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THE PREVALENCE OF LATENT TUBERCULOSIS INFECTION AND ASSOCIATED RISK FACTORS AMONG YOUNG PEOPLE IN SOUTH AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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A research report submitted to the Faculty of Health Sciences in partial fulfillment of the requirement for the Degree of

MASTER OF SCIENCE IN EPIDEMIOLOGY AND BIOSTATISTICS

SEPTEMBER 2018

DECLARATION

I, Judith Ngozi Udeh, student number 720384, declare that this research report is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my research report. It is being submitted in partial fulfilment of the requirements for the degree of Masters of Science in Epidemiology and Biostatistics at the University of the Witwatersrand Johannesburg. It has not been submitted before for any degree or examination at the University of the Witwatersrand Johannesburg or any other university.

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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her research report.

Articles 1: Title: The prevalence of latent Tuberculosis infection among young people in South Africa: A Systematic review and meta-analysis

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DEDICATION

I dedicate this work to my beloved husband, Mr Chukwudi Austin-Willy Udeh and my precious daughter, Miss Angel Chimamanda Udeh. Thank you for always standing by me.

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My warmest regard goes to my beloved husband who defiled all odds to ensure that I complete this programme and not forgetting to specially thank my little girl Angel Chimamanda Udeh who had to cope without me all through this research period. Above all, I thank the trinity for their divine enablement and for upholding me and my family to surmount all the challenges we encountered during the course of this programme.

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LIST OF ABBREVIATIONS

LTBI:	Latent tuberculosis Infection
TB:	Tuberculosis
mTB:	Mycobacterium Tuberculosis
PmTB:	Pulmonary Mycobacterium Tuberculosis
WHO:	World Health Organization
TST:	Tuberculin Skin Test
IGRAs:	InterFERON Gamma Release Assays
CL:	Confidence Interval
PRISMA-P:	Preferred Reporting Items for Systematic reviews and Meta-analysis Protocol

ABSTRACT

Background: Latent tuberculosis infection (LTBI) is a condition whereby people harbour live *Mycobacterium tuberculosis* (*M. tuberculosis*) without any evidence of active tuberculosis (TB) infection. The World Health Organisation (WHO) agenda for eradicating TB revolves on screening and treating people with LTBI in high TB prevalent regions. Studies on LTBI claim that by the typical age of sexual debut, about 50% of the young people in South Africa harbour LTBI and roughly 75% by the age of 25 years. It is imperative to contribute to South Africa's readiness towards WHO agenda for LTBI treatment. Using a Systematic Review and Meta-Analysis, we summed up study measures of effects on LTBI and made a conclusion on the purported prevalence and associated risk factors of LTBI among young people (0-19 years) in South Africa.

Method and analysis: We used studies which estimated the prevalence and risk factors of LTBI among young people (0-19 years) in South Africa as diagnosed by Tuberculin skin test (TST) and InterFERON Gamma Release Assays (IGRAs). Studies were selected using pre-defined eligibility criteria and quality assessment tools to minimize bias. Random-effects model was used to weight the studies and Heterogeneities were determined using I-squared (I^2) heterogeneity statistic. Effect measures were extracted at 95% confidence interval (CI) and the overall estimates pooled using Stata version 14 at 90% CI to accommodate minor variations in the selected studies.

Result: Due to lack of data for all the Provinces, the results obtained in this review are for two Provinces (Western Cape and Gauteng) only. We found the pooled prevalence of LTBI among young people in the two Provinces to be 37% (90% CI: 34%, 41%) using TST and 40% (90% CI: 34%, 46%) using IGRAs. Pooled prevalence for Western Cape is 41% (90% CI: 37%, 44%) and Gauteng is 23% (90% CI: 19%, 26%).

Conclusion: This Systematic review and meta-analysis did not establish the fact that the burden of LTBI among young people in South Africa is high as there were no studies in all the Provinces to back the claim. The available studies on the subject did not represent the national burden of LTBI among the study population given that they covered only two provinces of South Africa.

Keywords: LTBI, prevalence, risk factors, young people, South Africa.

INTRODUCTION
Background

LTBI is defined as a condition whereby people harbour live *Mycobacterium tuberculosis* (*M. tuberculosis*) without showing any clinical signs or symptoms of active tuberculosis (1). It has also been defined by World Health Organization (WHO) as an immune response to *M. tuberculosis* antigen with no medical evidence or symptom associated with active TB infection (2). LTBI is caused by an acid-fast bacillus; an agent which has the ability to remain dormant in its host for many years and can be transmitted through droplets of aerosols from an active TB patient to a susceptible host. Given that the period of latency cannot be predictable since *M. tuberculosis* can persist unnoticed for so many years inside its host; LTBI is a grave health concern worldwide and the principal contributory factor to active TB cases. Amongst individuals who have been exposed to active TB, 30% will show evidence of LTBI using TST and on the average, 5-10% of this number will progress to active TB in about two years (3). LTBI therefore, contributes massively to the 15% TB burden in young people which leads to about 1 million TB cases in the population group annually (4). It also adds to the global 8.8 million new TB cases and 1.4 million TB deaths that occur annually (2).

South African schools record LTBI prevalence as high as 50% or more among adolescents in poor socio-economic settings with high TB and HIV prevalent (5). On the whole, 80% of South African population in informal settlements and townships are reported to harbour LTBI (5). Young people who are HIV positive with household TB contact have been classified as a risk group for LTBI acquisition. Nevertheless, among healthy South African children and adolescents who are HIV negative, LTBI is still considered to be very high with some studies recording a prevalence of 28.0% in the age group 5-10 years representing about one third of the group; 41.7% in 11-15 years and 65.7% in 16-20 years which is a two third of the age category (6). By the average age of sexual debut, 50% of young people in South African communities have LTBI and by the age of 25 years, approximately 75% of the individuals will have evidence of LTBI (6) which is a public health concern. The above figures, therefore, imply that the risk of TB transmission in South Africa will remain high because of the massive pool of LTBI among young people and will consequently impact on the effectiveness of TB control programs in the country.

Some studies claim that it is not feasible to identify living bacilli in individuals who have LTBI (1). Other studies suggest that diagnosis of LTBI can be done using either TST (an in vivo method that uses a combination of antigens taken as a protein precipitate from *M. tuberculosis* liquid cultures) or IGRAs, (an ex vivo method which is designed to identify immune response against *M. tuberculosis* antigens) amongst other methods (7). Andvoid established that the pattern of TB infection in an adult cohort is determined by the same pattern of the infection in their childhood (8). This he explained by stating that TB death is trailed by the same pattern from childhood up to adulthood; hence, LTBI in young people develops into active TB in their adult cohort after so many years of primary infection. Some studies argue that although childhood infection determines TB mortality in later life, it is as a result of the immunological response from re-infection and not as a result of reactivation of LTBI (9). Canetti sustained this opinion by stating that most TB infection disappears after the primary infection causing TB recurrence to be due to re-infection and not due to reactivation of LTBI (10). According to, Mack et al (1),

> "the fact remains that testing positive to LTBI (using immune-based diagnostic tests) is mainly a measure of an immunological response to stimulation by mycobacterial

antigens that cannot necessarily be attributed to the presence of live *M. tuberculosis* in the human host" (1).

On the contrary, Tufariello et al (11) proved that *M. Tuberculosis* has the ability to persevere silently in the host with a minute number of bacilli which is insufficient to cause any clinical signs of TB infection until certain triggers that alter the immunological response occur, causing a higher metabolic rate and replication of the bacilli resulting in the clinical manifestation of TB disease (11). Without a doubt, the extent to which LTBI in young people can cause active TB later on in life is not well understood.

The immunological factors implicated in the causation and/or prevention of LTBI is complex. (12). Nevertheless, persons with LTBI are said to have a higher percentage of antigen-specific CD8 T cells that support bacterial killing needed to cause LTBI (12). Despite different opinions on this topic, current researchers use both TST and IGRAs amongst others to diagnose LTBI. These methods are widely used to diagnose LTBI in young people. Many studies which employed TST and IGRAs to determine the prevalence and risk factors associated with LTBI exist in South Africa although with undeniable discrepancies in their findings. This systematic review and Meta-Analysis, therefore, aims to pool the actual prevalence and risk factors of LTBI among young people in South Africa from existing studies.

Objectives:

Primary objectives

i. To estimate the pooled prevalence of LTBI among young people in South Africa.
ii. To determine the pooled effect estimates of the specified risk factors associated with LTBI prevalence among young people in South Africa.

Secondary objectives

i. To explore the trend over the study years and the effect of age groups on the prevalence of LTBI.
ii. To critically appraise the quality of the extracted data.

Review question:

This systematic review and meta-analysis will be guided by the question: what is the prevalence of LTBI and associated risk factors among the young people in South Africa?

MATERIALS AND METHODS

This review addressed the recommended items presented in the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 checklist (13). This review has been registered and published in the PROSPERO International Prospective Register of Systematic Reviews with PROSPERO Registration Number: CRD42016046228

Designs and scope

This systematic review and Meta-Analysis comprise research reports that examined the prevalence of LTBI and associated risk factors among young people in South Africa. We included both published and unpublished studies ranging from January 2000 to December 2016.

Eligibility criteria:

We included all studies irrespective of the study designs which investigated the prevalence of LTBI among young people in South Africa. Participants were within the age group 0 to 19 years and living in South Africa between the year 2000 and 2016. All recognized ethnic groups and socioeconomic status including academic backgrounds were considered. Only studies written in the English language were considered and included in the review if they met the criteria for inclusion. Only studies that determined LTBI using TST and or IGRAs were used. We used the most recent and comprehensive versions of same studies appearing in different journals. Studies that determined LTBI on subgroup of people different from young people in South Africa, example, the mine and healthcare workers were not included. Studies that reported the prevalence of LTBI that are restricted to only a subgroup of young people which are not representative of this population, example, studies on the prevalence of LTBI restricted to cancer patients or HIV positive individuals were not included. We examined studies that investigated LTBI on mixed population but extracted data only for our study population (0 to 19 years). All studies on the subject that lacked details of data collection or clear methods of analysis were not included. Case report or case series, personal opinions, personal write-ups and descriptive reviews on the subjects were excluded. Studies that did not meet the qualities stipulated in the eligibility screening were excluded. Studies on LTBI treatments outcomes were excluded.

Outcome measures

The outcome assessed in this review is the prevalence and risk factors of LTBI among young people in South Africa as reported in studies from the year 2000 to 2016. All considered studies reported the prevalence of LTBI by diagnosing *M. tuberculosis* using TST at 10mm cut off and or IGRAs. Young people with LTBI are classified as having TST or IGRAs positive results for *M. tuberculosis* but with no clinical signs or symptoms of TB infection. Studies that determined prevalence using TST at 10mm cut off and risk factors at 5mm cut off were included in the systematic review. Studies on established active TB cases were excluded.

Exposure measures

The risk factors associated with LTBI: covariates of interest in this review include demographic variables (gender, age, and racial groups); socioeconomic variables (subject's education, years of parents' education, parental income); Household level factors (prior exposure to active TB infection and density of household); HIV status and BCG scars. The covariates were identified with caution using our judgments with respect to the author's definitions.

All considered studies measured risk factors as Odd Ratios. Other measures other than Odd Ratios were not included in the risk factor review.

Search strategy
With the help of the Librarians at the School of Public Health Library, University of Witwatersrand Johannesburg, South Africa, we developed a comprehensive search strategy to identify the relevant studies. We used medical subject headings (MeSH) modified according to different databases for the search. We searched a number of databases which includes PubMed (Medline), SCOPUS, DARE, CINAHL and Web of Science on the subject. Using different MeSH combinations suitable for each database, we found studies with related keywords in table 1.

Table 1: Keywords modified as needed in different MeSH terms

#1	**LTBI**	**#7**	**tuberculin skin test**
#2	Latent TB	#8	TST
#3	Latent TB infection	#9	Interferon-gamma release assays
#4	Latent tuberculosis	#10	IGRAs
#5	Latent tuberculosis infection	#11	South Africa
#6	Latent mycobacterium tuberculosis	#12	

To ensure we had exhausted all the available studies on the subject, we examined the reference lists of the retrieved articles and authors' personal profiles for more studies.
Finally, we hand-searched the journal sections of libraries for published and unpublished articles and searched for presented papers on TB conferences. We used no language or time restriction in all our searches, however, only studies written in English language and from the year 2000 were filtered at the end of the search.

Screening and data collection
We used a reference manager (Mendeley 1.17.1) to download and handle the selected articles. The articles were passed through series of filters to select the ones that have the important data sets. Firstly, we independently scanned through the titles and the abstracts of the retrieved articles to select those that matched the predefined inclusion criteria in table 2. The studies were allocated any of the above: included (1), excluded (2) and uncertain (3) if the reviewer is not very sure. Articles that were marked "included" were assumed to have the matching titles and abstracts relevant to our study and hence, preceded to the second phase of the screening. We excluded the studies we considered inappropriate (those that were marked excluded). Collectively, we re-examined those that scored 3 (uncertain) and reached an agreement as which of the studies to exclude or include in the next phase of the screening.

At the second phase of the screening, we carefully and independently studied the articles that were marked included to determine their prospective significance to our review. The methods employed to screen LTBI, the study populations and other relevant information appearing in the included studies were recorded. The studies were further allocated any of the above words: (1) include, (2) excluded and (3) uncertain. Once again, we collectively, re-examined those that were marked uncertain and reached an agreement as to which of the studies to exclude or include in the assessment of bias phase.

Thirdly, we evaluated all included articles for quality and eligibility criteria by using Hoy et al (14) quality scores assessment tool to reduce the risk of bias. Standardized data extractions on the eligible studies were carried out independently by the two reviewers. The study information and data extracted include the authors and publication years, study settings, designs, sample size, age, the prevalence of LTBI at 95% CI and risk factors with their odd

ratios at 95% CI. The risk factors considered include the BCG scars, HIV status, age category, gender, race, socioeconomic status, prior exposure to TB and density of household. The two independent reviewers compared the extracted data sets and reached consensus where discrepancies were noted. We presented the selection procedures in a flow chart for transparency.

Table 2 **Inclusion criteria**

Characteristics	Criterion
Types of study	All study designs
Participants	Young people aged 0 to 19 years
Settings	Studies must take place in South Africa
Diagnoses	LTBI diagnosed with TST and/or IGRAs
Outcome measures	Prevalence rate at 95% CI
	Odd ratio (OR) for risk factors at 95% CI
Results	Prevalence and risk factors

Study quality and critical appraisal

We rated the study qualities by scoring them using the quality assessment checklist for prevalent studies adapted from (14). The scores ranged as follows: low risk (≤5), moderate risk (6-8) and high risk (>8). The scoring was independently done by the two reviewers and reconciliations were made afterward by the third reviewer. Articles that met the eligibility criteria were carefully selected to avoid potential bias and sensitivity analyses were carried out to check for causes of heterogeneity observed in the selected studies.

Quality assurance

We expected possible biases to arise from the following: publication, selection, misclassification, and confounding. To minimize these biases, we employed the following measures:

1. In case-control studies, we watched out for selection bias by checking if the same method was used to select the LTBI cases and the controls (LTBI negative) and if both arms came from the same study population. Only the articles that did not have selection bias were included in the review.

2. We only included longitudinal studies that used proper methods to determine the absence of LTBI before the study began and after a follow-up period and studies that selected exposure group with respect to their likelihood of acquiring LTBI.

3. We checked the comparability of the groups being compared to minimize confounding effects. Only studies with comparable baseline characteristics between the non-exposed and the exposed groups were included.

4. To avoid misclassification bias all the included studies met the quality and eligibility criteria.

5. Publication bias was investigated using funnel plot.

Data synthesis
We extracted the adjusted and the unadjusted prevalence rates at 95% CI and using the denominators (total number of participants); we re-calculated the numerators (cases) where they were not given. Using the numerators and the denominators, we re-generated the proportions and calculated the standard errors. We generated the constant and used the standard stata command (-vwls-) to get the inverse variance-weighted proportion. Random effect meta-analysis using metan command was used to calculate the pooled prevalence estimate across the studies at 90% CI. Only the unadjusted pooled prevalence was re-calculated using both TST and IGRAs while the adjusted prevalence was stated in the narrative review. The odd ratios at 95% CI were also presented and compared in the narrative review.

Data analysis
After we had extracted the relevant data sets, the combined estimates of the prevalence at 90% confidence interval were summed up in meta-analysis using STATA version 14. The confidence interval of 90% was used to accommodate little inconsistencies among the selected studies. We investigated the trend of LTBI over the study period and we compared the prevalence in the younger age group (≤ 10 years) and the adolescents (11 to 19 years) in the subgroup analysis.

Subgroup analysis
We carried out further investigation on heterogeneity using subgroup analysis of the studies classified into various groups. Examples of subgroup analysis that were performed include plotting and comparing results of different quality scores to ascertain how they vary from the overall results and assessing if different study designs and the settings used have effects on meta-analysis result. Studies were also analyzed based on their recruitment areas and sample size categories to check if they had an effect on the heterogeneity of the selected studies.

Assessment of heterogeneity
The extent of variation between the selected studies was accessed using I^2 heterogeneity statistic presented as percentages: ≤25% (low), 26%-50% (moderate), 51%-75% (significant) and 76% -100% (substantial). Using the forest plot, overlapped confidence intervals signified a non statistical significant difference in the prevalence of the selected studies. Poor overlaps of CIs or I^2 statistic ≥50% indicate significant heterogeneity. Where heterogeneity was significant, we performed subgroup analysis to investigate the causes of heterogeneity.

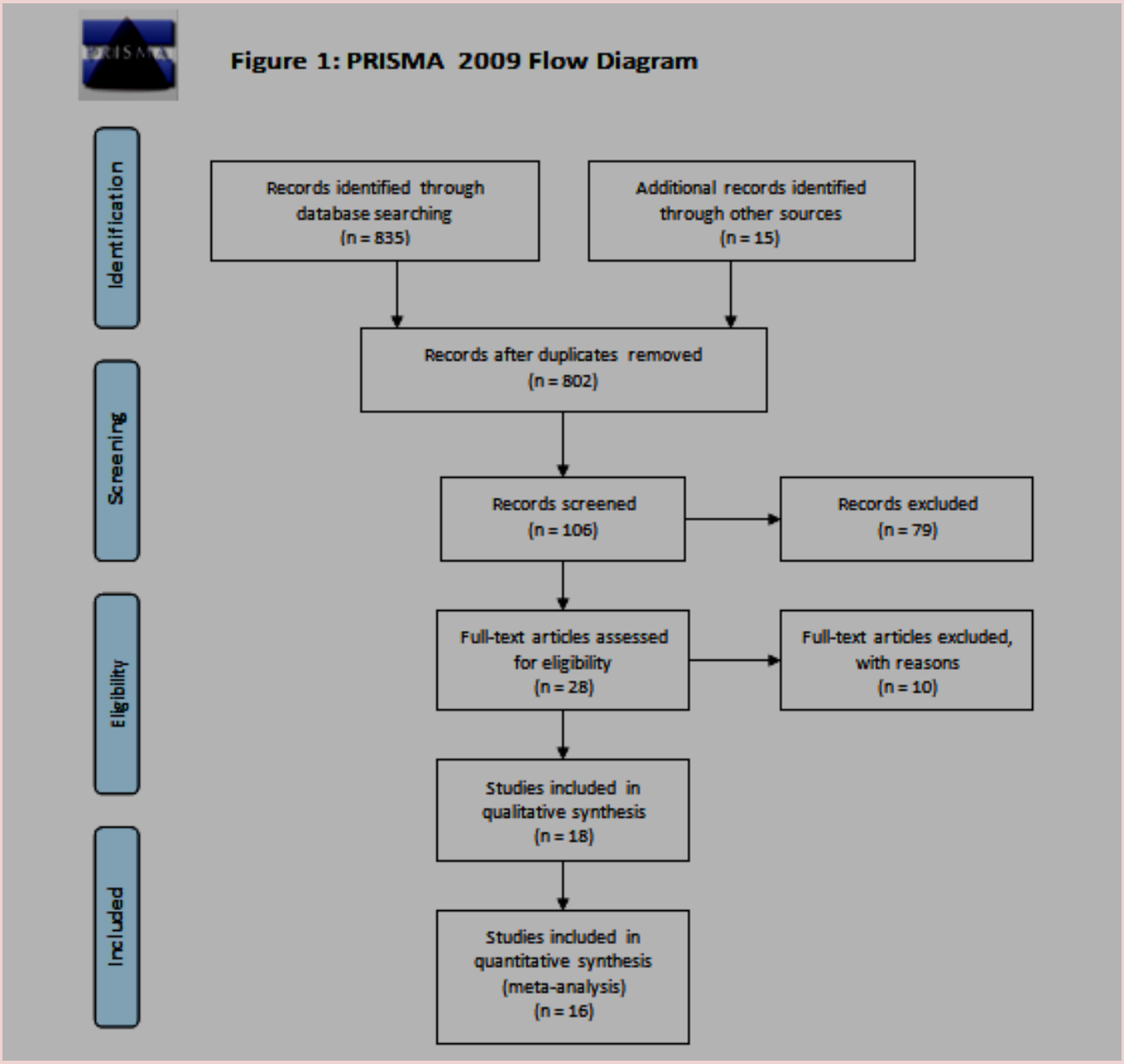
Approach to missing data
We wrote the corresponding authors requesting for information on the missing data. Only a few authors responded accordingly. However, no study was excluded on the basis of missing data.

RESULT

Study flow:

Figure 1 displays the study flow from the search result. We identified a total of 850 studies through databases (n=835) and other sources (n=15). We excluded 48 studies which were identified as having duplicates and screened 802 studies in the first phase. Of the total studies screened, 696 studies did not meet our desired title and abstract in the first screening. A total of 106 studies were screened in the second phase and 28 articles qualified for full-text eligibility assessments of which 10 studies were excluded with reasons. Of the remaining studies, 18 were included in the quantitative synthesis and 16 in the quantitative synthesis (meta-analysis).

Figure 1:



Summary of included studies:

Studies included in this review comprised of 18 peer-reviewed journals; 15 of which were conducted in Western Cape Province and 3 in Gauteng, precisely Soweto (n=2) and Northern Johannesburg (n=1). The bulk of the studies carried out in Western Cape were conducted in Cape Town (n=14) and only one in Worcester. Twelve of the studies measured LTBI by TST only; six by both TST and IGRAs and none measured by IGRAs only.

Two study designs were identified from the 16 studies included in the quantitative synthesis: cross-sectional (n=11) and longitudinal/cohort (n=5). Sample sizes ranged from 169 participants to 49,835 participants aged 0 to 20 years except for one study (15) that categorized age 18 to 22 years together; however, this was not included in the analysis. Some

of the studies were carried out in residential plots (households, n=7), schools (n=7), hospitals (n=2) and Epidemiological research sites (n=2). Mostly, random selection methods were used for the sampling of the households that participated in the studies.

Most of the studies were conducted in urban communities and township settlements with one study in a peri-urban area. Basically, all the settings were classified as impoverished South African settings with high TB and HIV prevalence. All the studies were conducted in only two provinces of South Africa and covered mainly the black populations. Population description of the participants cut across the relevant demographic variables (age and sex).

Table 3 **Summary of the included studies:**

STUDY			METHOD				
S/N	**Author/year of publication**	**Setting**	**Design**	**Sample size**	**Study age**	**Recruitment areas**	**Population description**
1	Shanaube et al, 2009	Western Cape	Cross-sectional	49,835	6 to 11 yrs	Schools	School children in both urban and rural communities
2	den Boon et al, 2007	Cape Town	Cross-sectional	1344	< 15 yrs	Residences	Children from low-income suburbs
3	Wood et al, 2010	Cape Town	Cross-sectional survey	832	5 to 20 yrs	Residences	Healthy school attendees from crowded townships rated among the townships with the highest prevalence of TB and HIV in the world
4	Middelkoop et al, 2014	Western Cape	Retrospective geographic analysis	1100	5 to ≥ 15 yrs	Schools	Children from crowded peri-urban township
5	Mandalakas et al, 2013	Cape Town	Cohort	247	3 Months to 15 yrs	Hospital	Children from impoverished urban communities presenting for out-patient care at Tygerberg Children Hospital
6	Preez, 2011	Cape Town	Cross-sectional	199	3 Months to 15yrs	Residences	Healthy South African children from impoverished urban communities
7	Middelkoop et al. 2011	Western Cape	Cross-sectional	820	13-22 yrs	Schools	Secondary school learners in a high HIV and TB prevalence community
8	Obihara et al, 2005	Cape Town	Cross-sectional	337	6-14 yrs	Epidemiological research site	Children from poor urban community
9	Shah et al, 2011	Soweto	prospective longitudinal	263	≥6 Months to ≤ 16 yrs	Residences	Children with adult household TB contact
10	Obihara et al, 2006	Cape Town	Cross-sectional	841	6 to 14 yrs	Epidemiological research site	Children from randomly selected households in Poor communities
11	Kritzingeret al, 2009	Cape Town	Longitudinal	1954	6 to 9 yrs	Schools	Children from all primary schools in the study setting
12	Mandalakas et al, 2015	Cape Town	Prospective community-based	1343	6 Months to <15 yrs	Residences	Children from high TB and HIV burden settings
13	Mahomed et al, 2011	Western Cape	Prospective community-based	5244	12 to 18 yrs	Schools	Adolescents attending high schools
14	Ncayiyana et al, 2016	northern Johannesburg	A community-based survey with a random sampling	169	0–14 yrs	Residences	Children living in one of the poorest urban informal settlements, Diepsloot, Johannesburg.
15	Kasambira et al, 2011	Soweto	Cross-sectional	254	⩾6 mon - ⩽16yrs	Hospital	Children with an adult household contact with pulmonary TB
16	Middelkoop et al, 2008	Western Cape	Cross-sectional	831	5–17 yrs	School	School going children from a community experiencing increasing TB and HIV prevalence.
17	Mahomed et al, 2013	Worcester	Cross-sectional	6363	12 to 18 yrs	Schools	Adolescents attending high schools
18	Mandalakas et al, 2012	Cape Town	Cohort	536	3 Months to 15.6 yrs	Residences	Children from impoverished urban communities

Table 4 **Excluded studies with reasons**

	Authors	Title	Reasons for exclusion
1	CID, 2009	On the relationship between ages, the annual rate of infection, and prevalence of *Mycobacterium tuberculosis* in a South African township.	Correspondence: methodology is not clear
2	Mahomed et al, 2013	TB Incidence in an Adolescent Cohort in South Africa 2	Bacteriologically confirmed cases of TB
3	Marais et al, 2005	The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community.	TST cut off point ≥15mm was used
4	Mahomed et al, 2011	The Tuberculin Skin Test versus QuantiFERON TB Gold (R) in Predicting Tuberculosis Disease in an Adolescent Cohort Study in South Africa	Comparing predictive value of TST and IGRAs
5	Van Wyk et al, 2012	Tuberculosis contact investigation in a high-burden setting	Small sample size (12 children)
6	Liebeschuetz et al, 2014	Diagnosis of tuberculosis in South African children with a T-cell-based assay	TB suspects were used
7	Webb et al, 2009	High prevalence of Mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus.	Children and adolescents with type 1 diabetes
8	Lebina et al, 2015	Latent tuberculosis infection in schoolchildren and contact tracing in Matlosana North West province, South Africa	LTBI measured by neither TST nor IGRAs
9	Moyo et al, 2011	Tuberculin skin test and QuantiFERON (R) assay in young children investigated for tuberculosis in South Africa	TB suspects were used
10	stefan et al, 2010	Interferon-gamma release assays for the detection of Mycobacterium tuberculosis infection in children with cancer 2	Children with cancer

Assessment of risk of bias

The included studies were assessed for nine bias items outlined in table 5 using Hoy et al (14). Four of the bias items were not identified in any of the studies and these include the non-response and instrument bias. According to our findings, the studies controlled for non responses bias satisfactorily and the instruments used to diagnose LTBI were shown to have reliability and validity. Data were collected directly from the subject as opposed to proxies since the test for LTBI requires a diagnosis on the subjects. Other data that could have been collected from the subjects' proxies such as the socioeconomic and religious variables were not considered in answering this question.

Table 5 Percentage risk of bias items in the included studies

	List of bias items	Total	Percentage (%)
A	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	10	41.67%
B	Was the sampling frame a true or close representation of the target population?	7	29.17%
C	Was some form of random selection used to select the sample, OR, was a census undertaken?	4	16.67%
D	Was the likelihood of non-response bias minimal?	0	0%
E	Were data collected directly from the subjects (as opposed to a proxy)?	0	0%
F	Was an acceptable case definition used in the study?	1	4.17%
G	Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	0	0%
H	Was the same mode of data collection used for all subjects?	0	0%
I	Were the numerator(s) and denominator r(s) for the parameter of interest appropriate	2	8.33%
	Total	**24**	**100**

The same mode of data collection was used for all the subjects in all the studies. Acceptable case definitions were used and all studies which measured LTBI by TST used the cut off point ≥ 10 mm except for one study (16), that used 5 mm cut off point in the analysis of risk factors. Unacceptable case definitions accounted for only 4.17% bias in the included studies while subjects' selection bias accounted for 16.6%.

The study's target populations were not a close representation of the national population in most of the studies (n=10). Inappropriate sample sizes accounted for 46.67% of the bias present in the included studies. In relation to age, all the study participants were within the study age group (0-19 years) except in one study (15), where participants up to 22 years were included in the age category. In terms of sex, the studies are representative of both sexes since most of the studies did not have baseline differences between the male and the female participants. Occupation wise, most of the participants can be classified as school going children and make up the bulk of the dependent population in the settings which is evident in some of the studies being conducted in primary or secondary schools and crèches (n=7). Seven studies did not have their sampling frame as a true or close representation of the target population and this accounted for 29.17% of the bias in the included studies.

The numerators and the denominators of the parameters of interest were appropriate for most studies and contributed only 8.3% of the examined bias. Overall, we classified 17 out of the 18 included studies as having low risk and only one study as having a moderate risk with none of the studies recording high level of risk (table 6).

Table 6 **Assessment of risk of bias items in included studies**

		Risk of bias items										
	Study	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**Quality scores**	**Level of Risk**
1	Shanaube et al, 2009	0	0	0	0	0	0	0	0	0	0	Low
2	den Boon et al, 2007	0	0	0	0	0	0	0	0	0	0	Low
3	Wood et al, 2010	1	0	0	0	0	0	0	0	0	1	Low
4	Middelkoop et al, 2014	0	0	1	0	0	0	0	0	0	1	Low
5	Mandalakas et al, 2013	1	1	1	0	0	0	0	0	0	3	Low
6	Preez, 2011	1	1	0	0	0	0	0	0	0	2	Low
7	Middelkoop et al, 2011	0	0	0	0	0	0	0	0	0	0	Low
8	Obihara et al, 2005	1	1	0	0	0	0	0	0	1	3	Low
9	Shah et al, 2011	1	1	1	0	0	0	0	0	0	3	Low
10	Obihara et al, 2006	1	0	0	0	0	0	0	0	0	1	Low
11	Kritzingeret al, 2009	1	0	0	0	0	0	0	0	0	1	Low
12	Mandalakas et al, 2015	0	0	0	0	0	0	0	0	0	0	Low
13	Mahomed et al, 2011	0	0	0	0	0	0	0	0	0	0	Low
14	Ncayiyana et al, 2016	1	1	0	0	0	1	0	0	0	3	Low
15	Kasambira et al, 2011	1	1	1	0	0	0	0	0	1	4	Moderate
16	Middelkoop et al, 2008	0	0	0	0	0	0	0	0	0	0	Low
17	Mahomed et al, 2013	0	0	0	0	0	0	0	0	0	0	Low
18	Mandalakas et al, 2012	1	1	0	0	1	0	0	0	0	2	Low

Figure 2 represents the chart for the percentage risk of bias as presented and narrated above. The bias with the most risk in the included study is ‘A’ representing the question: was the study’s target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation? Most of the studies used inadequate sample sizes which were not close to the study population at the study setting even though there was no much difference in the baseline characteristics in relation to age, sex, and occupation. ‘B’ accounted for the second highest in the study and it sought to know if the sampling frames were the true or close representation of the target population? ‘C’ accounted for the third most biased item and D, E, G and H accounted for 0% each.

Figure 2: Percentage risk of bias items in the included studies

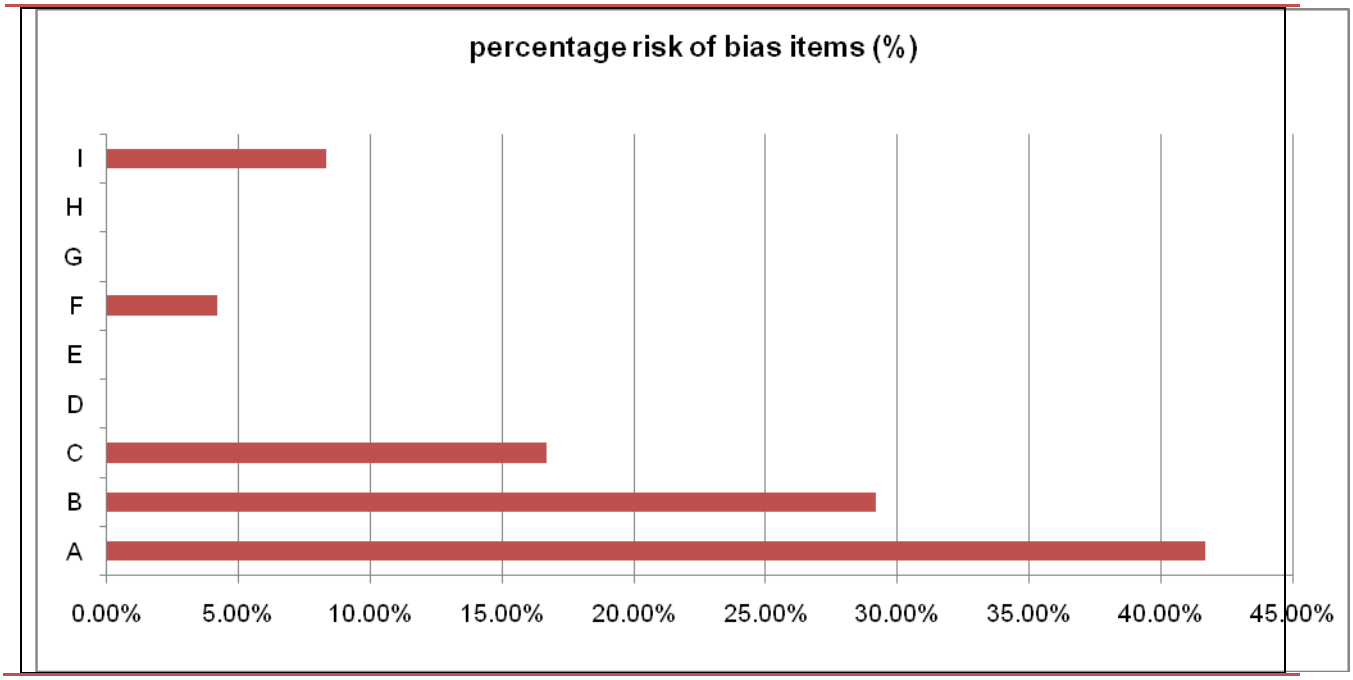


Table 7 **Results extracted on prevalence of LTBI**

STUDY		TST (cut off ≥ 10mm)				IGRAs	
S/N	**Author/year of publication**	**Sample size**	**TST+**	**Prevalence (95% CI)**		**Sample size**	**Prevalence (95% CI)**
				Unadjusted	**Adjusted**		**Unadjusted**
1	Shanaube et al, 2009	49,835	15199	30.3 (22.6–38)	30.5(22.9-38.2)		
2	den BOON et al, 2007	1344	430	32			
				Prevalence by age category			
3	Wood et al, 2010	832		28.0 (24.1–32.3)	5-10 yrs		
				41.7 (37.2–46.3)	11-15 yrs		
				65.7 (56.0–74.2)	16-20 yrs		
4	Middelkoop et al, 2014	1100	484		44		
				Prevalence by age category			
				5-9 yrs	29		
				10-14 yrs	41		
				≥15 yrs	54		
5	Mandalakas et al, 2013	247	84	34		228	25
6	Preez, 2011	199	99	49.5			
7	Middelkoop et al. 2011	820	365	44.5			
				Prevalence by Age category			
				28	5-9 yrs		
				42.4	10-14 yrs		
				50.6	15-17 yrs		
				58.8	18-22 yrs		
				Prevalence by gender			
				47.8	Male		
				41.8	Female		
8	Obihara et al, 2005	337	179	53			
9	Shah et al, 2011	263	70	27(21-32)			
10	Obihara et al, 2006	841	328	38.9			
11	Kritzingeret al, 2009	1954	565	28.9 (27.0–30.9)			
12	Mandalakas et al, 2015	1343	536	39.9		1343	41.2
13	Mahomed et al, 2011	5244	2213	42.2 (40.9–43.6)		5244	50.9 (49.5–52.2)
14	Ncayiyana et al, 2016	169	32	18.8 (10.0–32.5)			
15	Kasambira et al, 2011	254	56	22 (0.17–0.28)		270	29 (24–35)
16	Middelkoop et al, 2008	831	311	37.4			
				Prevalence by age category			

				26.2	5-8 yrs		
				31.5	9-11 yrs		
				45.1	12-13 yrs		
				52.5	14-1 7yrs		
17	Mahomed et al, 2013	6363	2679	42.1		6363	53.5
18	Mandalakas et al, 2012	536	305	56.9		536	52.4

Table 8 **Results extracted on risk factors of LTBI: OR (95% CI) using TST (cut off ≥10mm)**

Author/year of publication	Age			Gender	Race
	Age category	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**		
den Boon et al, 2007	0-4	1 (Reference)	1 (Reference)		
	5-9yrs	2.11 (1.57–2.84)	2.13 (1.57–2.89)		
	10-14yrs	3.39 (2.46–4.67)	3.60 (2.59–5.00)		
Preez, 2011					1.57 (0.82–3.00)
				Adjusted OR(95% CI)	
Middelkoop et al. 2011		1.10(1.01-1.21)		M: 1(Ref)	
				F: 0.65(0.47-0.9)	
Mandalakas et al, 2015		1.01 (1.01–1.02			
Mahomed et al, 2011	>15 years	1.4 (1.3–1.6)		Female: Reference Male:1.07 (0.96–1.20)	Indian/White (reference) Mixed race: 7.96 (5.97–10.64) Black race: 8.65 (6.35–11.82)
Kasambira et al, 2011	<2	Unadjusted Reference	Adjusted Reference	Male: Reference	
	2–5	1.9 (0.78–4.6)	1.5 (0.61–3.9)	Unadj: 1.2 (0.63–2.1)	
	6–10	1.3 (0.56–3.1)	1.2 (0.50–2.9)	Adj: 1.1 (0.57–2.0)	
	>10	2.5 (0.92–6.6)	2.4 (0.85–6.6)		
Middelkoop et al, 2008			1.19 (1.12– 1.25)		

	presence of BCG Scares	**HIV status**	**Exposure to TB**	**Years of parent's education**
den Boon et al, 2007			Unadj: 2.20 (1.63–2.96	
			Adj: 2.01 (1.46–2.77)	
Middelkoop et al, 2014			Adjusted	
			5-9yrs: 2.0 (1.1-3.5)	
			10-14yrs: 2.4 (1.5-3.6)	
			≥15yrs: 1.4 (0.9-2.0)	
			Total: 1.9 (1.4-2.4)	
		Adjusted		
Mandalakas et al, 2013	Adj: 0.72 (0.21, 2.46)	+ve: 1.04 (0.93, 1.16)	Unadj: 1.18 (1.04, 1.35)	
		_ve: 1.23 (1.08, 1.40)	Adj: 1.14 (0.99, 1.30)	
Preez, 2011			1.07 (1.01–1.13)	
		Unadjusted 0R(CI)		
Middelkoop et al. 2011		0.53 (0.27-1.05)		
Mandalakas et al, 2015	Present: reference Absent: 1.30 (0.85-1.99)	-ve: 0.99 (0.94–1.04)	1.17 (1.11–1.23)	
		+ve: 1.29 (1.07–1.57)		

Mahomed et al, 2011	Present (reference) Abscent:0.86 (0.75–0.99)		No (reference) 2.52 (2.20–2.88)	Yes:	Maternal highest education level ⩽ primary school: 2.49 (2.15–2.84)
					Paternal highest education level ⩽ primary school: 2.38 (1.97–2.87)
Kasambira et al, 2011	Present (reference)	-ve: Reference			
	Absent: Unadjusted: 2.6 (0.35–19)	Unadjusted: +ve: 1.0 (0.3–3.5)			
	Adjusted: 1.9 (0.25–15.1)	Adjusted: +ve: 1.1 (0.30–4.4)			

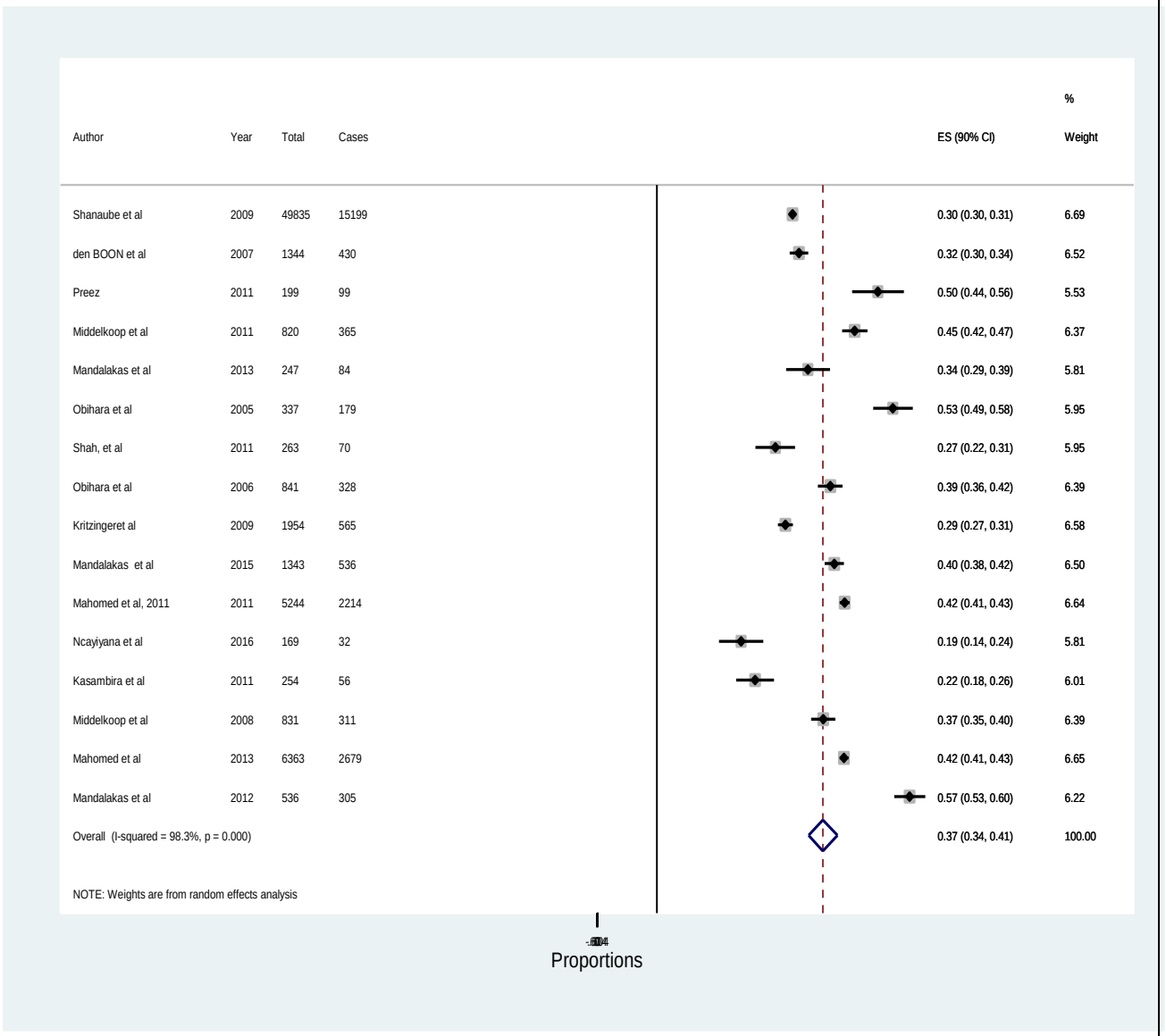
	Parental income	**Density of household**
Preez, 2011		0.96 (0.88–1.04)
Mahomed et al, 2011	>ZAR4000(reference) ⩽ZAR4000/month: 3.40 (2.91–3.97)	

Meta-analysis of prevalence using TST ≥ 10 mm

Overall prevalence

Figure 3 sums up the overall prevalence as presented by the selected studies. The graph includes the individual study prevalence, the Wald confidence intervals, the I^2 statistic and the overall pooled prevalence at 90% CIs. Using TST, this review found the overall pooled prevalence of LTBI to be 37% (90% CI: 34%, 41%). The I^2 statistic which describes the extent of variation due to inter-study heterogeneity shows a very high level of heterogeneity (98.3%, $p< 0.001$) among the studies. This result does not support the pooling of all the studies into one pooled measure and hence, subgroup analyses were carried out by stratifying the studies into subgroups to further investigate heterogeneity.

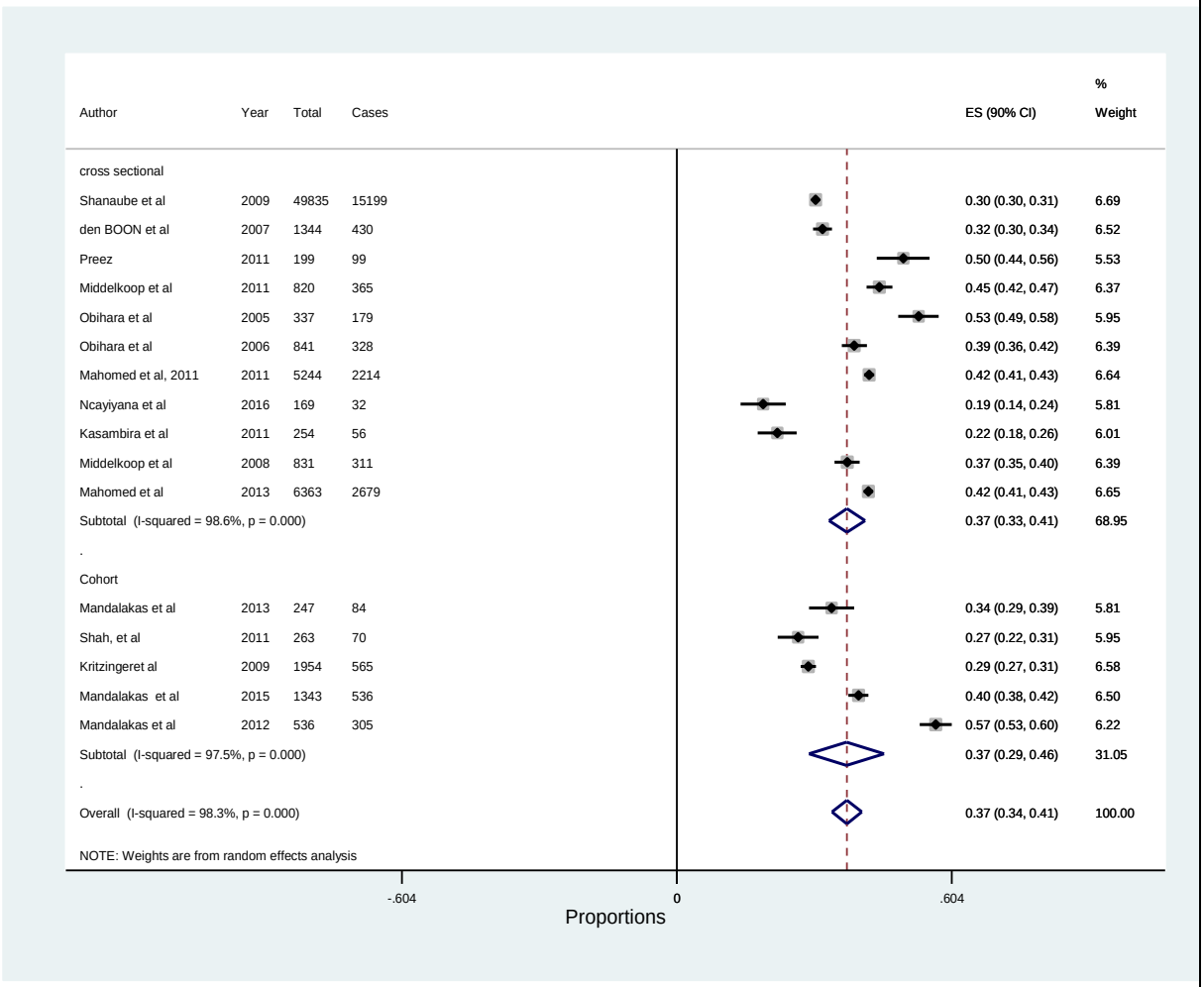
Figure 3 **Graph of the overall prevalence**



Prevalence stratified by study design

Studies were stratified into two groups according to their study designs: cross-sectional (n=11 studies) and longitudinal/cohort (n=5 studies). The pooled prevalence was the same for the groups (37%) with the cross-sectional design having a narrower confidence interval (90% CI: 33%, 41%) compared to the cohort group with confidence interval of 29% to 46%. The overlap of the two CIs shows that there is no statistical difference between the two study designs. However, both groups recorded very high heterogeneity statistic (I^2 = 98.6% and 97.5% for cross-sectional and cohort respectively and P<0.001).

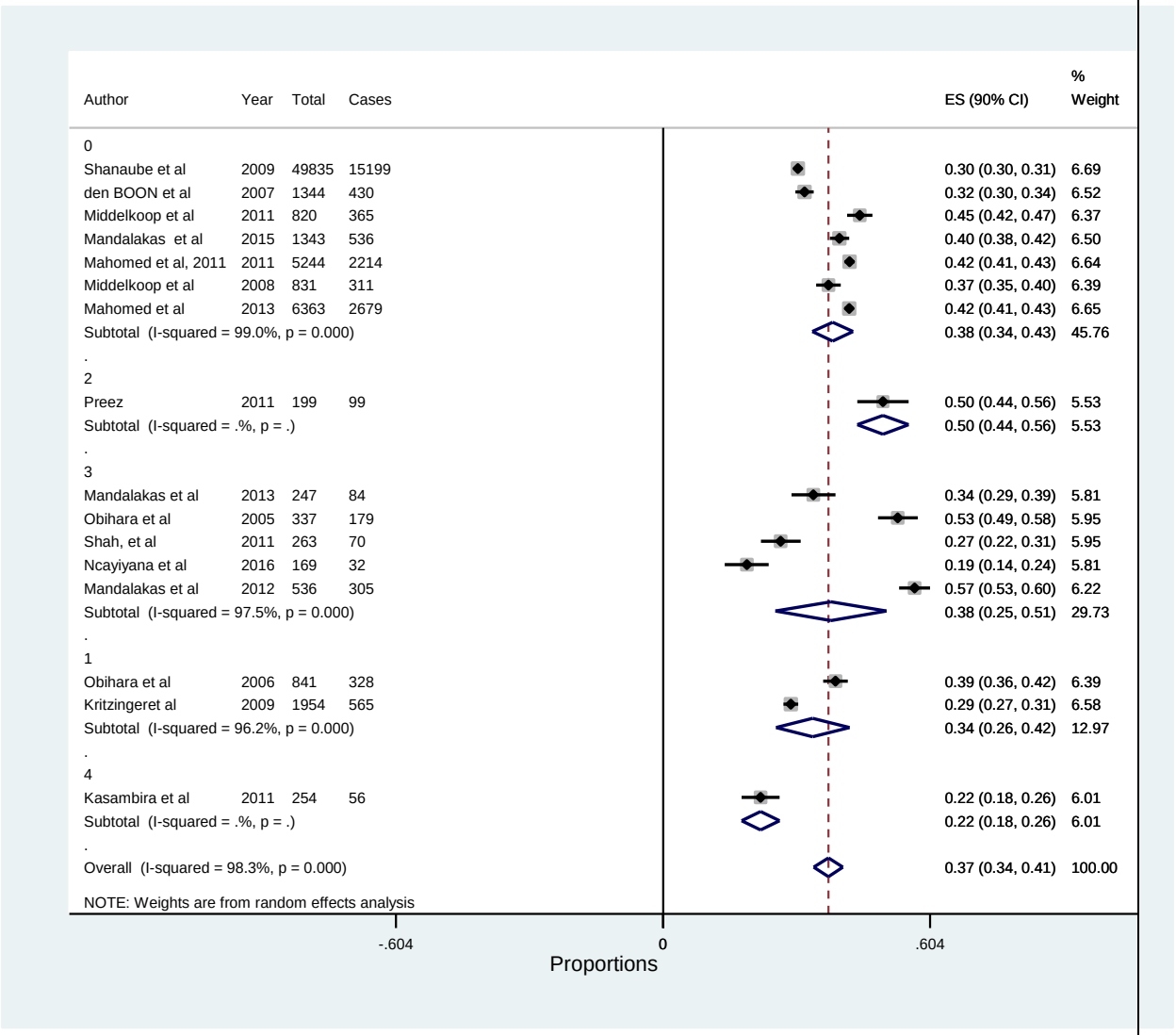
Figure 4 Graph of the prevalence stratified by study design



Prevalence stratified by the quality scores

All the studies recorded low level of bias with the exception of one (17) which recorded moderate level in the quality assessment scores. Due to lack of many groups in this category, the studies were therefore stratified into five groups according to their quality scores. The groups that scored '0', '3' and '1' have overlapped CIs indicating no statistically significant differences in the three groups while groups that scored '2' and '4' are statistically different from each other and from the rest of the groups. All the five groups recorded substantial heterogeneity with I^2 ranging from 96% to 99% and P< 0.001.

Figure 5 Graph of the prevalence stratified by quality scores

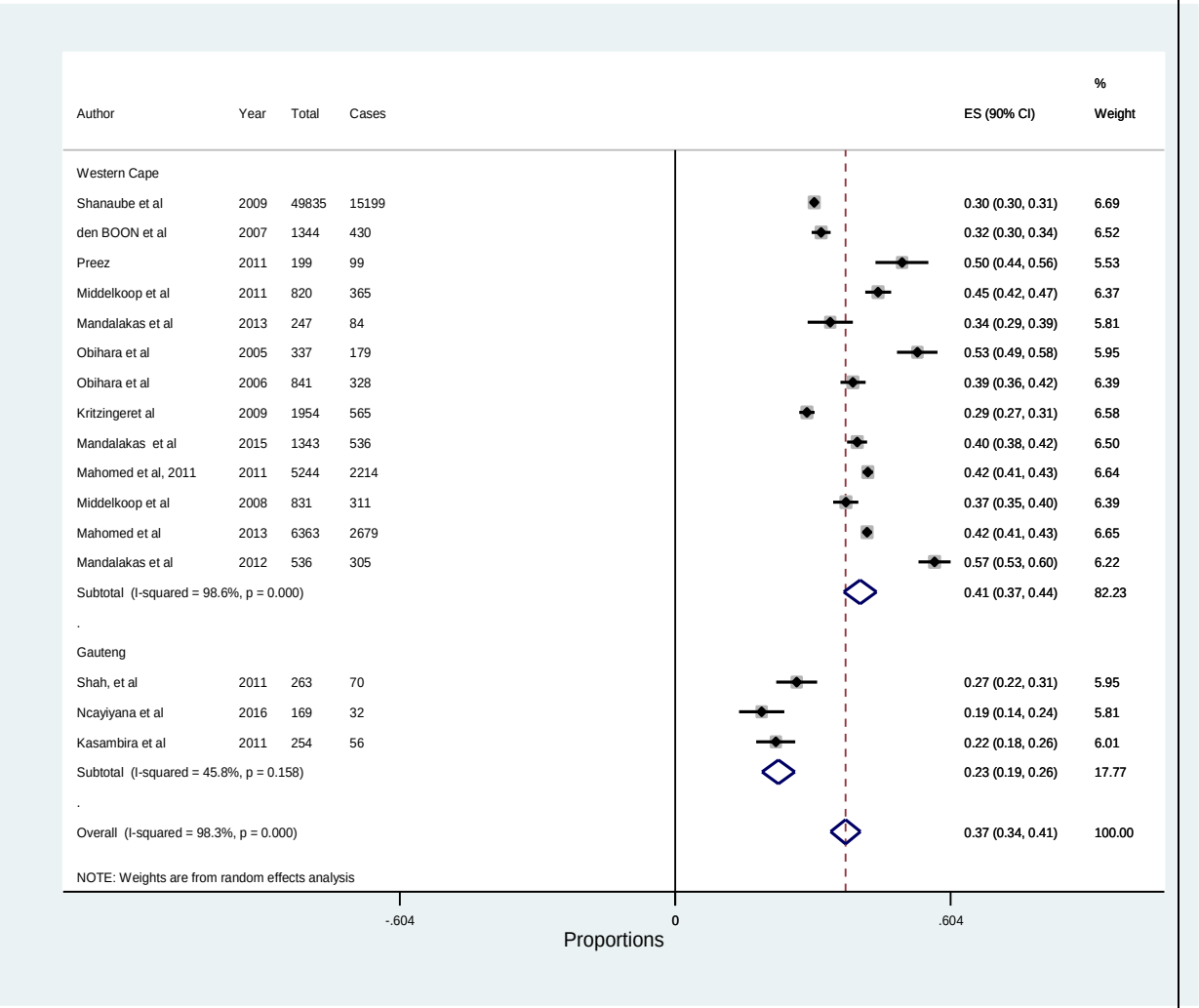


Prevalence stratified by province (the study setting):

The studies were stratified into two provinces according to their settings: Majority of the studies were conducted in Western Cape Province (n=13) while a few were carried out in Gauteng (n=3). Studies in Western Cape recorded a higher pooled prevalence of 41% (90% CI: 37%, 44%) compared to a pooled prevalence of 23% (90% CI: 19%, 26%) recorded by the studies in Gauteng. There is a statistically significant difference in the studies carried out in both provinces. Studies conducted in Western Cape showed a substantial heterogeneity within the group (I^2=98.6% and p< 0.001) but those carried out in Gauteng recorded medium heterogeneity (I^2 of 45.8% and p-value = 0.158).

However, it is important to note that the studies in Gauteng used very small sample sizes and the pooled prevalence might be misleading due to the poor coverage of the study population. On the other hand, this could be a very good hint that points to the fact that prevalence of LTBI is much lower among the young people in Gauteng compared to the young people in Western Cape.

Figure 6 Graph of the prevalence stratified by Province

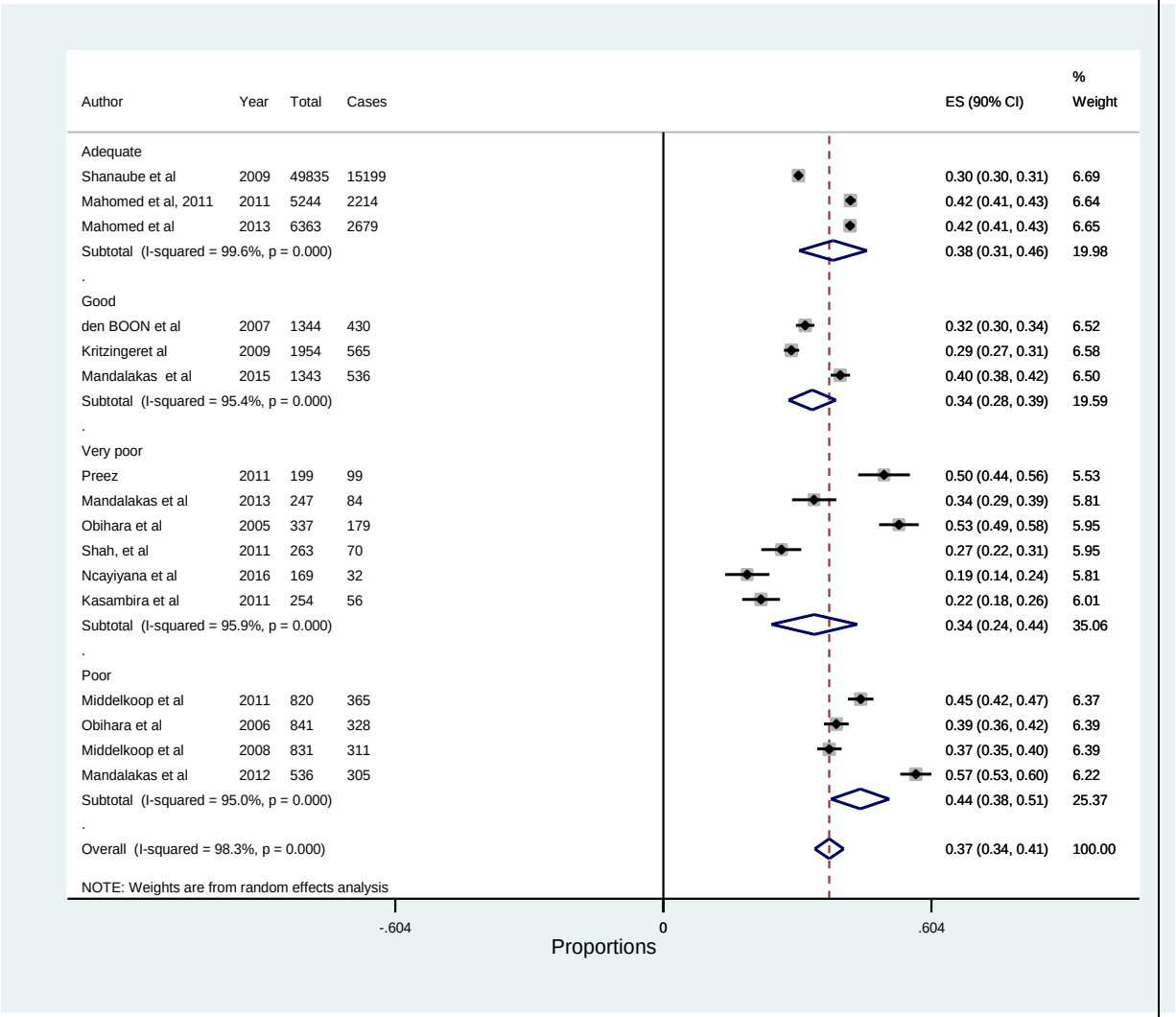


Prevalence stratified by sample size

Sample sizes of the included studies were categorized into four groups according to the levels to which they were considered to cover the target population in the study settings. The groups are as follows: adequate (≥ 5000), good (1000 to <5000), poor (500 to < 1000) very poor (<500).

Studies with adequate sample sizes recorded a pooled prevalence of 38% (90% CI: 31%, 46%). Studies classified as having good and very poor sample size levels recorded the same and the lowest pooled prevalence of 34% (90% CIs: 28%, 39% and 24%, 44% respectively) which indicates an overlap and no significant difference between the two groups. However, the category with poor sample sizes recorded the highest pooled prevalence of 44% (90% CI: 38%, 51%). The subtotal I^2 statistic for each group shows substantial heterogeneity with I^2 ranging from 95% to 99.6%, p<0.001. The levels of sample sizes used could not explain the heterogeneity observed among the identified studies. Therefore, the huge difference in the pooled prevalence noted by the provinces cannot be attributed to differences in the sample sizes.

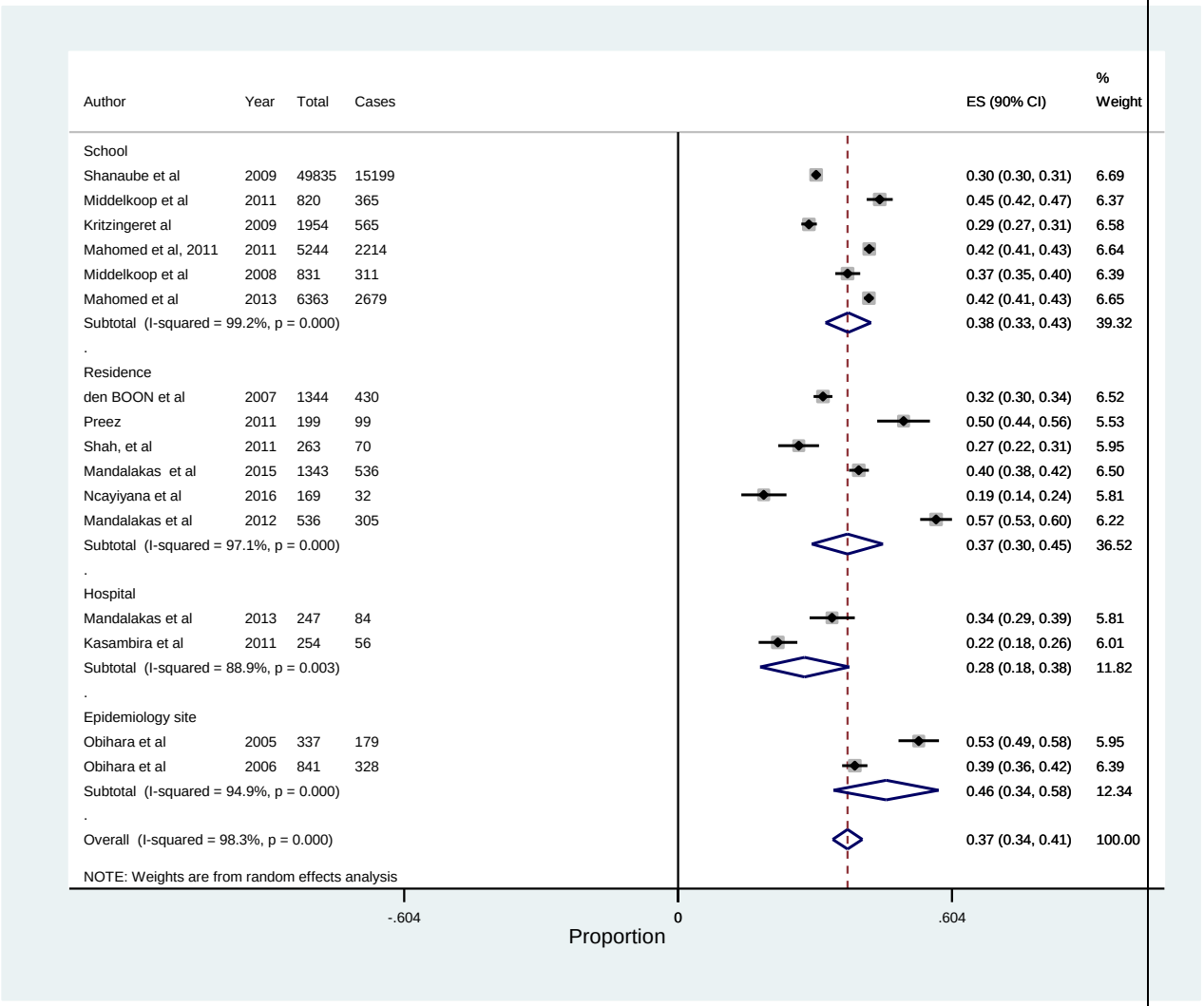
Figure 7 Graph of the prevalence stratified by sample size category



Prevalence stratified by the recruitment areas:

Studies were stratified by their recruitment areas into schools (n=6), residence (n=6), hospital (n=2), and epidemiological site (n=2). All the groups had substantial heterogeneity with I^2 ranging from 88.9% for the group conducted in the hospitals to 99.2% for the group conducted in schools. The studies conducted at epidemiological sites had the highest pooled prevalence of 46% (90%CI: 34%, 58%) while the studies carried out in the hospitals recorded the lowest prevalence of 28% (90% CI: 18%, 38%). There is no statistical difference between the groups that were carried out in the hospitals and residences.

Figure 8 Graph of the prevalence stratified by recruitment area



Prevalence stratified by age category

The data extracted on the prevalence of LTBI classified by age categories were not clear enough to analyze the influence of age group on the heterogeneity. Authors classified age groups based on convenience and not by the Standard International Age Classifications recommended by the United Nations (18). However, (15) and (19) had similar age categorization, but while one recorded the unadjusted prevalence, the other recorded the adjusted prevalence. For this reason, we could not combine the two studies to determine the age-specific pooled prevalence. Nevertheless, the two studies showed much similarity in the prevalence across the age categories as presented below:

Age 5-9 recorded the unadjusted prevalence of 28% and the adjusted prevalence of 29% in 2011 and 2014 respectively (15,19). Age group 10-14 years recorded the unadjusted prevalence of 42.4% and the adjusted prevalence of 41% in 2011 and 2014 respectively while age 15-17 years recorded the unadjusted prevalence of 50.6% in 2011 and age greater than 15 years recorded the adjusted prevalence of 54% in 2014 (15,19). Age group 18-22 years had the highest recorded prevalence of 58.8% in 2011 (15).

Prevalence stratified by Gender

From the selected studies, only (15) measured the prevalence of LTBI by the participants' gender. Therefore, there are not enough data to determine the effect of gender on the heterogeneity of the studies. The study recorded a higher prevalence of 47.8% in male and a lower prevalence of 41.8% in their female counterpart.

Prevalence stratified by the study year

Some of the studies were carried out over a long period of time making it difficult to determine the actual year that LTBI was screened in the participants.

Other factors

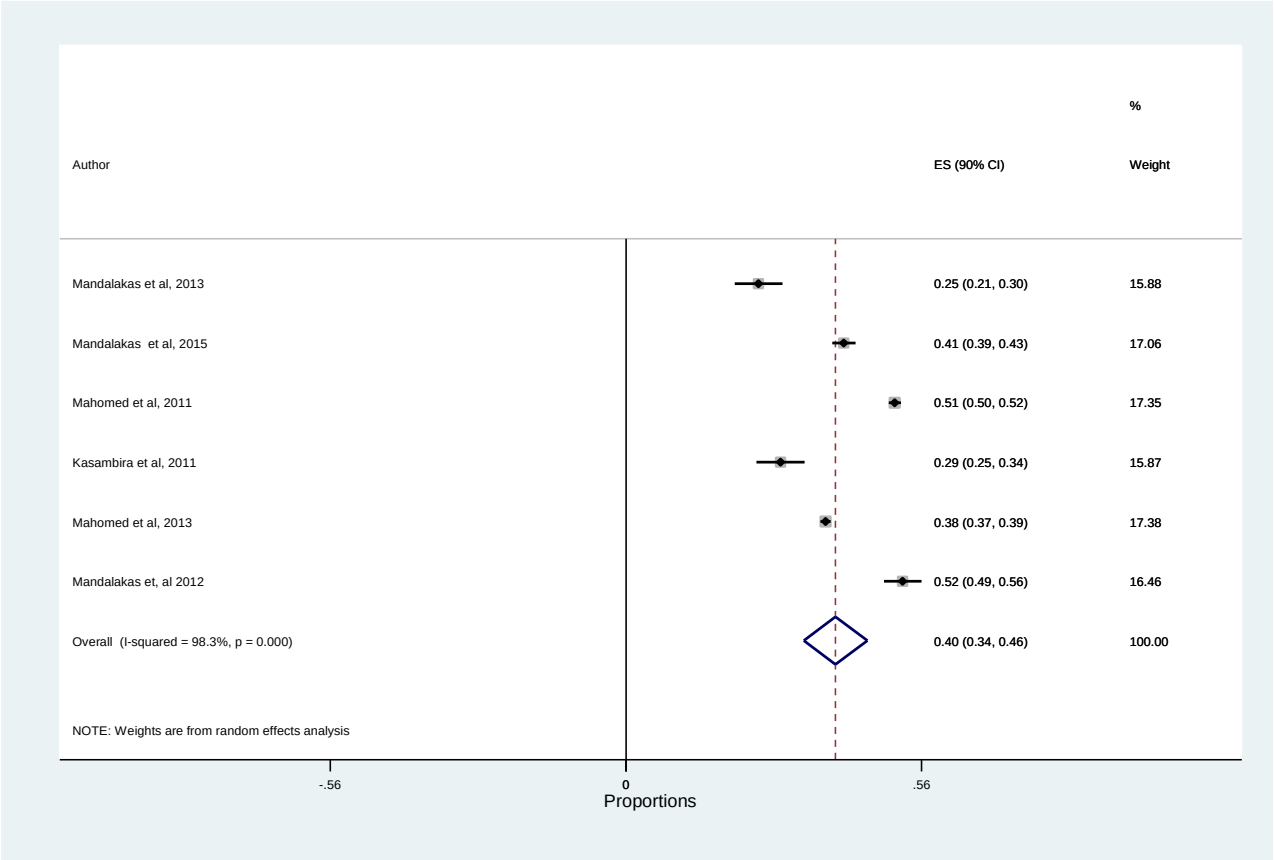
We did not find prevalence data on other factors such as the socioeconomic and household level factors.

Meta-analysis of prevalence using IGRAs:

Overall prevalence

Six eligible studies were selected for the meta-analysis of the prevalence using IGRAs. Like other graphs above, figure 8 illustrates the overall pooled prevalence of the studies at 90% CIs, the individual study prevalence, the Wald confidence intervals and the I^2 statistic. The pooled prevalence was 40% (90% CI: 34%, 46%). Despite the fewer number of studies analyzed in this session, substantial heterogeneity (I^2 = 98.3%, $p < 0.001$) was also observed as in the case of TST.

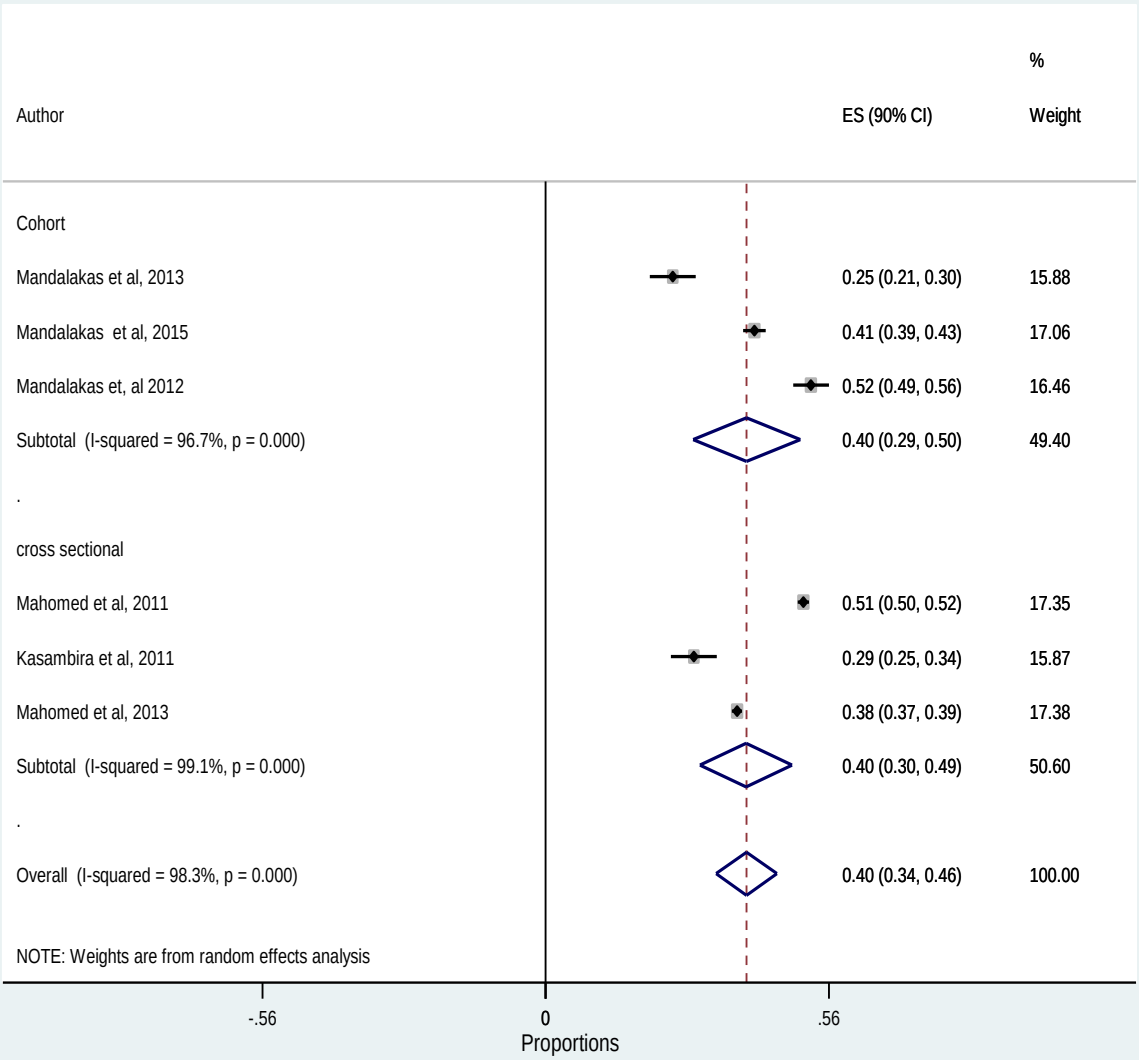
Figure 9 The overall prevalence (IGRAs)



Prevalence stratified by the study design

Figure 11 stratified the analysis by the two study designs: cross-sectional (n=3) and cohort (n=3). The two groups were very similar having the same pooled prevalence of 40% and overlapped CIs: 30%, 49% and 29%, 50% for cross-sectional and cohort respectively. Both had substantial heterogeneity and $p< 0.001$. There is no difference in the two study designs used and so they could not account for the heterogeneity in the studies.

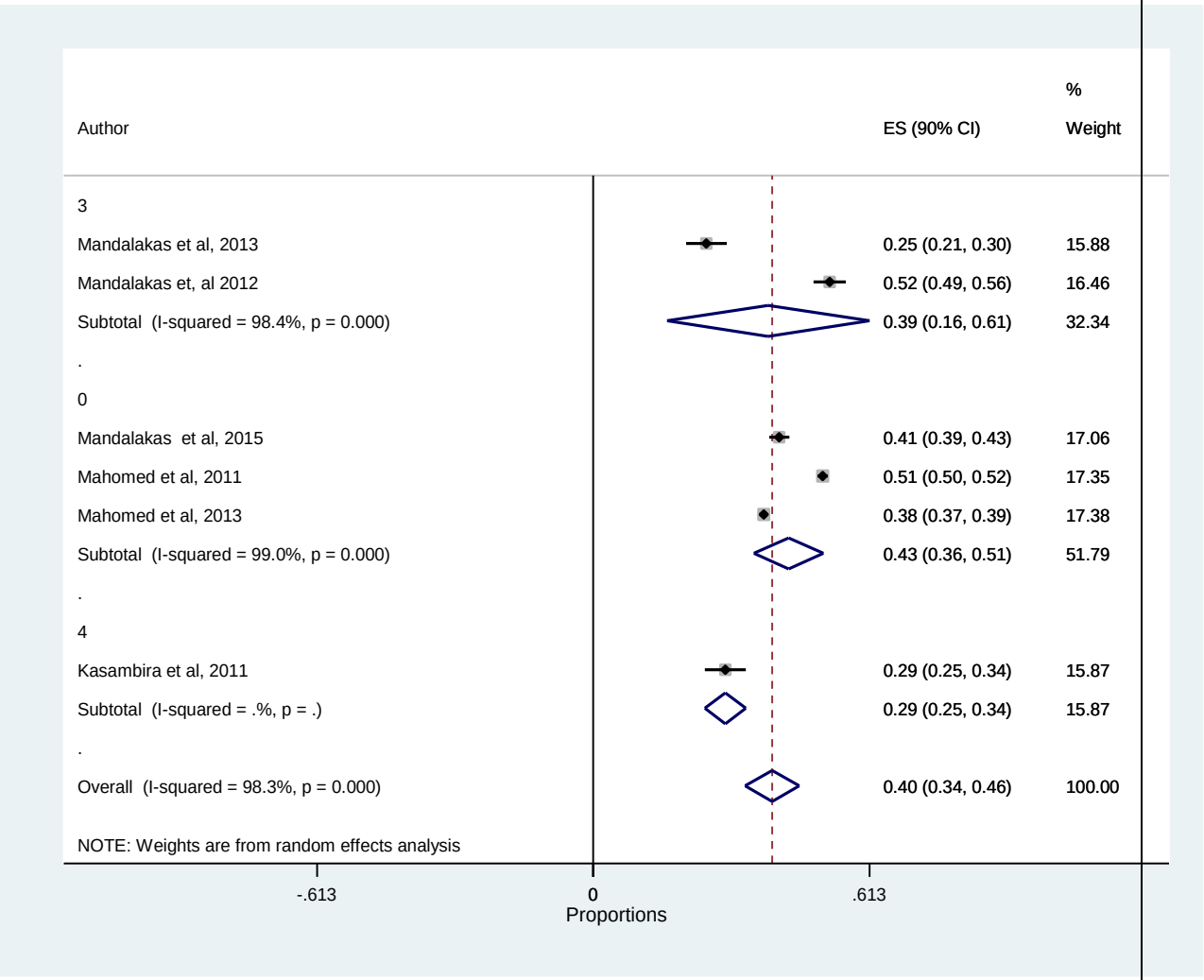
Figure 10: Graph of the prevalence stratified by study design



Prevalence stratified by the quality scores

Figure 12 shows the sensitivity analysis of the studies by their quality scores. The group which scored '0' (n=3) had the highest pooled prevalence of 43% (90% CI: 36%, 51%) followed by the group that scored '3' (n=2) with the pooled prevalence of 39% (90% CI: 16%, 61%). There is no statistical difference between the groups that scored '3' with the rest of the groups; however, there is a significant difference between the two groups that scored '0' and '4'. The heterogeneity statistic I^2 remain very high with $p<0.001$ in each group.

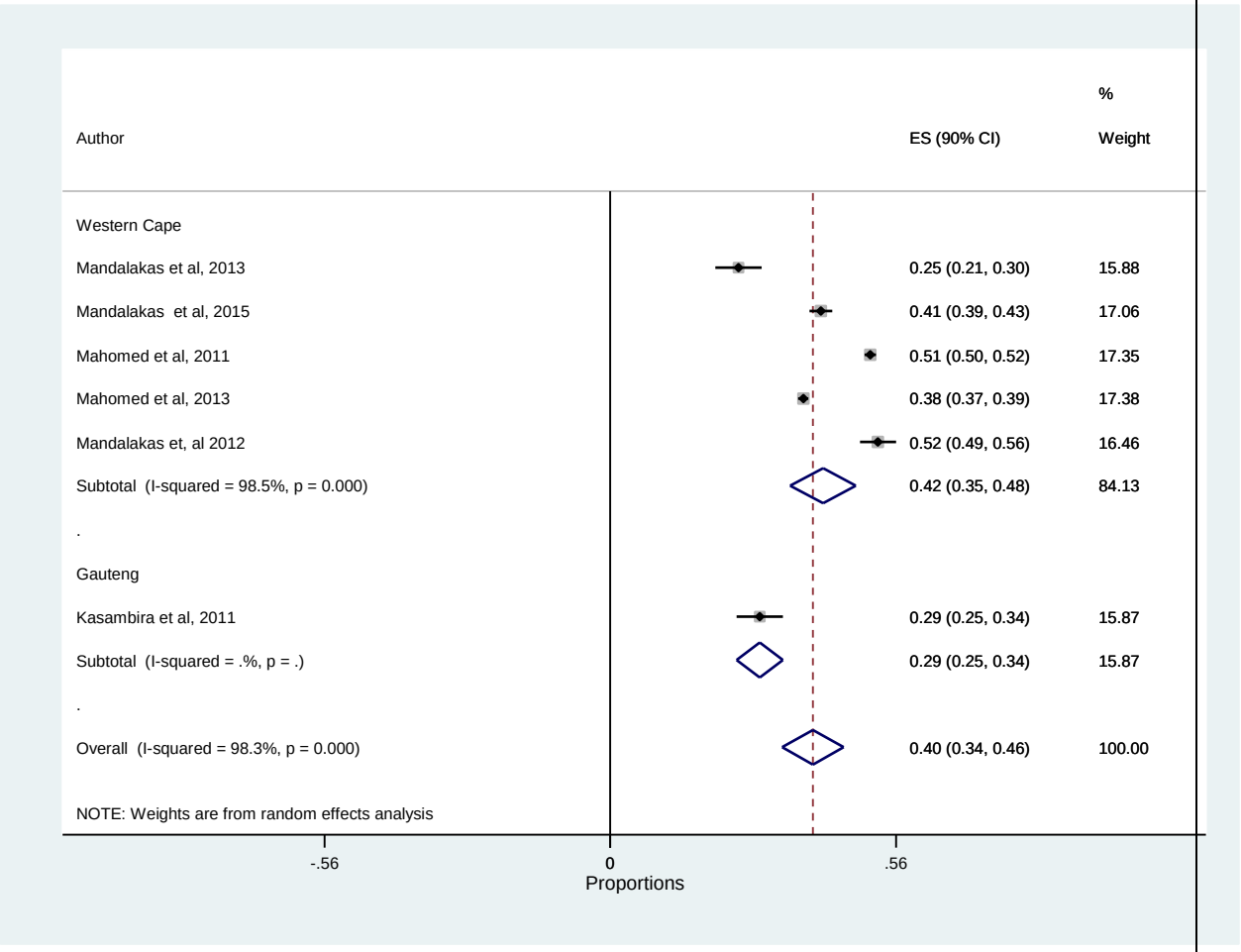
Figure 11: Graph of the prevalence stratified by quality scores



Prevalence stratified by province (the study setting)

Stratified by the study setting, there is an observed statistically significant difference between the studies carried out in Western Cape and the only study carried out in Gauteng. The studies conducted in Western Cape recorded a higher pooled prevalence of 42% (90% CI: 35%, 48%) compared to the study in Gauteng which has a prevalence of 29% (90% CI: 25%, 34%), (figure 13).

Figure 12: Graph of the prevalence stratified by Province



Other factors

There are no other available data to further explain the cause of heterogeneity among the studies.

Meta-analysis of risk factors

The available data are not adequate for the Meta analysis of the risk factors either due to lack of data for the groups or as a result of improper categorization of the groups. Nevertheless, the risk factors were presented as a narrative review in the discussion.

DISCUSSION

Prevalence

This systematic review and meta-analysis aimed to investigate the actual prevalence and the risk factors of LTBI among young people in South Africa. We found the pooled prevalence of LTBI to be 37% (90% CI: 34%, 41%) using TST and 40% (90% CI: 34%, 46%) using IGRAs. Both methods recorded substantial heterogeneity (I^2 = 98.3%, p< 0.001) and did not support pooling of the results into one group. Sub group meta-analysis showed inter study variations and could not explain causes of heterogeneity. Only two provinces of South Africa were represented in the selected studies. Western Cape Province has a higher pooled prevalence of 41% (90% CI: 37%, 44%) compared to Gauteng with pooled prevalence of 23% (90% CI: 19%, 26%). Studies conducted in Western Cape showed a substantial heterogeneity within the group (I^2=98.6% and p< 0.001) but those carried out in Gauteng recorded medium and acceptable heterogeneity (I^2=45.8%, p=0.158). There is a statistical significant difference in the studies carried out in both provinces. Due to the substantial heterogeneity observed in the studies, we further present this study as a narrative review.

In 2010, the study by Wood et al (6), carried out in a poor township setting of Cape Town among healthy children and adolescents who were HIV negative estimated a prevalence of 28.0% (95% CI: 24.1, 32.3) in the age group 5-10 years representing about one third of the group (6). About half of the adolescents aged 11-15 years were shown to have LTBI prevalence of 41.7% (95% CI: 37.2, 46.3) and 65.7% (95% CI: 56.0, 74.2) in the age group 16-20 years old which is a two-thirds of the age category (6). These indicate that the prevalence of LTBI increases with increase in age category among healthy South African children. This observation was established to be true in this review even though we could not illustrate it graphically due to the inappropriate categorization of age groups by authors and the mixed ages (0-20 years) used in the studies. Notwithstanding the differences in the age categorizations, the prevalence of LTBI increased significantly with increase in age category in all the selected studies that examined prevalence by age group (6,15,19,20,25). Wood et al (6) demonstrated in their study that the prevalence rate changes significantly from age 5 and peaks at age 13 but with much similarities between male and female within each age category (6). In addition, the study maintained that there has been a decrease in LTBI transmission in recent years which was indicated by the concave upward shaped transmission curve in the age group 5-15 years old.

In a retrospective geographic analysis of household contributions to TB in young South African Township Children, Middelkoop et al (19) showed that the adjusted prevalence of TST positive infection among children and adolescents in 2014 was 44% (19). This is a common finding among our selected studies and points to the fact that exposure to adult TB cases is a strong predictor of LTBI among the young people that share the same residential plots with adult TB patients. Middelkoop and associates' study was almost a confirmation of Mahomed et al (21,22) studies which recorded the prevalence of 42.2% and 42.1% in 2011 and 2013 respectively (19,21,22). The results were consistent regardless of the different study years and the fact that two different study designs with two different study samples in the same age group (12-18 years) were used (21,22).

On the other hand, the study by Du Preez and colleagues which investigated the effect of environmental tobacco smoke exposure and the risk of TB infection in children shows LTBI prevalence of 49.5% in 2011 using TST (23). Du Preez et al (23) study is one example of such studies which demonstrated that about half of the adolescents in South Africa have LTBI (13,23,24).

In 2009, a cross-sectional study of children aged 6-11 years by Shanaube and associates on the annual risk of TB infection in eight South African communities with high prevalence of TB and HIV reported a total adjusted prevalence of 30.5% (95% CI: 22.9, 38.2) and the unadjusted prevalence of 30.3% (95% CI: 22.6, 38.0) (20). In general, the study showed that there is a high degree of variability in the LTBI prevalence between communities in the same region among household contacts (range: 24.8% to 42.6 %) (20). Similar to Shanaube and associates, Middlekoop et al (25) study which investigated the rate of TB transmission to children and adolescents in a South African community with high prevalence of HIV infection among adults reported a prevalence of 31.5% (25). These two studies reported almost the same prevalence in 2008 and 2009 in age groups 9-11 and 6-11 respectively. Although the total prevalence stipulated by Middlekoop and associates among children and adolescents aged 5-17 years was 37.4%, the prevalence for age category 9-11 was similar to those aged 6-11 years in Shanaube et al, (20,25). Nevertheless, it is important to note that while Shanaube and associates did not report prevalence by age categories, Middlekoop et al (25) used age categories (5-8, 9-11, 12-13, and 14-17) which are not supported by the Standard International Age Classifications (25).

Obihara et al (26), recorded a higher prevalence of 53% in 2005 in a cross-sectional study of Cape Town children aged 6-14 years (26). The high prevalence seems improbable considering the reports from 2006 and onwards but could be proper and might have resulted from improper TB intervention at the time. Another study by the same authors in 2006 reported a lower prevalence of 38.9% in children of the same age group (6-14 years) in Cape Town (27). Kritzingeret et al (28), reported even a much lower prevalence of 28.9 (95% CI: 27.0, 30.9) in a longitudinal study of children aged 6-9 years in the same Cape Town in 2006 (28). These reports demonstrate that, though the prevalence of LTBI was very high in 2005, it drastically reduced in 2006 probably due to the efficacy of the TB interventions adopted that year. A cross-sectional study of children aged 13-22 years by Middlekoop et al (15), confirmed the last report (prevalence of 28%) in a related age category (5-9 years). Webb et al, recorded slightly higher prevalence 29.8% in age < 21 years in Western Cape in 2009 (29). These reports might appear irregular but are very informative on the actual pattern of the prevalence of LTBI in the study settings over time.

Mandalakas et al (12), reported the highest prevalence (56.9%) in 2012 in children 3 months to 15.6 years in Cape Town (12). There are no other identified studies carried out in 2012 to confirm this high prevalence. Further, if Libeschuetz and associates' claim that TST sensitivity is greatly reduced in children < 36 months is true, one should expect a lower prevalence by Mandalakas study considering the study age (3 months to < 16 years). Despite the rise and fall in prevalence noted by this review, an up shoot to 57% is unclear although not disputable.

Ncayiyana et al (16), reported the lowest prevalence of 18.8% in 2016 among northern Johannesburg children aged 0-14 years (16,30). This low prevalence is also not consistent with the observed trend in our review but could be attributed to the young age of the study participants and the study setting (Northern Johannesburg). Our findings show that prevalence of LTBI is much lower in Gauteng province compared to Western Cape Province (table 6).

In general, South Africa has a much higher prevalence of LTBI among young people when compared to other African countries with high TB burden. For example, in 2015, Mumpe-Mwanja and associates reported only a prevalence of 16.1% among adolescents in Uganda (31). Although the study reported an increase in LTBI prevalence with an increase in the age

which is consistent with studies in South Africa, a total prevalence of 16.1% is far less than what is reported in South Africa. According to Kizza et al (32), a high prevalence of 36% was observed in 2015 in Kampala Uganda though among the age group 15-24 years (32). In 2010, the prevalence of LTBI was estimated to be 10.2% in a national TST survey of Kenyan children aged 6-14 years and this has been consistent for over two decades (33).

Risk factors:

Age:
From the included studies, the odds of age being a predictor of LTBI range from 1.01 (1.01–1.02) to 3.39 (2.46–4.67); and 2.13 (1.57–2.89) to 3.60 (2.59–5.00) for the unadjusted and adjusted OR respectively. Six studies investigated age as a risk factor in their studies (15,17,24,25,29,34). According to De Boon et al (34), the odds of LTBI increases with increase in age category in the study population both in the adjusted and the unadjusted models. Age 5-9 years had about two times the odds of LTBI (unadjusted OR: 2.11, 95% CI: 1.57, 2.84; adjusted OR: 2.13, 95% CI: 1.57, 2.89) compared to age 0-4 years (34). Age 10-14 years had about 3 times the odds of LTBI in the unadjusted model (OR: 3.39, 95% CI: 2.46, 4.67) and about four times the odds when adjusted for the effect of passive smoking (unadjusted OR: 3.60, 95% CI: 2.59, 5.00) compared to age 1-4 year (34). Similarly,(15,17,24) found significant association between age and LTBI among the study population (OR: 1.10, 955 CI: 1.01, 1.21; OR: 1.01, 95% CI: 1.01, 1.02; and OR: 1.4, 95% CI: 1.3, 1.6) respectively. These studies are of the same opinion with another study by Middlekoop et al (25) which reported in 2008 that age category was positively associated with TST positivity (adjusted OR=1.19; 95% CI, 1.2, 1.25; P<0.001) (25). Middelkoop and associates confirmed their previous report in another study which recorded increase in the prevalence of LTBI with the increase in age category in 2014 (15,19).

On the contrary, in the study by Kasambira et al (17), TST positivity is not associated with any age category. According to the study, there is no difference in the odds of LTBI among ages: 2-5 (unadjusted OR: 1.9, 95% CI: 0.78, 4.6); 6-10 (unadjusted OR: 1.3, 95% CI: 0.56%, 3.1%); >10 (unadjusted OR: 2.5, 95% CI: 0.92, 6.6) and <2 years (reference age) (17).

Gender:
The odds of gender being a risk factor for LTBI from the included studies range from 1.07 (0.96-1.20) to 1.1 (0.57-2.0). Three studies (15,17,24) examined the relationship between gender and LTBI. Whilst (17,24) found no association (OR: Male: 1.07, 95% CI: 0.96, 1.20 and OR: female: 1.2, 95% CI: 0.63, 2.1 respectively); (15) found that the females have a slight lower odds of LTBI compared to the males (OR: 0.65, 95% CI: 0.47, 0.9). Otherwise, no association was found between LTBI and gender within this study population.

Race:
The ranges of the included studies are 7.96 (5.97-10.64) to 8.65 (6.35-11.82) for mixed and black races respectively. Two of the selected studies (21,23) analyzed the effect of race on LTBI and had contrary views in their findings. Du Preez et al (23) recorded no significant relationship between ethnicity and LTBI in both univariate (OR: 1.54; 95% CI: 0.82, 3.00) and multivariate (OR: 0.68; 95% CI: 0.27, 1.69) analyses (23). The odds of LTBI were the same for the mixed and black races while Mahomed et al (21) recorded a higher odds in mixed race (OR: 7.96; 95% CI: 5.97, 10.64) and black race (OR: 8.65; 95% 6.35, 11.82) compared to Indian/White races (reference) (21) .

Presence of BCG Scares:

The BCG scares not being a predisposing factor to LTBI ranges from 0.86 (0.75-0.99) to 2.6 (0.35-1.9). From the four studies (17,21,24,34) which examined BCG scars; one (17,21) slightly disagreed with the findings reported by others. According to Mahomed et al (21), people with BCG scars have a slightly lower odds of LTBI (OR: 0.86; 95% CI: 0.75, 0.99) compared to people without BCG scars implying that little association exists between BCG and LTBI. Contrary to this finding, Kasambira et al (17) reported that there is no relationship between BCG and LTBI (OR: 2.6; 95% CI: 0.35, 19) (17). Concurrently, the two studies by Mandalaka et al (24,34) have similar opinion whereby, they reported no relationship between BCG scars and LTBI in 2013 and 2015 respectively (OR: 0.72, 95% CI: 0.21, 2.46 and OR: 1.30, 95% CI: 0.85, 1.99). The above three reports established Middlekoop et al (25) earlier study in 2008 which reported no significant difference in the prevalence between those with BCG scars and those without BCG scars (mean reaction indurations' sizes of 6.2 and 7.0mm respectively, P-value=0.28) (25).

HIV status:

From the selected studies, the ranges of the odds of HIV infection being a risk factor to LTBI are 0.53 (0.75-0.99) to 1.30 (0.85-1.99). Amongst the studies (15,17,24,34) in this category, Mandalakas et al (34), reported that TST is more likely to be positive in HIV uninfected individuals (OR: 1.23, 95% CI: 1.08, 1.40) than HIV infected individuals (OR: 1.04, 95% CI: 0.93, 1.16) but no difference in IGRAs positivity between the two groups (34). This observation was contradicted by the same authors in 2015 where they reported TST positivity being more likely to be positive in HIV infected persons (OR: 1.29, 95% CI: 1.07, 1.57) than the HIV uninfected persons (OR: 0.99, 95% CI: 0.94, 1.04) (24). On the other hand, the two remaining studies found no relationship between HIV status and LTBI (OR: 0.53, 95% CI: 0.27, 1.05 and OR: 1.1, 95% CI: 0.3, 3.5) (15,23).

Prior exposure to TB:

The unadjusted OR ranges from 1.18 (1.04-1.35) to 2.20 (1.63-2.96) from the included studies. According to Du Boon et al (23), those who had prior or current exposure to TB have 2 times the odds of LTBI (Unadjusted OR: 2.20; 95% CI: 1.63, 2.96) compared to those who had no exposure (23). This was supported by Middlekoop and associates which reported 2 times the odds of LTBI (adjusted OR of 1.9, 95% CI: 1.4, 2.4) in the TB exposed compared to TB non exposed individuals (24). Mahomed et al (21), reported about 3 times odds (OR: 2.52, 95% CI: 2.20, 2.88) in the same group and (23,24) reported associations between the two variables (OR: 1.07, 95% CI: 1.01, 1.13 and OR: 1.17, 95% CI: 1.11, 1.23 respectively).

Middlekoop et al (19) found associations in the age group 5-9 (AOR: 2.0; 95% CI: 1.1, 3.5) and the age group 10-14 years (AOR: 2.4, 95% CI: 1.5, 3.6) but no association in age greater than 15 years (AOR: 1.4, 95% CI: 0.9, 2.0) (19). Reasons for no association between adult TB cases in the residential plot and age 15 years and above is unknown. Nevertheless, this could probably be linked to this age group being more independent and having fewer interactions with the adults in the same residential plot.

Ncayiyana et al (15) although used TST cut off point of 5 mm, showed that those with the history of previous household TB contacts had twice the odds of LTBI compared to those with no previous household TB contact (OR = 2.33, 95 % CI: 1.03, 5.28) (15).

Mandalakas et al (34) reported an association in the unadjusted model (OR: 1.18, 95% CI: 1.04, 1.35) and no association in the adjusted model (OR: 1.14, 95% CI: 0.99, 1.30) (34).

The density of household:
Du Preez and associates found no relationship between the household membership size and the prevalence of LTBI (OR: 0.96; 95% CI: 0.88, 1.04) (23)

Year of parents' education:

Only Mohamed et al (21) found that children with parents who have no formal education or whose highest education level are primary educations had a higher odd of LTBI compared to children with parents that have more than primary education (Maternal: OR: 2.49, 95% CI: 2.15, 2.84; paternal: OR: 2.38, 95% CI: 1.97, 2.87).

Parental Income:
Mahomed et al (21) examined this relationship and found that children whose parents earned less than ZAR4000/month had about 3 times the odds of LTBI (OR: 3.40, 95% CI: 2.91, 3.97) compared to children whose parents earned greater than ZAR4000/month.

Other factors:

Other factors such as the participants' education level and type of residence as outlined in the study protocol were not examined in this review for lack of data.

In general, the strong predictors of LTBI recorded by Mumpe-Mwanja et al and associates in Uganda were consistent with the findings in South Africa. However, this review neither supports nor disproves Mumpe-Mwanja et al and other studies on the claim that HIV is not a predictor of LTBI. Going by Libeschuetz et al, TST sensitivity is greatly reduced in children who are HIV positive and this factor might have led to under-reporting of prevalence in HIV positive participants in some studies which could explain the disagreement arising from the association between LTBI and HIV in our review. Similar opinions were noted on the relationship between gender and LTBI as recorded in South Africa and other countries. Whilst some studies in other countries supported by some studies in South African observed no association between gender and LTBI, a few studies in South Africa associated female gender with a lower prevalence of LTBI. Such studies suggested that high social mixing and mode of interaction among South African males such as the inappropriate drinking habits usually observed among group of male friends predispose them to LTBI more than their female counterparts. However, in this review, the above theory did not hold considering the fact that our study population are young and have less independence for certain social mixing and interaction compared to the older populations. Therefore, most studies in this review concluded that gender is not a predictor of LTBI.

Our finding on BCG scars partly disagrees with Young et al work on risk factors associated with LTBI where the record of BCG scar was established to have a relationship with LTBI among children in Mexican American and confirmed by Mumpe-Mwanja et al among Ugandan children. We were not able to conclude on the relationship since different conclusions were drawn by different authors on the association.

The authors suggest that the huge proportion of LTBI in children and young adults were as a result of household exposure to TB cases and associated the increasing LTBI among young children with the accumulative exposure to TB due to increasing social mixing and interaction. This finding is also common among our selected studies and points to household exposure or prior exposure to TB as the strongest predictor of LTBI in the study group.

From the discussion on the parental income and level of education, we observed that low parental education and income which is synonymous with low socioeconomic status is associated with LTBI compared to higher parental education and income which is synonymous with high socioeconomic status. This could be ascribed to more social interaction and inappropriate mixing among those with a low socioeconomic status which could aid more LTBI acquisition and transmission in the group compared to those with high socioeconomic status.

Black populations have a higher prevalence of LTBI compared to White/Indian races. This finding may be explained by the poor socioeconomic setting such as overcrowding, poor housing, and pattern of mixing and interaction among the South African black community. However, most of our selected studies did not examine this variable.

Finally, the density of household was found not to be associated with LTBI in the only study which examined it in our review. We expected the opposite, whereby young people in crowded households will be more likely to have a higher prevalence of LTBI. Although this could depend on other factors such as the presence of TB in the household, this finding may call for further investigations knowing that overcrowding could be a risk factor in TB spread especially in TB endemic areas.

CONCLUSION

This review has shown that the prevalence of LTBI among young people in South Africa is not as high as some studies purport. From our meta-analysis results, we have been able to prove that not up to half (50%) of the young people in South Africa have LTBI. The prevalence of LTBI seemed to be on the decrease for sometime but gradually increases in recent years; hence this review confirms the pattern of PTB infection reported by NICDs in Cape Town area.

Regardless, available studies on this subject do not represent South Africa's national population of this study population since they were carried out in only two provinces out of the nine Provinces in South Africa. Socioeconomic markers such as race, religion, wealth indices and geographical locations were not adequately covered in the available studies and so the findings in this review cannot be generalized to the national population of young people in South Africa.

This review demonstrates that LTBI increases with increase in the age group in the study population hence making the adolescents (15-19 years) to be at the highest risk of LTBI acquisition. Adult TB contact is a very strong predictor of LTBI among young South African People; hence, TB management and interventions should be strengthened in South Africa especially the Western Cape Province. Urgent treatment of young people with LTBI particularly in Western Cape is paramount to controlling TB epidemics in South Africa to avoid conversion of this pool of LTBI to active TB.

We, therefore, recommend more screening of LTBI among this population in other provinces and across all socioeconomic variables and geographical settings in South Africa. In addition to treating and caring for active TB patients, urgent and mass treatment of LTBI should be given an immediate consideration to curb TB epidemic in South Africa.

Strengths and limitations of this review:

- To our knowledge, this review is the first systematic review conducted on the prevalence and risk factors associated with LTBI in South Africa.
- This review provided insight as to why adolescents in Western Cape Province of South Africa should be considered as a high-risk group for LTBI and should be enrolled for screening and treatment of LTBI as recommended by WHO.
- This review will encourage more studies on Systematic review and meta-analysis to investigate the alleged prevalence of LTBI among different population groups in high TB burden counties in Africa.
- Our report was guided by the Preferred Reporting Items for systematic reviews and meta-analysis (PRISMA) guidelines.
- Our review was restricted to studies written in the English language and these could have led to inexhaustibility of the available studies.
- This review was limited to only two Provinces in South Africa for lack of data in other Provinces.

- The precise location of some studies carried out in the Western Cape could not be confirmed hence, a generalised conclusion on the burden of LTBI in the Province was made.
- Data on Socioeconomic status was not sufficient to investigate heterogeneity in the study.
- There was an absence of a clear use of PICO framework in the review which may have caused some bias. Example, Shanaube et al has Zambia comparator which could have affected its method and scope with respect to other included studies.
- The study population is a broad age group with wide variations in characteristics that could result to diverse risk factors of LTBI that are logically conflicting.

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APPENDICIES:

Appendix A: Additional figures and tables

Figure 13: Funnel plot of the selected studies indicating asymmetry and publication bias.

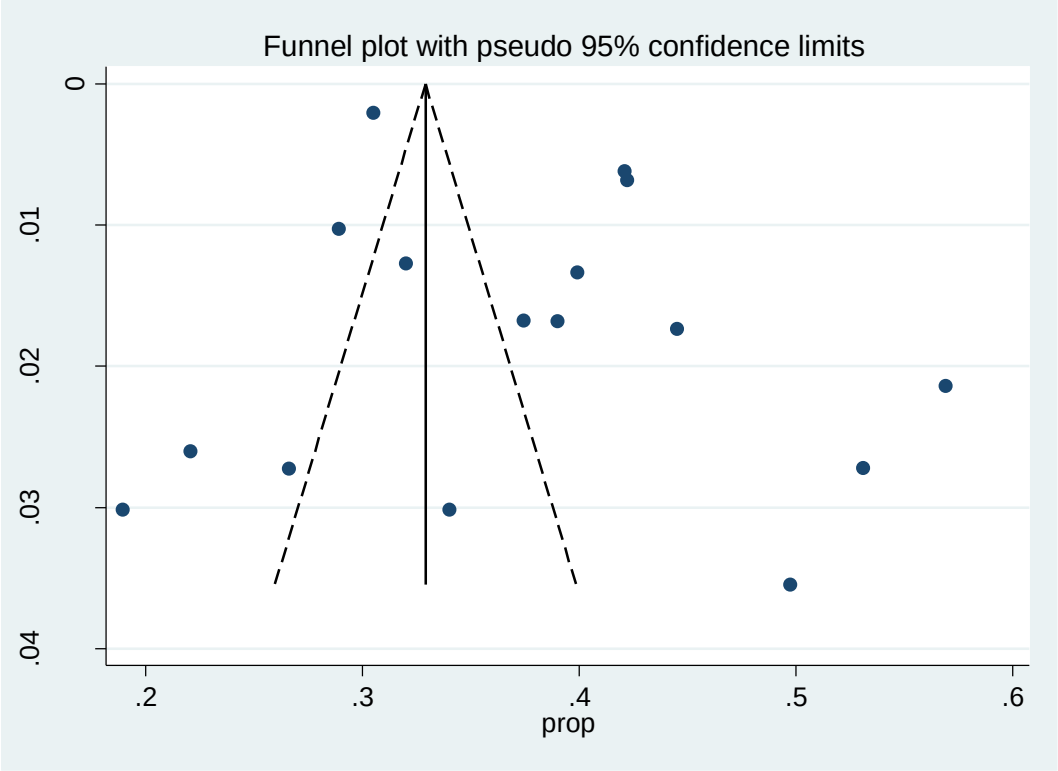


Table 9: Screening Form 1

List of identified studies	Topic *Passed*=√ *Failed=X*	Abstract *Passed*=√ *Failed=X*	Study population *Passed*=√ *Failed=X*	Study setting *Passed*=√ *Failed=X*	Included	Excluded	Reasons for exclusion	Pending
							1. 2.	

Do not proceed if excluded/pending.

Table 10 Screening form 2

Study ID
Title
Author(s) /year of publication
Outcome measured

Prevalence?	Yes
	No
If Yes: Diagnostic method used	TST (≥ 10 mm)
	IGRAs
	Both TST and IGRAs
	None of the above
Risk Factors?	Yes
	No

1. Included **2. Excluded** **3. Uncertain**

REASONS:
1. 1.
2. 2.

Do not proceed if excluded

Table 11 Data extraction form

Study ID
Title
Author(s) /year of publication
METHODS
Setting
Design
Sample Size
Age
Population description
MEASURES OF EFFECT

TST ≥ 10 mm Prevalence (95% CI)		IGRAs Prevalence (95%)		Risk Factors: OR (95% CI)
Adjusted	Unadjusted	Adjusted	Unadjusted	

Comment(s):

Name of the reviewer:

Supplements:

Table 12: Quality Assessment checklist for prevalence studies (adapted from Hoy et al [19)

Name of author(s): Year of publication: Study title:		
	Risk of bias items	**Risk of bias levels**
1	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population.
		No (HIGH RISK): The study's target population was clearly NOT representative of the national population
2	Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population.
		No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population
3	Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).
		No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.
4	Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders
		No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant responders and non-demographic characteristics between responders
5	Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.
		No (HIGH RISK): In some instances, data were collected from a proxy.
6	Was an acceptable case definition used in the study?	**Yes (LOW RISK):** An acceptable case definition was used.
		No (HIGH RISK): An acceptable case definition was NOT used
7	Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re-test, piloting, validation in a previous study, etc.
		No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary)

8	Was the same mode of data collection used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects	0
		No (HIGH RISK): The same mode of data collection was NOT used for all subjects	1
9	Were the numerator(s) and denominator r(s) for the parameter of interest appropriate	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
		No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10	**Summary of the overall risk of study bias**	**LOW RISK**	**0-3**
		MODERATE RISK	**4-6**
		HIGH RISK	**7-9**

Table 13: Checklist PRISMA-P (Preferred Reporting Items for Systematic review and meta-analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		**The prevalence of latent tuberculosis infection and associated risk factors among young people in South Africa: a systematic review and meta-analysis protocol.**
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection	11c	Describe planned method of extracting data from reports (such as piloting forms, done

process		independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix B: Approved protocol



DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS
FACULTY OF HEALTH SCIENCES, SCHOOL OF PUBLIC HEALTH

TITLE:

THE PREVALENCE OF LATENT TUBERCULOSIS INFECTION AND ASSOCIATED RISK FACTORS AMONG YOUNG PEOPLE IN SOUTH AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL.

AUTHOR

UDEH JUDITH NGOZI

BACKGROUND

Introduction:

Latent tuberculosis infection (LTBI) is a condition whereby individuals harbour live *Mycobacterium tuberculosis* (*M. Tuberculosis*) without presenting with clinical manifestations or symptoms of active tuberculosis (TB) infection [1,2]. According to the Global Tuberculosis Report [3], "LTBI is also defined as the immune response to *M. tuberculosis* antigen without clinical evidence of active TB" [3]. The causative agent for LTBI is *M. tuberculosis*; an acid-fast bacillus which can persevere for decades within a human host. *M. tuberculosis* is highly infectious and can be transmitted from an active TB infected person to a susceptible host via droplets of inhaled aerosols. LTBI can be diagnosed either by tuberculin skin test (TST) in vivo or by using ex vivo interferon-gamma release assays (IGRAs) to detect memory T-cell response against *M. tuberculosis* [4].

Literature review

The degree to which latent TB in children or re-infection can cause TB in later life is not clearly understood. For example, Andvoid's [5] early work in the 20th century demonstrated that the epidemiology of TB infection in children determines its consequent epidemiology infection in adults [5]. According to the same author, an increase or decrease in TB mortality during childhood is followed by a similar increase or decrease in TB mortality when the cohort has reached adulthood. This can be explained by the prevalence of LTBI in children which progresses to active TB in the same cohort after many years of primary infections. In reconciling the historical, epidemiological, bacteriological and immunological observations in TB, Kuh [6] highlighted that being infected as a child establishes the mortality from TB in later life not as a result of the reactivation of LTBI, but as a result of immunological response from re-infection as suggested by Koch [7] in his study on aetiology of TB [6,7]. However, Canetti [8] disagreed with the above views by emphasizing that most TB primary infections die off and TB recurrence can only be due to re-infection and not as a result of latent TB reactivation [8]. According to Mack et al [2]:

> "the fact remains that testing positive to LTBI (using immune-based diagnostic tests) is mainly a measure of an immunological response to stimulation by mycobacterial antigens that cannot necessarily be attributed to the presence of live *M. tuberculosis* in the human host" [2].

Conversely, Tufariello et al [9] have shown that *M. Tuberculosis* persist latently with a small number of bacilli not sufficient to cause the clinical manifestation of the disease until certain changes in immunological response occur [9]. According to Tufariello [9], these changes result in higher rates of metabolism and multiplication of the bacilli which leads to clinical disease manifestation [9].

Understanding LTBI in humans is very challenging since it is difficult to interpret which immunological factors are responsible for preventing or establishing LTBI [10]. However, patients with LTBI have been shown to have much higher proportion of antigen-specific CD8 T cells which produces protein inflammatory Th1-type cytokines such as interferon gamma (IFN-y), tumor necrosis factors (TNF) and interleukin-2 (IL-2) that promote bacterial killing necessary to establish latent infection [10]. In a study by Mahomed et al [11] on predictive factors for LTBI in high-burden areas in South Africa; the following factors were found to predict LTBI using TST: male gender; age greater than 15 years; black racial group and mixed races compared to white and Indian racial groups. Low parent's income classified as earning less than 4000 Rands per month and parents education classified as maternal and paternal highest education level were associated with LTBI. Young people who had current

or prior household TB exposures and those without BCG scars had lower odds of LTBI compared to those with no prior household TB exposure and with BCG scars. Current allergy-related conditions such as asthma and hospitalization six months prior to enrolment into the study were not predictors of LTBI [11]. The above finding on BCG scars contradicts an earlier study by Young et al [12] on risk factors associated with LTBI whereby the history of BCG vaccination was found to be associated with LTBI in Mexican American Children [12]. Another study on the prevalence and risk factors of LTBI in rural Eastern Uganda by Mumpe-Mwanja et al [13] confirmed the presence of BCG scars to be a predictor of TST confirmed LTBI. According to Mumpe-Mwanja et al [13], the covariates: male gender, age 15-18 years, out of school and household TB contact were strong predictors of LTBI while HIV infection is not associated with LTBI [13].

Amongst TB exposed individuals, 30% will test positive to LTBI using TST and an average of 5-10% will develop active TB within two years of exposure [10]. On the other hand, a majority of the exposed persons will develop LTBI and this is estimated at 2 billion persons worldwide, which is a massive pool for possible future transmission [10]. Studies conducted in developing countries on LTBI show that the burden of LTBI is quite high (greater than 48%), which causes an enormous barrier to global TB management and control [11,14,15]. In Uganda, the prevalence of LTBI was reported to be 16.1% among adolescents but increased progressively with increasing age among this group [13]. About half of the adolescents in South African schools especially in areas with high TB prevalence and poor socio-economic status had LTBI [11,14]. In general, South Africa has 80% of the population with LTBI, and 88% of the infection recorded among the age group 30-39 years in informal settlements and townships [4].

In LTBI, the period of latency is unpredictable and so LTBI has a great effect on the approach to TB interventions due to its massive pool of TB transmission. Current studies on TB treatment and control have acknowledged that control of TB depends on identifying and treating individuals who have LTBI [16]. Therefore, embarking on TB elimination or eradication strategy will require a reduction of the prevalence of LTBI in those who are at risk of TB reactivation in future [16]. In view of this, the objective of this review is to estimate the prevalence of LTBI and associated risk factors among young people in South Africa.

Problem statement

M. tuberculosis in its latent state has the ability to persist unnoticed for years inside the human host; hence, it is a serious global health concern and a major factor contributing to the pool of active TB cases worldwide. It has been shown that by the average age of sexual debut (15 years), that 50% of young people in South African communities have LTBI and by the age of 25 years, approximately 75% of the individuals will have evidence of LTBI [11] which is a public health concern. The above statement, therefore, implies that the risk of TB transmission in South Africa will remain high because of the massive pool of LTBI among young people and will consequently impact on the effectiveness of TB control programs in the country. Therefore, testing and treating LTBI in young people will reduce the recent TB transmission and improve the effectiveness of TB control in the country [17].

Study justification

The global TB eradication effort is currently focused on detecting and treating cases of LTBI in high-risk groups in TB prevalent regions. This is the World Health Organisation (WHO) call for reducing TB incidence and mortality rates by 90% and 95% respectively by 2035

compared to 2015 levels [3,18]. As a result, there is an urgent need to contribute to South Africa's preparedness for the programmatic implementation of LTBI management and intervention as a component of the new post-2015 End TB Strategy. It has been reported that young people are a high-risk group, and LTBI is a strong predictor of active TB in this group in South Africa [14,19]. Therefore, young people, especially the adolescents from poor communities in South Africa should be considered as the target groups for LTBI treatments and interventions. However, there have been some discrepancies arising from studies on the factors associated with LTBI among these age groups and this call for further investigation using systematic review and meta-analysis. Such discrepancies include the presence of BCG scars: Whereas some studies associate BCG scar with LTBI, other studies suggest otherwise [11–13,20]. We, therefore, propose a systematic review and meta-analysis to examine the burden of LTBI and verify its predictive factors among young people resident in South Africa as reported in studies from 2000 to 2016.

REVIEW QUESTION

This review will be guided by the question: what is the prevalence of LTBI and associated risk factors among young people in South?

AIM: To conduct a systematic review and meta-analysis of research studies (from 2000 to 2016) that investigated the prevalence of LTBI and its associated risk factors among young people in South Africa.

REVIEW OBJECTIVES

1. To estimate the prevalence of LTBI among young people in South Africa.
2. To determine pooled effect estimates of the specified risk factors associated with LTBI prevalence among young people in South Africa.
3. To critically appraise the quality of the extracted data.

Inclusion criteria:

1. All study designs (except case reports or case series) used to estimate the prevalence of LTBI among young people (0-19 years) in South Africa including all ethnicity, socio-economic and educational backgrounds.
2. Only studies that determined LTBI as diagnosed by TST and or IGRAs.
3. Published and unpublished studies on the subject presented at meetings and conferences from 2000 to 2016.
4. Articles that are written in English.

Exclusion criteria:

1. For the same articles published in different journals, the most comprehensive and recent version of the study will be used.
2. Studies on subgroups of people with LTBI (other than young people) such as healthcare workers or miners.

3. Descriptive reviews, personal opinions, write-ups or articles without primary data collections and/or clear methodology for analysis.
4. Studies which did not meet the quality and eligibility criteria.
5. Studies on outcomes of LTBI treatments.

Study population: Young people (from the age of 0 to19 years) who are resident in South Africa from 2000 and 2016.

Variables to be considered in the review: The variables will be defined using various definitions stipulated by the authors.

Covariates:

- Demographic and socio-economic factors: Parental income, years of parent's education, gender, income, racial group, education, place of residence.
- Household level factors: Having a family relationship with a TB patient, type of residence and density of household members.
- The presence of BCG TB vaccine scar: BCG is a TB vaccine used in children in regions where TB prevalence is high.
- HIV status.

Outcome:

- The prevalence of LTBI among young people as confirmed by TST and or IGRA in South Africa from the year 2000 to 2016.

METHODS

Search strategy

The search approach for this paper will include searching databases such as PubMed (Medline), SCOPUS, DARE, CINAHL, Web of Science, and TB journals on the prevalence and associated factors of LTBI among young people in South Africa. Medical subject headings (MesH) will be used to extensively search the appropriate literature on electronic databases using related keywords to latent TB. Expansive search terms will include the following: tuberculosis, TB, latent TB, LTBI, and different MeSH heading terms and keywords. We will search specific TB journals examples, the International Journal of TB and Lung Disease, the Indian Journal of TB as well as the WHO bulletins on TB. To ensure that articles are exhausted, we will examine the reference lists of the articles that are included or related reviews that will be collected and author's personal profiles. This study will address the recommended items presented in the Preferred Reporting Items for Systematic reviews and Meta- Analyses Protocols (PRISMA-P) 2015 checklist [(21)].

Study selection:

Firstly, the titles of the identified studies will be scanned through and the abstracts thoroughly studied by two independent reviewers to recognize their potential relevance to the topic. The

two reviewers will independently evaluate and appraise the search results and allocate marks to the studies as follows 1 (included), 2 (excluded) and 3 (uncertain; if the reviewer is not able to make a decision). Studies considered not to be relevant based on topics or abstract will be excluded. Secondly, all qualified full-text articles will be evaluated for quality and eligibility through the use of quality score assessment tool to minimize the risk of bias and a standardized data extraction will be carried out. The independent results will then be compared, differences discussed and agreement reached between the two reviewers; if necessary, a third reviewer will act as arbitrator. Transparency of the selection process will be represented in a flow chart.

Data extraction and management

Mendeley (a reference manager) will be used to retrieve and manage the relevant articles which will pass through a multi-level filter to select those with relevant data sets. Eligible studies for inclusion will be fully studied and data extracted using self-designed data extraction forms by two independent reviewers. The data extracted will include specific details about the topic and all study methods eligible for inclusion will be used. All outcomes of significance to the review questions and objectives will be extracted. The extracted data sets will be compared and sent to a third reviewer for the reconciliation of any disagreements arising between the two reviewers.

Quality assessment:

Study quality will be rated using a quality assessment tool and scored as ≤5 (low risk), 6-8 (moderate risk) and >8 (high risk). All the eligible articles will be independently scored by the two reviewers using the quality assessment tool. The result of the scores from the independent reviewers will be compared and discrepancies discussed and resolved by agreement or by a third reviewer where consensus is not reached. After consensus is reached, data will be extracted from the chosen articles and risk of bias evaluated using sensitivity analysis.

Data synthesis and analysis:

Objective 1: Outcome variable; count: Data sources will be identified and extraction of the estimates of the prevalence of LTBI carried out. The prevalence will be extracted using STATA version 14 and the aggregates of the pooled estimates at 90% confidence interval will be summed up using meta-analysis so as to account for variability between studies. The trend of LTBI over time may be investigated and the prevalence in adolescents (11 to 19 years) and younger ages may be compared. Standard errors will be determined where the numerators and denominators are known and non-overlapped confidence intervals will signify the statistically significant difference.

Objective 2: Categorical explanatory variables: gender, age group, race, socioeconomic status, education level, BCG scars, Parents' income and parents' education levels. Extraction of the risk factors associated with LTBI will be carried out and random-effects model in STATA version 14 will be used to combine the Odds Ratios. If adequate data collections are made, subgroup meta-analyses will be carried out by the participant's HIV status, BCG scars, and socioeconomic markers.

Objective 3: Heterogeneity test: The extent of variations in the studies will be determined using I^2 heterogeneity statistic reported as a percentage which will range as follows: low (≤25%), reasonable (26 – 50%), significant (51 – 75%) and extensive heterogeneity (76% - 100%). Further investigation of heterogeneity will be carried out with a forest plot at alpha 10% significant level and 1^2 statistic with ≥50% or poor overlap of confidence interval signifying a significant heterogeneity. If heterogeneity is statistically significant, sensitivity analysis will be carried out to check for possible causes and explanations. Examples of sensitivity analysis that will be performed include plotting and comparing results of high qualities to ascertain how they vary from the overall results and assessing if different study designs and the model used have effects on meta-analysis result. Studies with considerable heterogeneity will be narrated and presented using tables and figures where necessary.

Discrepancies between reviewers will be discussed and resolved; however, where consensus is not reached, a third reviewer will intervene. Finally, a list of excluded studies will be produced with reasons for their exclusions.

Assessment of biases:

Possible bias will be minimized by carefully selecting articles that meet the eligibility criteria. The symmetry of funnel plot will be used to check for selection of unbiased studies if more than ten eligible studies are identified.

Reporting:

This review will be reported according to the Preferred Reporting Items for systematic reviews and Meta-analysis (PRISMA) guidelines [(21)]. Flow diagrams will be used to summarize the eligibility criteria and selection process used. Supplementary documents will also be published and these will include the tools employed for quality appraisal assessments and the search strategies.

Limitation:

Excluding studies done in languages other than English may lead to poor exhaustion of available studies and datasets.

Ethics and Dissemination:

There is no formal ethical review required since this study is a systematic review of documents which are publicly available and so does not directly involve human participation. This systematic review will be presented in conference proceedings and published in peer-reviewed journals for open access.

Appendices:

Search table: MeSH term (modified as needed for use in other databases)

#1	LTBI	#8	TST
#2	Latent TB	#9	Interferon-gamma release assays
#3	Latent TB infection	#10	IGRAs
#4	Latent tuberculosis	#11	South Africa
#5	Latent tuberculosis infection	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#6	Latent mycobacterium tuberculosis	#13	#11 AND #12
#7	tuberculin skin test		

TIMELINE

	Schedules	Jun 16	Jul 16	Aug 16	Sep 16	Oct 16	Nov 16	Dec 16	Jan 17	Feb 17	Mar 17	Apr 17
1	Protocol development											
2	Literature Search											
3	Assessors meeting											
4	Data extraction											
5	Introduction and literature review											
6	Systematic review and meta-analysis											
7	compilation of reports											
8	Submission for corrections											
9	Final corrections and assessment											

BUDGET

S/n		COST (Rand)
1	Internet and modem	1,800
2	Printer	1,500
3	Printing papers	700
4	Conference paper presentation	5,000
5	Protocol publication	29,064.75
6	Project publication	29,064.75
Total		**67,129.5**

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Appendix C: Approved ethics waiver

Human Research Ethics Committee (Medical)

Golden Jubilee: October 1966 – October 2016

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 301,
29 Princess of Wales Terrace, Partktown, 2193 Tel +27 (0)11-717-1252 /1234/2656/2700
Private Bag 3, Wits 2050, email: zanele.ndlovu@wits.ac.za
Office email: hrec-medical.researchoffice@wits.ac.za
Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Ref: W-CJ-161118-4 18/11/2016

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Mrs Judith Ngozi Udeh (Student No 720384)**

Project title: **The prevalence of latent tuberculosis infection and associated risk factors among adolescents in South Africa: a systematic review and meta-analysis.**

Reason: This is a review of information in the public domain. There are no human participants.

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2016 -11- 18
JOHANNESBURG

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Zanele Ndlovu, Rhulani Mkansi.

Appendix D: Turnitin plagiarism report

720384:FINAL_RESEARCH_
REPORT_UDEH_JUDITH_N_1_
(2).doc
by Tamelyne Van Tonder
Submission date: 29-Mar-2018 03:51PM (UTC+0200)
Submission ID: 938193477
File name: -a24f -2528292df f
47_FINAL_RESEARCH_REPORT_UDEH_JUDITH_N_1__2.doc (1.9M)
Word count: 11715
Character count: 61599
10%
SIMILARIT Y INDEX
8%
INT ERNET SOURCES
7%
PUBLICAT IONS
3%
ST UDENT PAPERS
Exclude quotes On
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a0034413:FINAL_RESEARCH_REPORT_UDEH_JUDITH_N_1…
ORIGINALITY REPORT
MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)
3%
Tariro J Basera, Jabulani Ncayiyana, Mark E Engel.
"Prevalence and risk factors of latent tuberculosis
infection in Africa: a systematic review and metaanalysis
protocol", BMJ Open, 2017
Publication

Appendix E: Author's guideline for publication (BMC Public Health Journal)

Bottom of Form

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BMC Public Health

Submission guidelines

Our 3-step submission process

Before you submit

Now you've identified a journal to submit to, there are a few things you should be familiar with before you submit.

Make sure you are submitting to the most suitable journal - Aims and scope

Understand the costs and funding options - Fees and funding

Make sure your manuscript is accurate and readable - Language editing services

Understand the copyright agreement - Copyright

Ready to submit

To give your manuscript the best chance of publication, follow these policies and formatting guidelines.

BMC Public Health publishes the following article types:

Research article

Technical advance article

Database article

Software article

Debate

Case report

Study protocol

Click the relevant link to find style and formatting information for the article you are going to submit.

General formatting rules for all article types - Preparing your manuscript

Make sure your submission is complete - Prepare supporting information

Copyright and license agreement - Conditions of publication

Read and agree to our Editorial Policies - Editorial policies

Submit and promote

After acceptance, we provide support so your article gains maximum impact in the scientific community and beyond.

Please note that manuscript can only be submitted by an author of the manuscript and may not be submitted by a third party.

Who decides whether my work will be accepted? - Peer-review policy

Want to submit to a different journal? - Manuscript transfers

Spreading the word - Promoting your publication

Bottom of Form

Top of Form

Bottom of Form

Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

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researchers who should use a specific community-endorsed repository are advised of the best option for sharing and archiving their data. Use of Research Data Support is optional and does not imply or guarantee that a manuscript will be accepted.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

present a title that includes, if appropriate, the study design e.g.:

"A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

or for non-clinical or non-research studies a description of what the article reports

list the full names, institutional addresses and email addresses for all authors

if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below

indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

Background: the context and purpose of the study

Methods: how the study was performed and statistical tests used

Results: the main findings

Conclusions: brief summary and potential implications

Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively

(before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

the aim, design and setting of the study

the characteristics of participants or description of materials

a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate

Consent for publication

Availability of data and material

Competing interests

Funding

Authors' contributions

Acknowledgements

Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

include a statement on ethics approval and consent (even where the need for approval was waived)

include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state “Not applicable” in this section.

Availability of data and materials

All manuscripts must include an ‘Availability of data and materials’ statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article [and its supplementary information files].

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

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Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each author's competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

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This section is optional.

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Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

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Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse

Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

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Article within a journal
Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

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Article within a journal by DOI
Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book
Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.
OnlineFirst chapter in a series (without a volume designation but with a DOI)
Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored
Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document
Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

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Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

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FTP site
Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

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ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier
Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables additional files

See General formatting guidelines for information on how to format figures, tables and additional files.