement some of the activities already included in policies such as the National Adolescent and Youth Health Policy described above, and the NSP 2017-2022 (6). Data from the South African National Health and Nutrition Examination Survey (36) found that approximately only a fifth (21.5%) of participants correctly identified any three of the six key symptoms of TB from a WHO standard list of TB symptoms and that about two thirds (63.0%) correctly identified the primary transmission route of TB.

Approximately a fifth (19.5%) of symptomatic participants who were survey TB cases who had sought care for their symptoms had been diagnosed and started on treatment. This could indicate missed or delayed opportunities for diagnoses and treatment for the rest of the survey cases that had sought care. This finding is consistent with previous analyses of TB data which showed that in 2013, while 95% of all estimated TB cases accessed a TB test, 82% had a TB diagnosis and only 70% were notified and treated (37). There should thus also be heightened vigilance among healthcare workers in assessing TB symptoms among those who attend health facilities as well as adherence to the TB management guidelines to promote early diagnosis and initiation of treatment for all cases.

5.1.5 Use of Xpert Ultra for TB prevalence surveys and interpretation of Xpert Ultra trace results in TB prevalence surveys

This survey is one the first national TB surveys to use Xpert Ultra for active case detection. South Africa routinely implemented Xpert MTB/RIF Ultra in a phased approach in 2017, the same year that the prevalence survey was initiated. When compared to Xpert MTB/RIF, Xpert Ultra has a higher sensitivity among smear negative (63.0% vs 46.0%) and among HIV-infected patients (90% vs 77.0%) (38), although the higher sensitivity is coupled with a reduction in specificity (96.0% vs 98.0%). The specificity is even further reduced among patients with a previous history of TB (93.0% vs 98.0%). The semi-quantitative result of Xpert Ultra 'trace' also contributes to the reduced specificity (98% without trace i.e. study participants testing trace-positive reclassified as negative vs 96% with trace results), this was mostly seen in patients with a previous history of TB. Therefore, confirmation of a positive Xpert Ultra result is required in active case finding in general populations.

At the time of this survey, there was minimal data regarding trace results (apart from Dorman et al (38)), and we therefore opted to classify all trace results as Xpert Ultra negative. Among the 71 samples with Xpert Ultra trace results, 26 were culture positive and 38 were culture negative. Culture negativity was more frequent in participants with a previous history of TB. 60% (23/38) of those participants with a negative culture had a previous history of TB. These findings were used to develop a national algorithm for managing patients with an Xpert Ultra trace result, which will be included in the updated National TB guidelines that are expected to be released in 2022.

We also noted discordant Xpert Ultra and culture results. Sixty-six participants with Xpert Ultra positive results had a negative culture result. Among these, 34 (51.5%) had a history of previous TB and 18 (27.3%) were on treatment at the time of participation in the survey. These findings are in keeping with studies by Mishra and colleagues who found a reduction in specificity of Xpert Ultra in patients with a history of previous TB (39). The same was found by Theron and colleagues for the Xpert MTB/RIF G4 (40). Due to the reduction in specificity, the case definition was amended and only included Xpert Ultra positive and culture not positive as survey cases among patients with no prior or current history of TB and CXR abnormalities suggestive of TB.

5.2 Strengths and limitations

The survey was a nationally representative population-based survey that for the first time provided a national estimate of the true burden of TB in South Africa. This was made possible by close collaboration of major public institutions in the country working with the Department of Health. The survey followed the WHO standardized methodology ensuring robust estimates that can be compared with those from surveys conducted in other countries and regions. The important issues that were identified by the survey will inform future strategies to effectively address the TB epidemic.

Other strengths are that testing for TB was conducted in a SANAS accredited and WHO supranational reference laboratory (41); availability of a reliable and dedicated sample courier system that assured the integrity of samples and their delivery to the laboratory within the required timelines, and a robust data management system. Using a single laboratory optimized the testing of samples with low levels of loss and contamination. SOPs ensured standardized activities across all clusters. Use of an integrated electronic data collection system facilitated data merging, cleaning and analysis, and supported data of high quality and this was monitored by a strong data management team. Finally no major negative incidents affected the survey staff or the equipment in the field.

Textbox 2. *Best practices instituted for the TB prevalence survey*

- Social media enabled real-time communication between the survey staff (between the field staff and between the central and field teams). This included communication to coordinate activities as well as the central radiologist providing support to MOs on CXR interpretation. It was also used to remind potential participants to attend the SFS at the correct time and place.
- The introduction of reimbursements for participants to compensate them for time spent on survey activities, as advised by the local community leaders to improve participation.
- Where possible within supply chain prescripts, the survey sourced consumables from local vendors within the community as part of fostering relationships with communities.
- After the laboratory investigations were completed, the case management team reviewed all positive laboratory results and sent a close-out report of each participant (including the relevant identifiers for tracing) to the TB focal person with a referral letter for immediate follow-up and linkage to care.

As with other national surveys of this scale there were a number of limitations that may have impacted the prevalence estimates. The participation rate of 66.1% was below the target level of 85%. Participation was lowest in urban clusters and among men, as has been described in other surveys (11). The low participation in particular by males and young people may reflect migrant labour status, economic or other social concerns. Moreover, it has shown that uptake of HIV testing among males is poor in South Africa and similar behavioural patterns may have been operational here among potential male participants (42). In the analysis, it was assumed those who participated were of the same risk of getting TB as those who did not as has been done in other similar surveys.

Approximately 20% of participants who screened positive did not submit sputum sample for MTB/RIF Xpert Ultra or for culture. It was assumed that these results were missing at random. Another limitation was the performance of Xpert Ultra in active case finding activities. Given the specificity of Xpert Ultra (96% (95% CI 94-97%)) the rate of false-positive results for TB disease is high in low prevalence settings such as the general community which was targeted in this survey (this is in contrast to testing symptomatic individuals presenting for routine TB diagnosis). A history of TB can reduce specificity even further (93% CI 89-96%) (38). The survey case definition was therefore amended as follows: a positive culture result or a CXR suggestive of active TB was used to confirm TB survey cases in those participants with an Xpert Ultra positive result and no history of TB treatment. The analysis thus used a conservative approach. The well-established WHO recommended methodologies of multiple imputations with inverse probability weighting were used to account for many of the relevant limitations, allowing robust estimates to be derived.

Another potential limitation is that the HIV status for many participants was based on self-report, as only 24.1% of those participants eligible for sputum examination were tested for HIV on DBS. The HIV coinfection proportions in this survey should be interpreted with this potential limitation in mind. However we note that the overall prevalence estimate among all those with a known status (17.1%) is similar to the estimated HIV prevalence for people 15 years and older in South Africa in 2017, (18,8%, 95% CI-17.5-20.1). (43) Additionally, although the survey field staff were trained for the TB symptom screening interview it is possible that some participants with symptoms may not have disclosed them.

5.3 Survey challenges and resolutions

In many areas, people had other activities which they prioritized (attending the fields, funerals, weddings, work, grant payments) and could not dedicate time to the TB survey, even where field teams made special arrangements to accommodate these alternative activities. Efforts to accommodate the competing activities included opening screening sites until late in the evening where it was safe to do so or opening the screening sites very early in the morning and extending the days of operations in the clusters. In some areas, people were also suspicious of the survey and opted not to participate. Interventions to increase participation included communication and community awareness activities about the survey as described in Section 3.8.1. In some areas, there were misunderstandings about the aim of the survey, how the survey clusters and screening sites were selected and why treatment of other conditions was not included as part of the survey. These challenges were addressed by sustained community awareness activities about the survey such as loud hailing (where acceptable), distributing pamphlets about the survey, text messaging potential participants on social media groups, phoning potential participants and implementing door-to-door revisits, with clarification through reiteration of the aim of the survey as well as its value and benefit for the country. Individuals who had medical aid (health insurance) frequently argued that they already had their health checks done and hence they did not see any need for them to participate. These challenges were addressed by re-education campaigns in the local communities and clarification of the aim of the survey as well as its value and benefit for the country.

As with other surveys, unfavourable weather conditions affected activities (Figures 23 and 24). Difficult and uneven terrain in some areas resulted in damage to the CXR machine and caused delays to the survey activities.

Figure 23. Poor weather conditions negatively affected enrolments at some study sites.

Figure 24. A tractor from a local farm assists the survey team by pulling one of the survey vehicles from a muddy track.

Community unrest and concerns about safety of the survey teams meant that in some areas, activities were cut short, as the areas were deemed unsafe during certain hours of the day. Five clusters were thus replaced due to ongoing security concerns including concerns about criminal gangs in the areas. In these clusters the fieldworkers were concerned about their own safety, even when they were accompanied by community volunteers.

A few individuals reported that they were annoyed with texting and phone calls from the survey and withdrew their pledge to participate.

In some areas, the survey teams faced difficulties as they undertook stakeholder engagements to gain entry in certain communities. This was frequently in urban and more affluent areas, where the community was uninterested in the survey and perceived TB as "not a problem" to them.

6. CONCLUSION

The First National Tuberculosis Prevalence Survey, South Africa, 2018, identified a high TB burden 737 per 100,000 population (all forms, all ages). This was higher in males than in females and was highest among individuals aged 35-44 years and those aged 65 years and older. The largest prevalence to notification gap was in the youth aged 15-24 years and in those aged 65 years and older. A higher proportion of TB was detected among HIV-uninfected individuals, with most reporting no symptoms. HIV-infected participants identified as TB cases had more symptoms and hence they are more likely to be detected and treated in contrast to those who are HIV-uninfected who are less likely to report symptoms and potentially contribute to ongoing transmission of TB. Subclinical TB has emerged as another area that requires further research and that will be important for long term control efforts. Although TB symptoms at first may be perceived to be benign, leading to delays in seeking healthcare, this perception needs to be corrected since TB remains the commonest cause of mortality due to infectious disease in South Africa. Finally, a high index of suspicion, evaluation and follow-up of people presenting with TB-related symptoms by health care providers is needed to improve case detection and contact tracing.

7. REFERENCES

1. World Health Organization. Global Tuberculosis Report 2017. 2018.
2. World Health Organization. Global Tuberculosis Report 2018. 2019.
3. National Institute for Communicable Diseases. National TB Surveillance Report 2004- 2015. 2017.
4. World Health Organization. Global Tuberculosis Report 2019. 2019. Report No.: ISBN 978-92-4-156571-4.
5. Statistics South Africa. Mortality and causes of death in South Africa, 2007: Findings from death notification. 2008.
6. South African National AIDS Council. National Strategic Plan (NSP) 2017 – 2022. 2018.
7. South African National Government. National Development Plan 2030 Our Future-make it work. 2012.
8. Osler M, Boulle A. Three interlinked electronic registers (TIER. Net) Project. Working Paper. University of Cape Town; 2010.
9. Seddon J, Schaaf H, Du Preez K, Hesseling A. Where are we in the battle of ending tuberculosis in children and adolescents in South Africa? South African Medical Journal.110(5).
10. Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, Floyd K. National tuberculosis prevalence surveys in Asia, 1990–2012: an overview of results and lessons learned. Tropical Medicine & International Health. 2015;20(9):1128-45.
11. Law I, Floyd K, AfricanTB Prevalence Survey Group, Abukaraig EAB, Addo KK, Adetifa I, et al. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308-27.
12. Qadeer E, Fatima R, Yaqoob A, Tahseen S, Ul Haq M, Ghafoor A, et al. Population based national tuberculosis prevalence survey among adults (> 15 years) in Pakistan, 2010–2011. PloS one. 2016;11(2):e0148293.
13. van der Heijden YF, Hughes J, Dowdy DW, Streicher E, Chihota V, Jacobson KR, et al. Overcoming limitations of tuberculosis information systems: researcher and clinician perspectives. Public health action. 2019;9(3):120-7.
14. Organization WH. Assessing tuberculosis under-reporting through inventory studies. 2012.
15. World Health Organization. Tuberculosis Prevalence Surveys: a handbook. 2011.
16. Statistics South Africa. Census 2011, South Africa. 2011.
17. World Health Organization. Global tuberculosis report 2014. WHO Geneva. 2014.
18. National Department of Health. National Tuberculosis Management Guidelines, South Africa. 2014.
19. National Department of Health. National HIV Testing Services: Policy 2016. 2016.
20. South African Government. Public Finance Management Act No. 1 of 1999. 2010.
21. Patridge EF, Bardyn TP. Research electronic data capture (REDCap). Journal of the Medical Library Association: JMLA. 2018;106(1):142.
22. Find. A multicentre non-inferiority diagnostic accuracy study of the Ultra assay compared to the Xpert MTB/RIF assay. 2017.
23. World Health Organization. WHO TB Supranational Reference Laboratory Network 2016 [Available from: https://www.who.int/tb/areas-of-work/laboratory/srl-network/en/.
24. International Organization for Standardization. ISO 15189:2012 Medical laboratories — Requirements for quality and competence 2012 [Available from: https://www.iso.org/standard/56115.html.
25. Floyd S, Sismanidis C, Yamada N, Daniel R, Lagahid J, Mecatti F, et al. Analysis of tuberculosis prevalence surveys: new guidance on best-practice methods. Emerging Themes in Epidemiology. 2013;10(1):10.

26. United Nations Department of Economic and Social Affairs Population D. World population prospects. 2019.
27. National Department of Health. National adolescent and youth health policy, 2017. 2018.
28. Enos M, Sitienei J, Ong'ang'o J, Mungai B, Kamene M, Wambugu J, et al. Kenya tuberculosis prevalence survey 2016: Challenges and opportunities of ending TB in Kenya. PloS one. 2018;13(12):e0209098.
29. Mavhu W, Dauya E, Bandason T, Munyati S, Cowan FM, Hart G, et al. Chronic cough and its association with TB–HIV co-infection: factors affecting help-seeking behaviour in Harare, Zimbabwe. Tropical Medicine & International Health. 2010;15(5):574-9.
30. Chikovore J, Hart G, Kumwenda M, Chipungu GA, Desmond N, Corbett L. Control, struggle, and emergent masculinities: a qualitative study of men's care-seeking determinants for chronic cough and tuberculosis symptoms in Blantyre, Malawi. BMC public health. 2014;14(1):1-12.
31. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical tuberculosis disease-a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020.
32. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clinical Microbiology Reviews. 2018;31(4):e00021-18.
33. Dowdy DW, Grant AD, Dheda K, Nardell E, Fielding K, Moore DAJ. Designing and Evaluating Interventions to Halt the Transmission of Tuberculosis. J Infect Dis. 2017;216(suppl_6):S654-S61.
34. World Health Organization. The End TB Strategy 2015 [Available from: https://www.who.int/tb/post2015_strategy/en/.
35. Law I, Floyd K, Group ATPS, Abukaraig EAB, Addo KK, Adetifa I, et al. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308-27.
36. Naidoo P, Simbayi L, Labadarios D, Ntsepe Y, Bikitsha N, Khan G, et al. Predictors of knowledge about tuberculosis: results from SANHANES I, a national, cross-sectional household survey in South Africa. BMC public health. 2016;16(1):1-12.
37. Naidoo P, Theron G, Rangaka MX, Chihota VN, Vaughan L, Brey ZO, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. The Journal of infectious diseases. 2017;216(suppl_7):S702-S13.
38. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. The Lancet Infectious Diseases. 2018;18(1):76-84.
39. Mishra H, Reeve BW, Palmer Z, Caldwell J, Dolby T, Naidoo CC, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF for diagnosis of tuberculosis in an HIV-endemic setting with a high burden of previous tuberculosis: a two-cohort diagnostic accuracy study. The Lancet Respiratory Medicine. 2020;8(4):368-82.
40. Theron G, Venter R, Smith L, Esmail A, Randall P, Sood V, et al. False-Positive Xpert MTB/RIF Results in Retested Patients with Previous Tuberculosis: Frequency, Profile, and Prospective Clinical Outcomes. Journal of Clinical Microbiology. 2018;56(3):e01696-17.
41. World Health Organization. World Health Organization TB Supranational Reference Laboratory Network. 2016.
42. Baisley K, Chimbindi N, Mthiyane N, Floyd S, McGrath N, Pillay D, et al. High HIV incidence and low uptake of HIV prevention services: The context of risk for young male adults prior to DREAMS in rural KwaZulu-Natal, South Africa. PLoS One. 2018;13(12):e0208689.
43. Simbayi L, Zuma K, Zungu N, Moyo S, Marinda E, Jooste S, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. 2019. Report No.: 978-0-7969-2444-5.

ANNEXURE I:

List of clusters

KwaZulu-Natal	Eastern Cape	Gauteng	Western Cape
Isipingo	Izilangwe	Zithombeni	Delft
Waterloo	Kubhonga	Soshanguve South Ext2	Athlone
Zwelisha	Lutubeni	Sunnyside	Sillwood
Matimatolo	Qwabe	Soshanguve H	Vredenburg
Ntolwane	Nyandeni	New Eersterust	Townsend Estate
Nyonebomvu	Ndimakude	Mabopane	De Oude Spruit
Mangeza	Nqabana	Nellmapius	**Limpopo**
Eradamishini	Doti	Kagiso	Ga-Molepo
Bethe	Stutterheim	Diepsloot	Vaalkop
Emthombeni	Rabe	Drie Ziek	Phagameng
Nongoma	Runletts	Pimville Zone 3	Lenyenye
Dayeni	Lennox	Pimville Zone 3-1	Rapitsi
Mkhambathini	Mdantsane	Mofolo North	Tlhohoyanku
Mhlangamkhulu	Bloemendal	Dobsonville Ext1	PPRust
The Ridge	**Free State**	Motswaledi	Mahlanyea
Phoenix	Sebokeng	Tshikwarani	Madiseng
Escombe	Brandfort	Ivory Park	Makhado
Kokstad	Thaba Nchu	Winnie Mandela	Phokwane
Phumamuncu	Rooibult	Daveyton	
Marburg	Wesselton	Centurion Central	
Amaoti	Brandfort	Wierda Park	
Northern Cape	Thaba Nchu	Bredell	
Pampierstad	Rooibult	Selection Park	
Homevale	Lenyenye	Strathavon	
Mpumalanga	Rapitsi	Malanshof	
Wesselton	Matjhabeng	Veleria	
Voksrust	**North West**	**Western Cape**	
Siyathemba	Dannhouse	Knysna	
Hlalamnandi	Moruleng	Langrug	
Driekoppies	Mmabatho	Cloetesville	
Nelindia	Mokgareng	Panorama	
Die Heuwel	Promosa	Khayelitsha	
Dennesig	Segwaelane	Masiphumelele	
Marapyane	Lethabong	Portland	

ANNEXURE 2:

List of Fieldwork Staff

Name	Role	Name	Role
Zola Slimfe	*Team leader*	Helen Visser	*Community Liason Officer*
Ntsandeni Moseya	*Team leader*	Petrus Arnoldus Taljaard	*Community Liason Officer*
Naum Sehlako Masibi	*Team leader*	Magdelene M Nyathi	*Interviewer*
David Ranthimo	*Team leader*	Richard S G Matjeni	*Interviewer*
Mmatsie Manentsa	*Medical Officer*	Idah M Motsoane	*Interviewer*
Asari Villeshni	*Medical Officer*	Dineo Ngwenya	*Interviewer*
Sibusiso Ncangayi	*Medical Officer*	Siphiwe Mathebula	*Interviewer*
Harold Hlophe	*Medical Officer*	Mpho Tilly Rakgalakane	*Interviewer*
Patience Gugulethu Sithole	*Professional Nurse*	Madikila Nicolus Chaba	*Interviewer*
Dolly Nonjabulo Ngcobo	*Professional Nurse*	Chanche Remus Matlala	*Interviewer*
Tebello Motalingoane	*Professional Nurse*	Lungile Lynette Sibisi	*Interviewer*
Wendy Saphokazi Linganiso	*Professional Nurse*	Mercia Felicity Coetzee	*Interviewer*
Sithombe Mkhize	*Professional Nurse*	Mahlubi Steven Sityata	*Interviewer*
Gugulethu Mbalenhle Kunene	*Assistant Nurse*	Thandile Deone Slandela	*Interviewer*
Zukiswa Cakwebe	*Assistant Nurse*	Mzwandile Godfrey Maphanga	*Interviewer*
Thokozile Xulu	*Assistant Nurse*	Hlengiwe Zulu	*Receptionist*
Nondumiso Perseverance Hlongwa	*Assistant Nurse*	Sharolene Coetzee	*Receptionist*
Feziwe Duku	*Assistant Nurse*	Micheal Scheepers	*Receptionist*
Naomi Geraldine Langeveldt	*Assistant Nurse*	Simphiwe Phetha	*Receptionist*
Tsakani Normia Khubayi	*Assistant Nurse*	Matlamela Maria Ramano	*Receptionist*
Salizwa Mgquba	*Assistant Nurse*	John Jabu Mokoena	*Security Officer*
Martha Mokwena	*Data Team*	Johannes Mashala	*Security Officer*
Edith Smangele Hudla	*Data Team*	Tshepo Mcdonald Makubyane	*Security Officer*
Tozi Bobane	*Data Team*	Kgoboki Nkosi	*Security Officer*
Pinky Mononyane	*Data Team*	Jabulani N Mathenjwa	*Driver*
Solomon Setsiba	*Data Team*	Greg Molefe	*Driver*
Seipati Sekole	*Data Checker*	Dennis Phetha	*Driver*
Omaar Moshia	*Data Checker*	Sifiso Madela	*Driver*
Nomma Xakaxa	*Data Checker*	OHS Care radiographers	
Johannes Mkhize	*Data Checker*	OHS Care mobile truck drivers	
Piet Fourie		*Community Liason Officer*	

HOW WILL I KNOW?

Knowing starts with getting screened for TB