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A 10-year Review of TB Notifications and Mortality Trends Using a Joint Point Analysis in Zambia - a High TB burden country Invited article – IJID World TB Day Series 2022

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A B S T R A C T

Background: Zambia is one of the TB high-burden countries. It is important to track the progress being made towards enhancing case finding and reducing mortality. We reviewed routine TB notifications and mortality trends, over a decade from all facilities in Zambia.
Methods: A 10-year retrospective study of TB notifications and mortality trends was performed using a Joint Point Analysis version 4.9.0.0, NCI. We extracted the annual national TB program data for the period under review.
Results: There was a decline in annual point average for notification between 2010 and 2020 in both males and females, but the females notification rates had a higher rate of decline (AAPC = -6.7, 95%CI:-8.3 to -5.0), $p<0.001$) compared to the decline in males notification rate (AAPC = -4.1, 95%CI:-4.1 to -5.1, $P<0.001$). We found a significant growth rate in the proportion of TB patients that were bacteriologically confirmed (AAPC = 6.1, 95% CI: 3.6 to 8.7, $p< 0.001$), while the proportion of clinically diagnosed patients declined (AAPC= -0.1, 95%CI: -2.3 to 2.1, $p<0.001$). Notification of drug-resistant TB increased exponentially (AAPC=27.3, 95% CI: 13 to 41), $p< 0.001$) while mortality rate declined from 21.3 in 2011 to 12.7 in 2019 per 100,000 population (AAP=-5.6, 95%CI: -9.6 to -1.5, p=0.008).
Conclusions: This study has illustrated the importance of reviewing and analyzing routinely collected TB data by national programs. The study revealed areas of improvement in terms of TB control and underscores the need for increased and sustained investment in case detection and diagnostics.

Abbreviations: TB, Tuberculosis; AAPC, Average annual point change.

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Author declarations

All authors have a special interest in global epidemic of TB, COVID-19 and HIV, and One Health. All authors declare no conflicts of interest.

Introduction

Tuberculosis (TB) is the second most common cause of deaths globally from an infectious disease(WHO, 2021). There are concerns that achieving the UN General Assembly targets of eliminating TB (Sahu *et al.*, 2020) as a global health threat by 2035 may now not be possible in lieu of the COVID-19 pandemic. The WHO annual TB Report (2021) estimates that there were 10 million new TB infections and 1.5 million deaths globally. Both the WHO End TB Strategy milestones for 2020 on reducing TB incidence and mortality by 20% and 35% respectively compared to the 2015 baseline were missed. Zambia remains one of the 30 high TB burden countries in the World and TB trends show a steady slow decline over the years (Kapata *et al.*, 2011)(Stuck *et al.*, 2022). The TB burden in Zambia is driven by several factors including the high HIV/AIDS rates currently standing at 11.3%, undernutrition, smoking, and diabetes mellitus (WHO, 2018)(Global AIDS Monitoring, 2020)(WHO, 2021).

Zambia pro-actively conducted a national TB prevalence in 2013/2014 which revealed the burden of TB in the country and prospectively informs annual estimates. This is the first-ever National TB prevalence revealed that the burden of TB was higher than earlier estimated. From the 2014 survey, the prevalence of all forms of bacteriologically confirmed TB was estimated to be 638/100,000 population (Kapata *et al.*, 2016). In Zambia, at least 30% of mortalities are attributed to TB among people living with HIV. This is due to many factors among them late diagnosis of both TB and HIV, high loss to follow up rates on anti-retroviral treatment(Lungu *et al.*, 2021)(Lungu *et al.*, 2021),(Melgar *et al.*, 2021) (World Health Organization, 2018).

Following the advent of the COVID-19 pandemic and associated mitigation measures, most TB control program services were negatively affected. Trends of TB and TB its associated mortality in Zambia have not yet been reviewed. Trends analysis may be of paramount importance at this point in time. We performed a 10-year retrospective review of TB notifications and mortality trends using key TB performance indicators (KPIs) in order to understand the current disease trajectory and inform strategic approaches for appropriate mitigation measures.

Materials and methods

Data source

The data analyzed in this study was extracted from official Zambia National TB and Leprosy Program (NTLP) database. We reviewed reports, returns and data that is routinely collected by the Zambia National TB Program including reports that are submitted to the World Health Organization annually. The records reviewed were from 2010 to 2020. The program collects aggregated data on a quarterly basis from diagnostic and notification facilities using an excel powered tool. Facility Focal Point Persons aggregates age and gender disaggregated data from all the entry points including the chest clinic and conducted initial quality checks before hard copies of completed reports were submitted to the District TB Coordinator, who also conducts quality checks and aggregates data from all the reporting facilities in the district before submitting the district report to the Provincial Health Office. The District TB Coordinator and the District Information Officer also enter the validated district data into the Ministry of Health DHIS2 database. At provincial level, the Provincial TB Coordinator validates the data submitted in both excel and DHIS2 version and then submits to NTLP national office where data for the whole country is managed in DHIS2 database.

Data for mortality analysis was collected from official facility TB treatment registers. TB patients initiated on treatment and those who died before treatment initiation are recorded in the TB register to be notified. On a weekly basis, Facility TB Focal Point Person conduct reconciliations by reviewing patient files, death certificates, admission and discharge registers and the round books to update records of patients diagnosed with TB who died before and after treatment initiation. This information is entered into the TB register which serves as a database for all TB patients at the health facility.

Data Analysis

We conducted Joinpoint regression analysis to determine the magnitude of time effects on TB notification rates for both drug sensitive TB and drug resistant TB and mortality rates of Tuberculosis. The annual percentage change rates (APC) were generated using Joinpoint software (Joinpoint Regression Program, version 4.9.0.0, NCI) provided by the US National Cancer Institute. The Joinpoint regression analysis was based on grid search method with minimum number of 2 observations from a Joinpoint. Period in years was the independent variable while mortality and notifications were dependent variables, with homoscedasticity assumed over the years. The regression model fit one Joinpoint for mortality, notifications by sex and by age. Confidence intervals for the annual percentage change (APC) and the average annual percentage change (AAPC) were determined using the parametric method and permutation test method was used for model selection with overall significance level of 0.05. TB notification rates were calculated using the total number of TB patient notified during the year as the numerator and the population for the respective year (as published by the Zambia Statistics Agency in the 2010 Census of Population and Housing Report) as denominator. The result was multiplied by hundred thousand to obtain notification rate per 100,000 population. Annual mortality statistics were calculated using the total number of TB deaths recorded during the year as the numerator and the population for the respective year (as published by the Zambia Statistics Agency in the 2010 Census of Population and Housing Report) as denominator. The result for each year was multiplied by hundred thousand to obtain mortality per 100,000 population.

The DR-TB data was analyzed using Joinpoint Regression Analysis Tool, for the annual trend rates and their associated significance statistics for both the number of DR-TB patients detected and the proportion of bacteriologically confirmed cases with RR detected, while Microsoft Excel Power BI was used to analyze the distribution of the bacteriologically confirmed cases and the proportion of bacteriologically confirmed cases with RR detected with a 2 year moving average trend for the two variables. The relationship between the number of Xpert MTB/Rif machines and number of drug resistant TB patients was analyzed using Pearson correlation in GraphPad Prism version 9.3.1 (471).

The proportions of TB patients tested for HIV and initiated on ART was analyzed in Joinpoint Regression Analysis Tool, for the annual change rates and their associated levels of significance, and by using Microsoft Excel Power BI, for the cascade graphs and the trend lines. Proportion of TB patients tested for HIV was calculated using the number of TB patients tested for HIV as a numerator and the total number of notified TB patients as a denominator. The proportion of HIV positive (co-infected) TB patients was calculated using the number of TB patient tested HIV positive as a numerator and the total number of TB patients tested for HIV as a denomina-

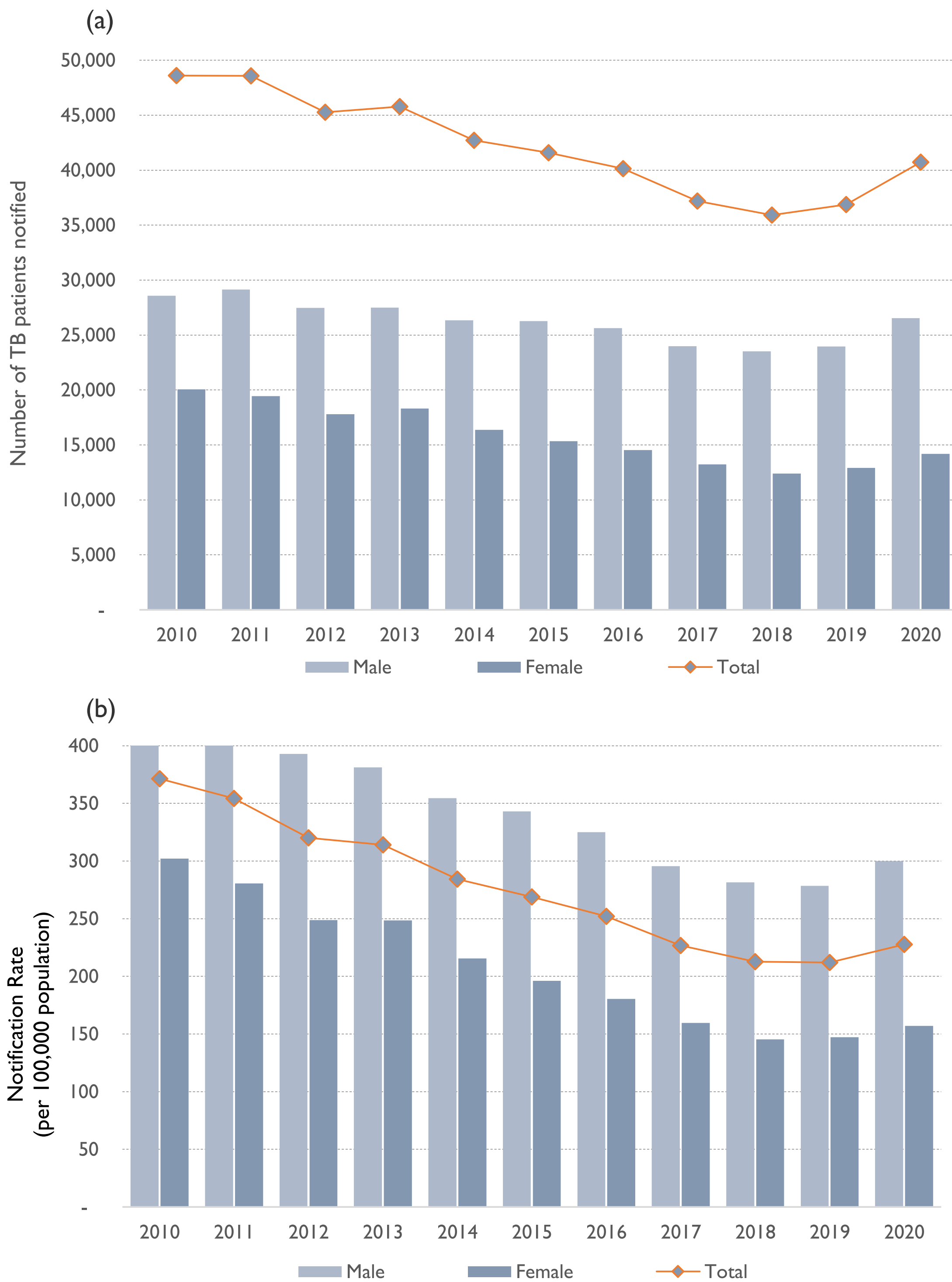


Figure 1. (a) Graph showing TB patients notified in Zambia. (b): Graph showing annual TB notification rates per 100,000 population.

tor. The proportion of TB patients on ART was calculated using the number of co-infected TB patients on ART as a numerator and the number of HIV co-infected TB patients as a denominator.

Results

TB Case notifications rates were on a downward trend from 2011 to 2018, there after Zambia recorded increased case notifications for both males and females (figure 1b). The actual case notification numbers were 48,616 in 2010 and 40,726 in 2020 (figure 1a). TB notifications were higher in males than females throughout the review period (figure 1). Although Joinpoint regression analysis showed a significant decreasing pattern in notification rates between 2012 and 2018 for both male and female, larger decline was observed in females AAPC [−6.7; (95% CI: −8.3 to −5.0); $p < 0.001$)] as compared to males AAPC [−4.1;(95% CI: −5.1 to 3.1; $p < 0.001$)] (figure 2c).

The analysis further revealed an increasing rate in the proportion of bacteriologically confirmed cases (AAPC: 6.1; 95% CI: 3.6 to 8.7; $p<0.001$) (figure 4a) as compared to the proportion

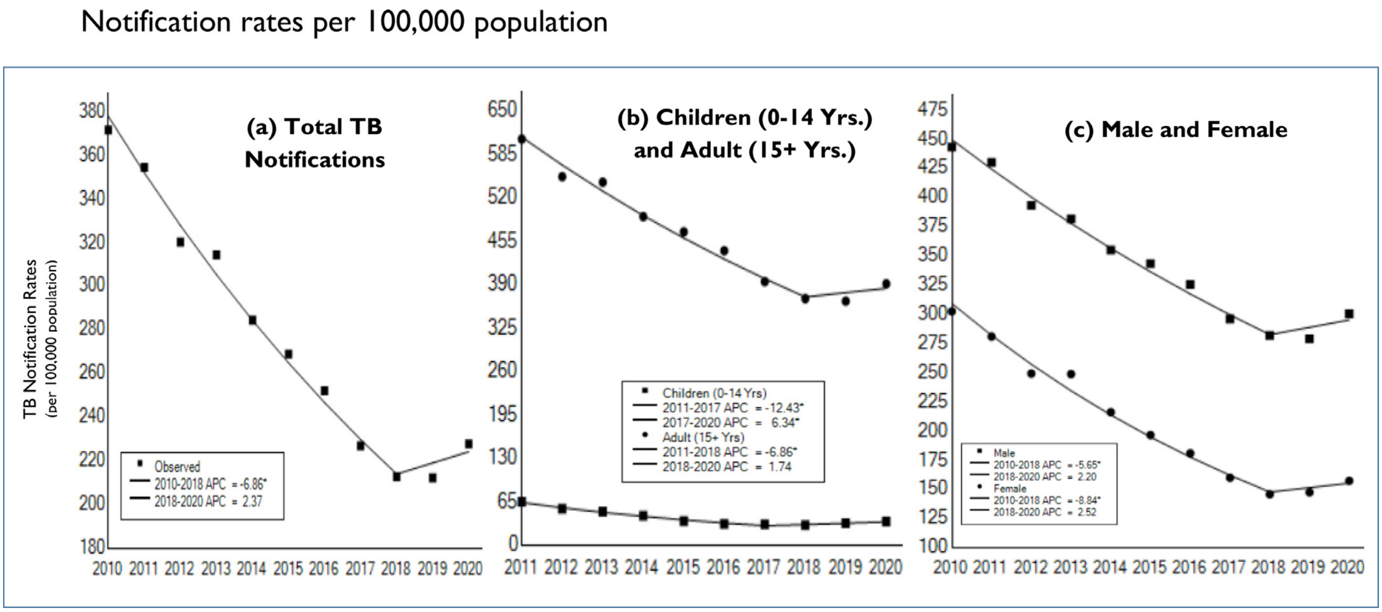


Figure 2. (a): Joinpoint regression showing trends in TB notifications rate. (b): Joinpoint regression showing trends in TB notifications rate adults (15+ years) vs. children (0-14yers). (c): Joinpoint regression showing trends in TB notifications rate by sex.

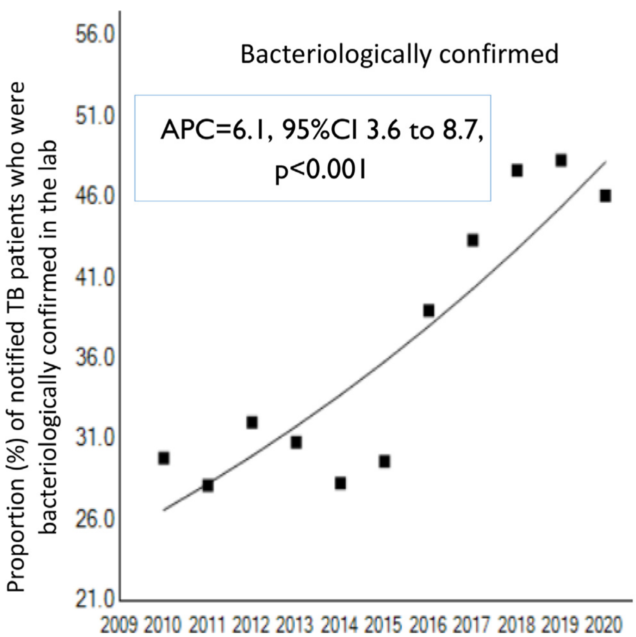


Figure 3. Shows the trend of in proportion of TB patients bacteriologically confirmed in the laboratory.

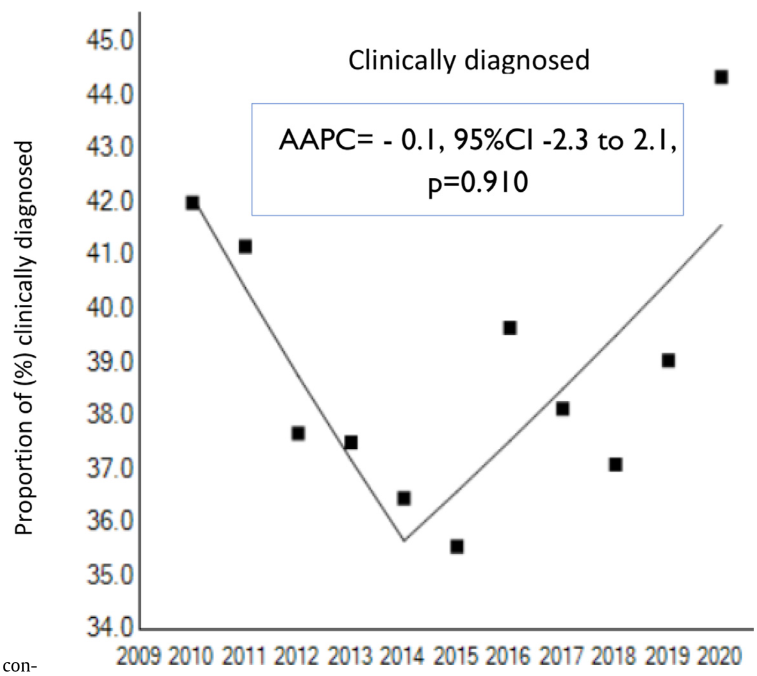


Figure 4. Shows the proportion of TB patients who were clinically diagnosed.

of clinically diagnosed cases that showed a decreasing annual trend rate (AAPC: -0.1; 95% CI: -2.3 to 2.1; p<0.910) (**figure 4b**). Further, pairwise comparison of children (0-14 years) to adults (15 years and above) showed that although both children and adult notification rates had a decreasing pattern, notification rates of children had a higher decreasing rate (AAPC: -6.6; 95%CI: -8.1 to -5.1; p<0.001) compared to notification rates of adults (AAPC: -5.0; 95%: -6.5 to -3.5; p<0.001). However, from 2017 to 2020, a significant increasing notification rate was observed in children (APC: 6.3; 95%CI: 0.9 to 12.1; p=0.03) (**figure 2b**).

DR-TB

The study showed an exponential increase in case detection of DR TB with an average annual growth rate of 27.2 (**figure 7a**). There was a strong positive correlation between the number of bacteriologically confirmed drug susceptible TB cases and the bacteriologically confirmed cases with RR detected (r(9)=.80, p=.003) (figure 7d). The trend in the proportion of bacteriologically confirmed drug susceptible TB cases with RR detected over the 10 years of analysis was increasing at an average annual rate of 25.0 (p<0.001) (figure 7e). A 2-year moving average trend shows that from 2014 to 2017, the proportion of bacteriologically confirmed cases with RR results remained positive, but from 2018 to 2020

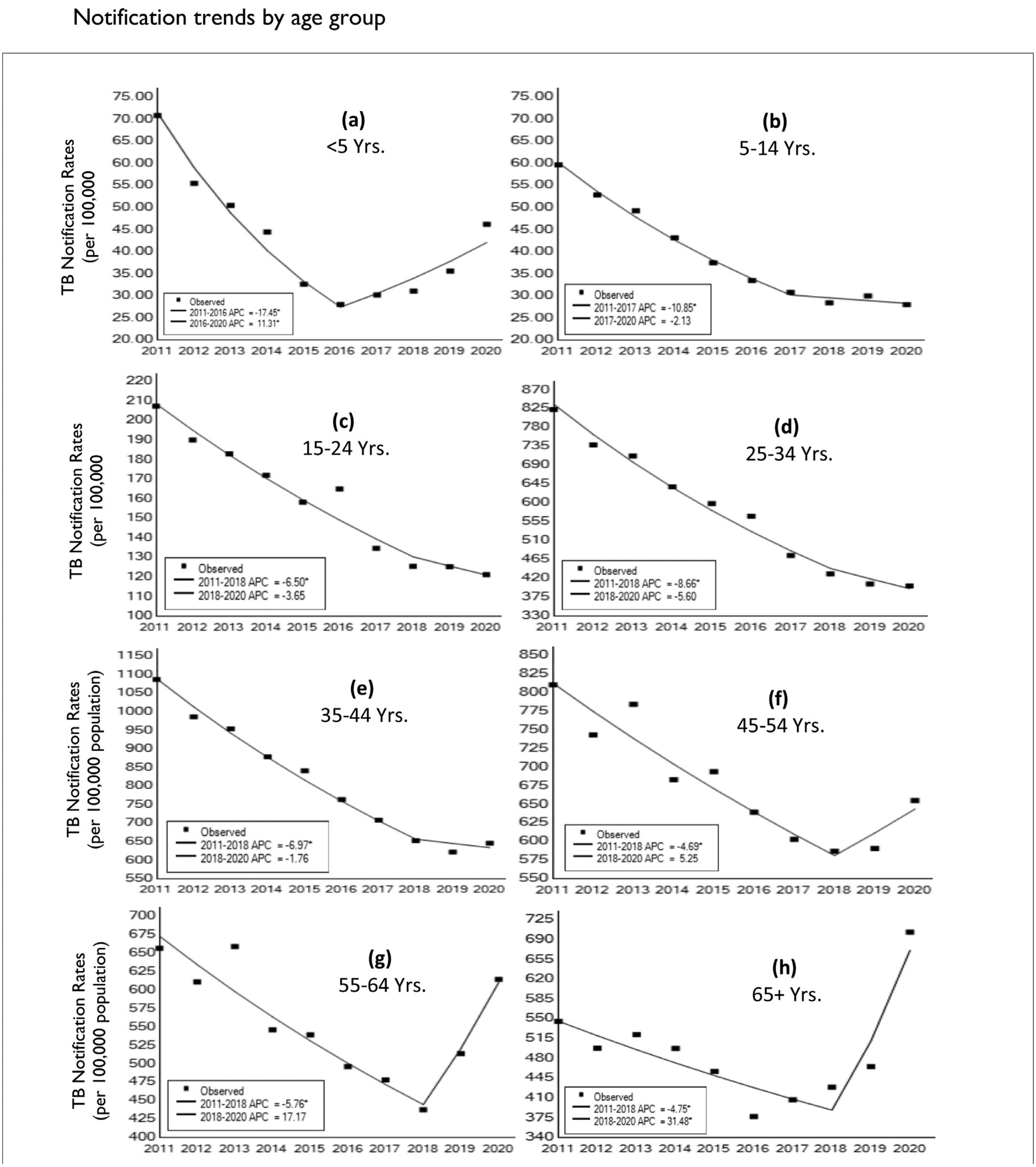


Figure 5. Joinpoint Regression graphs showing trends in TB notification rates per 100,000 population, by age group.

the trend begun to tilt downwards (figure 7a). And Pearson correlation showed a positive association between the number of Genexpert machines and the case detection of drug resistant TB (r (9) = 0.8499 [95% CI, 0.474 – 0.9638], $p = 0.0018$) (**figure 7b**).

TB Mortality

Analysis of TB mortality data revealed a statistically significant decreasing trend in mortality rates from 21.3 in 2011 to 12.7

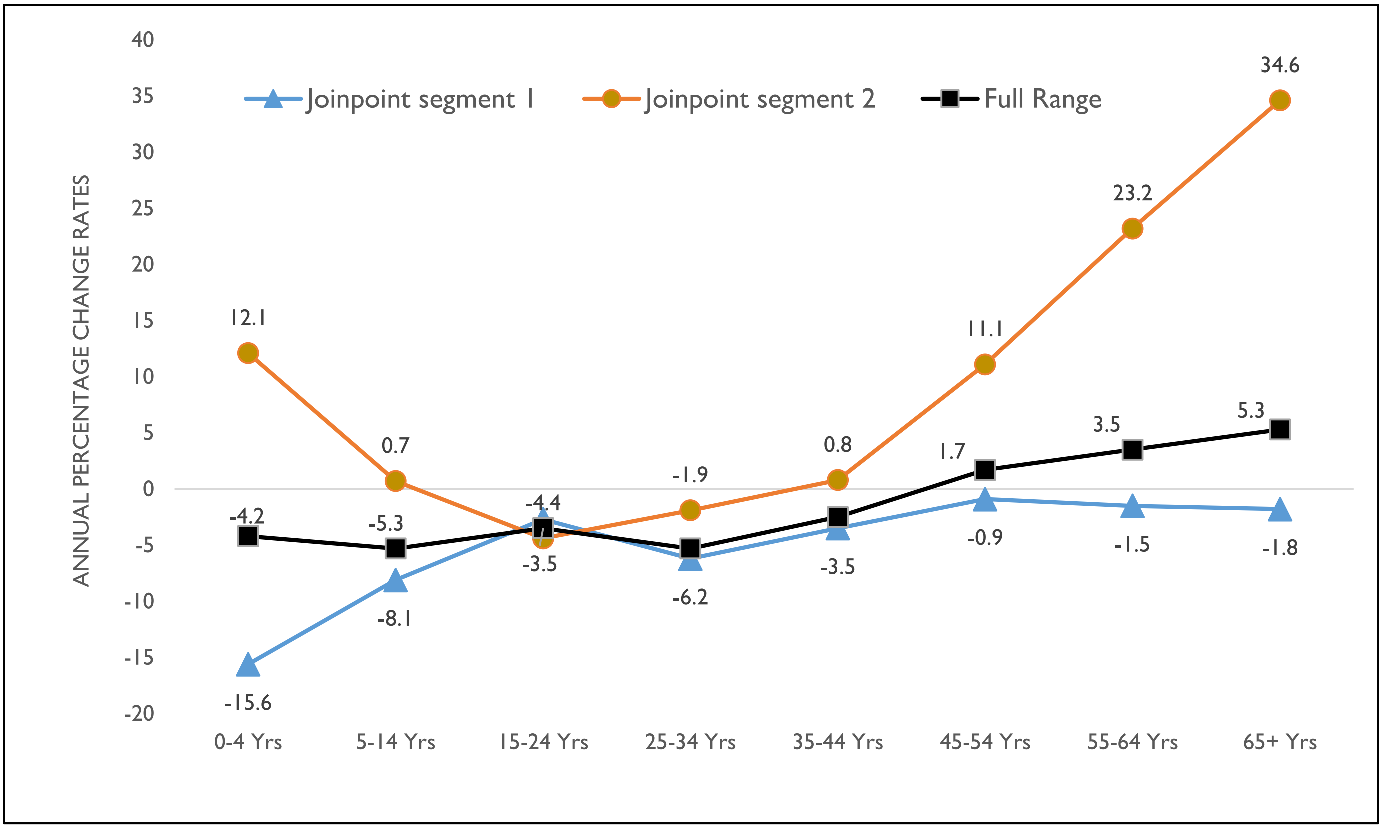


Figure 6. Graph showing trend of average annual percentage change (AAPC) rates in notifications.

per 100,000 population in 2020 (AAPC: -5.6; 95% CI: -9.6 to -1.5; p=0.008) (**figure 8**).

TB HIV Collaboration

Analysis of TB/HIV data revealed a moderate increasing trend of HIV testing rates among TB patients. The proportion of notified TB patients tested for HIV increased from 84% in 2010 to 93% in 2020 at an average annual growth rate of 0.96 ($p<0.001$) (figure 10). However, the analysis showed significant rates of change in the trends of the proportion of TB patients tested HIV positive (HIV positivity rates) and the trend of HIV co-infected TB patients initiated on ART. The proportion of TB patients tested HIV positive decreased from 65% in 2010 to 39% in 2020 at an average annual decreasing rate of -4.9 ($p<0.001$). The proportion of HIV co-infected TB patients on ART increased from 48% in 2010 to 98% in 2020 at an average annual growth rate of 7.8 ($p<0.001$) (figure 11). Further the results showed that HIV positivity rates among TB patients and ART uptake negatively correlated ($r(9)= -0.76$, $p=0.006$).

Discussion

This article highlights several significant findings that need critical consideration to improve TB program services in Zambia. These findings may also be relevant to other national TB control programs, especially those in settings like Zambia, including the sub-Saharan Africa. Our study revealed a significant reduction in the average annual percentage change in notifications for male and female TB patients. There was also a decline in the average annual point average for clinically diagnosed TB; most importantly the country recorded an increase in bacteriological confirmation of TB. Stratified by age showed a negative change with reduced notifications of childhood TB compared to adults with a comparative increase. Observed a sharp increase in TB in adults aged above 45. Additionally, there was an increase in the notification of drug-resistant TB cases. Notably, there was an increase in the average annual percentage of TB deaths.

The reduction in TB notifications was observed between 2010 and 2018, the period preceding 2014 when the first ever TB prevalence survey was done in Zambia. Before the TB prevalence surveys it was perceived that TB treatment coverage was near optimum as the TB notification rate in 2013 was at 289/100,000 against an estimated incidence of 338/100,000 with a TB treatment coverage of 85.5% above the target of the STOP TB Strategy of 70% that time. The prevalence survey of 2013-2014 revealed the inverse of the earlier narrative. The prevalence survey showed that the TB burden in Zambia was 455/100,000 population (Kapata et al., 2016). Therefore, indicating that the estimates arising from routine surveillance data largely under-estimated the burden of TB in Zambia (Kapata *et al.*, 2016). Other factors leading to the decline in TB cases is under-reporting. The national TB programme in 2019 conducted a countrywide data quality assessment that confirmed and revealed a 33.0% under notification in the first 3 quarters of 2019 (MOH Report). As observed from our data which showed a disproportionately higher decline in case notifications among females than males. Further, the study adds to recent calls for more gender-equitable TB programming with gender-responsive approaches for TB prevention, diagnosis, treatment and care (GDP Collaborators, 2022). Inequities in gender may be influenced by cultural factors and expected roles and responsibilities (Jayachandran, 2015) and much remains to be done to develop more gender equitable programs.

Annual point increase of bacteriologically confirmed TB patients may explain the decline in clinically diagnosed TB patients between 2010 to 2018. We argue that this decline in clinically diagnosed TB patients may be due to low index of suspicion by

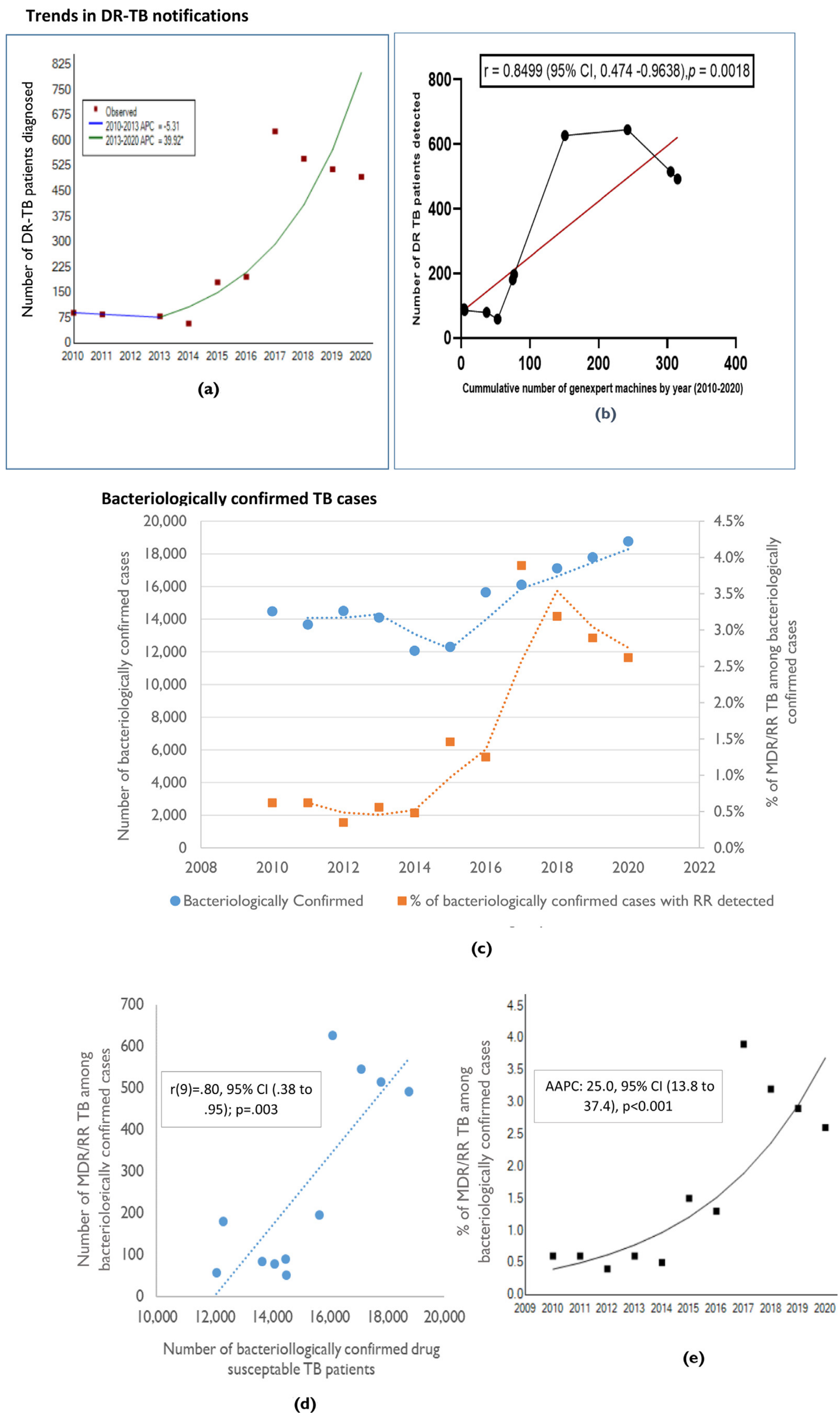


Figure 7. (a) Graph showing trend of annual percentage change rate in DR-TB detected over the 10 years of analysis. (b) Correlation of the number of Genexpert machines with the number of DR TB patients detected. (c). Scatter plot showing the distribution of bacteriologically confirmed drug susceptible TB cases and the proportion of the bacteriologically confirmed cases with RR detected results. (d) Graph showing correlation between number of bacteriologically confirmed drug susceptible TB cases and the number of bacteriologically confirmed susceptible TB cases with RR detected. (e). Graph showing trend in the proportion of bacteriologically confirmed drug susceptible TB cases with RR detected.

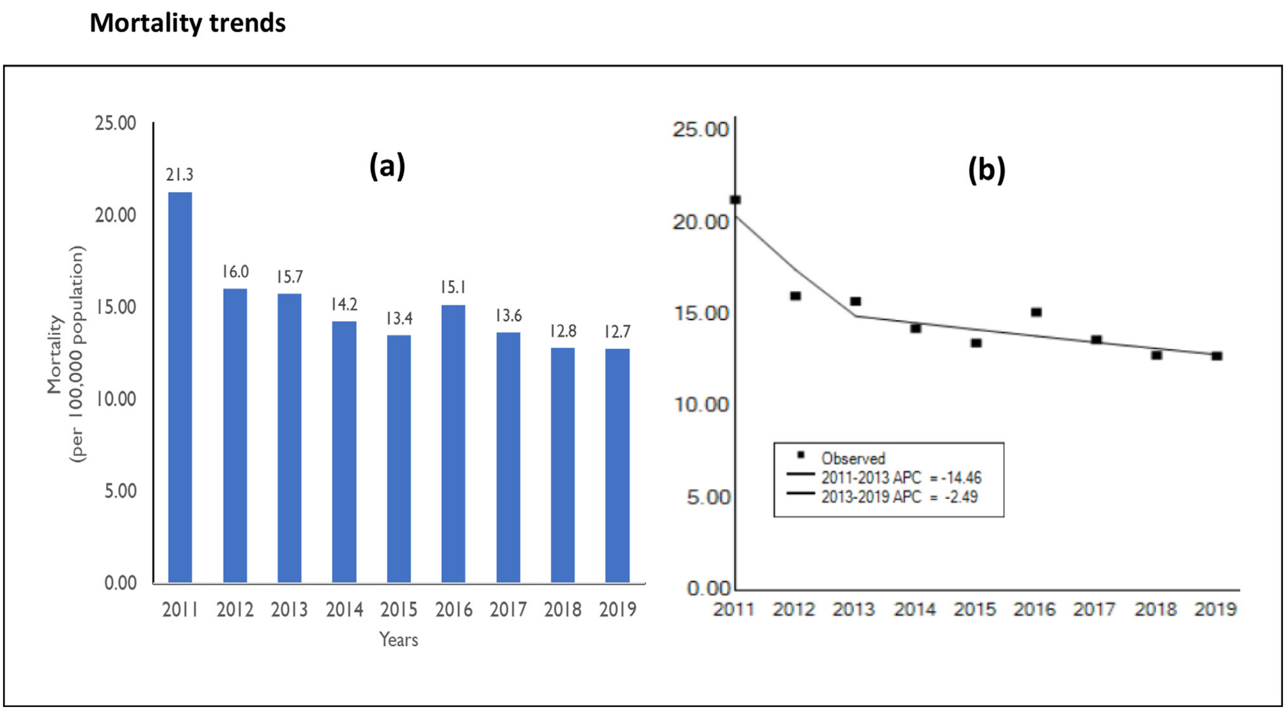


Figure 8. (a) Trends in mortality rates per 100,000 population, from 2011 to 2019. (b) Joinpoint Regression line graph showing the Joinpoint segment slopes and the observed annual percentage change rates for each Joinpoint segment.

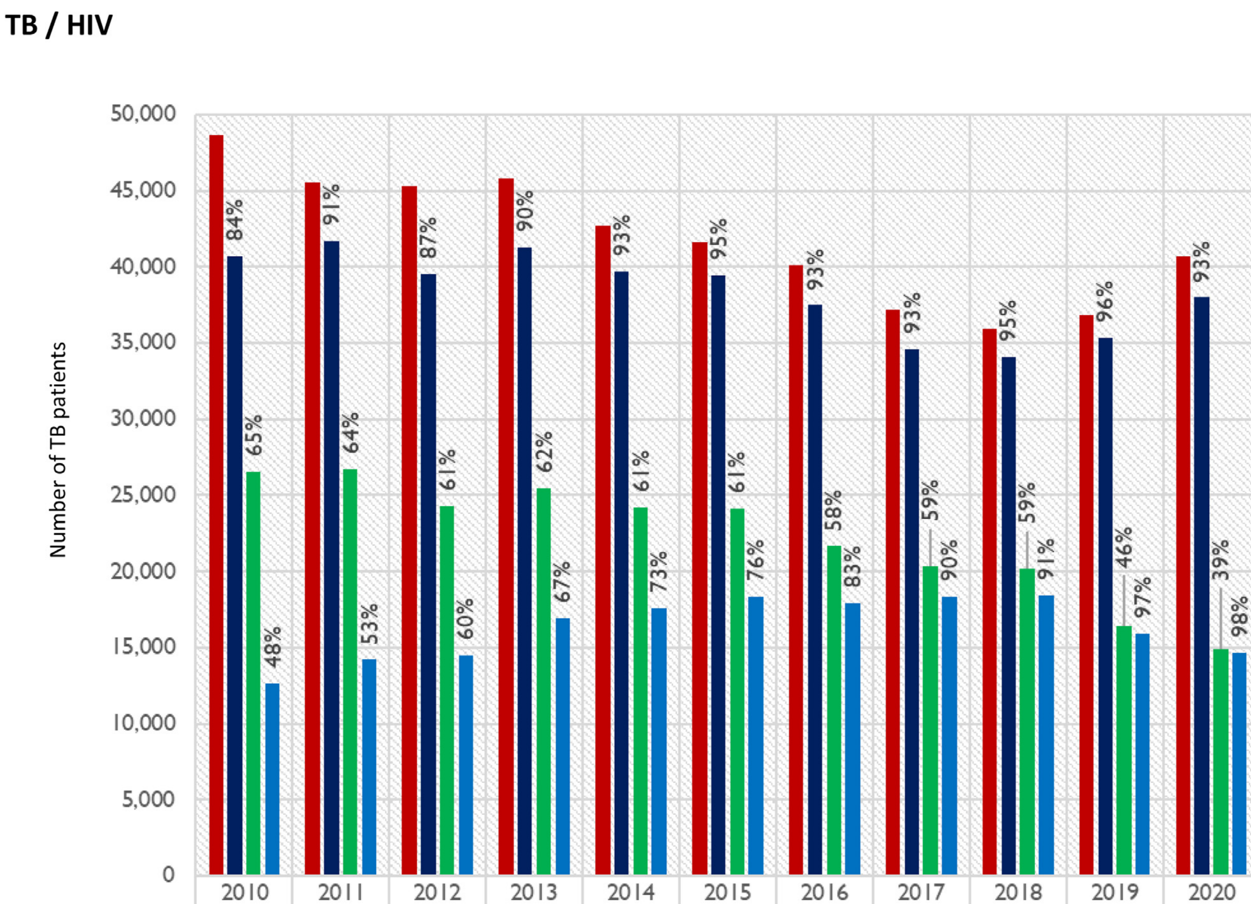
health practitioners, especially for subclinical TB cases. A significant proportion of these cases are indicatively extra pulmonary TB as shown by postmortem study that thought to establish the burden of TB antemortem (Bates *et al.*, 2015). Under reporting may also be a contributing factor to decline in clinically diagnosed. This is supported by the findings of the data quality assessment mentioned above which revealed 38.5% under-notifications of the clinically diagnosed TB patients (program data). The postmortem study conducted in Zambia revealed that 25.6% were not diagnosed antemortem and further, demonstrated that 44.9% of the cases of TB found at post-mortem had extra-pulmonary TB (Bates et al., 2015). In the same study they found that 16.7% of the TB diagnosed antemortem was MDR-TB. (Bates *et al.*, 2015). Thereby qualifying our association of the decline in clinical cases of TB to low index of suspicion and low skill set to diagnose a case of extra-pulmonary TB. We therefore advocate for comprehensive evaluations of presumptive TB patients starting with a detailed history, physical examination, increased access to more sensitive and the rapid development of newer and highly sensitive TB diagnostic tools to cartel missed cased of TB.

A recent study from Zambia showed that facility active case finding was more effective in detecting TB cases than community active case finding. Thus, strengthening health systems to identify and evaluate patients for TB needs to be optimized (Kagujje et al, 2020). TB symptom screening could be aligned to screening for other causes of fever or respiratory infections when patient presents at points of care, or when contact screening is being implemented and testing through a diagnostic cascade. Systematic community screening should be re-ignited after the lull created by the COVID-19 pandemic disruptions and barriers to accessing health services identified and removed

This study as outlined above revealed an increase in the TB patients that are bacteriologically confirmed, this is attributable to the expansion in the TB diagnostic network which has increased access to sensitive TB diagnostic tools. Our observation in this study is in concordance with the finding by Rokosaminana and colleagues who demonstrated that TB case detection increased with the use of molecular diagnostic tools (Rakotosamimanana *et al.*, 2019). Steingart et al established that the Genexpert brought about a tangible shift in TB case detection when it was used as the first line TB diagnostic tool (Steingart *et al.*, 2013).

Our study shows a negative growth in childhood TB notifications, this is a critical indicator for each country under the resolutions of the first ever United Nations High Level Meeting on TB of 2018. The suboptimal childhood TB case finding is similar to what was earlier documented in Zimbabwe (Nzombe *et al.*, 2020). In contrast AAPC for adults shows a positive increase in a similar setting, this requires further exploration on the attributing factors to a lower performance in childhood TB. Elhassan et al from a study conducted in Sudan highlighted that the challenges of diagnosing TB in children are brought about by being poor quality of specimens and the paucibacillary nature of the disease in children (Elhassan *et al.*, 2016). Additionally, TB often presents with non-specific symptoms coupled by lack of highly sensitive tools leads to childhood TB being missed and under-diagnosis (Holmberg, Temesgen and Banerjee, 2019),(Togun, 2021),(Meyer-Rath *et al.*, 2012). Quick actions are urgently required to address the factors leading to under-performance in childhood TB. New advances need to be taken forward to close persistent gaps in Childhood TB services adolescents inclusive (Marais *et al.*, 2021).

Strikingly, we observed an exponential increase in TB notifications in patients aged above 45 years between 2019 and 2020 while the age groups 15 to 24, 25 to 34 and 35 to 44 continue with a downward trend in the same period. The largest burden of HIV in Zambia is in the age group 15 to 44. Our observation coincides with one made in figure 11, which shows a downward trend in TB/HIV co-infections. We consciously attribute these two observations to an increased uptake of TB preventive therapy in PLHIV from 2018 through to 2020. We think TPT effectively reduced the risk of TB in the HIV population, which is not the case in the those aged 45 and above who are mostly HIV negative. To date uptake of TPT in high-risk HIV negative remains low.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
No. Notified	48,616	45,594	45,269	45,793	42,716	41,588	40,153	37,203	35,922	36,866	40,726
No. tested for HIV	40,704	41,701	39,543	41,305	39,685	39,464	37,480	34,622	34,075	35,376	38,000
No. HIV positive	26,571	26,737	24,309	25,476	24,198	24,116	21,655	20,362	20,202	16,424	14,925
No. on ART	12,646	14,213	14,471	16,945	17,611	18,381	17,914	18,341	18,421	15,915	14,673

Figure 9. Graph showing the cascade of TB / HIV data.

The significant number of drug resistant TB detected and notified were mainly rifampicin resistant through GeneXpert testing. This may reflect the expansion in the access to molecular tools such as GeneXpert MTB/Rif Assay (Meyer-Rath *et al.*, 2012). A study by Kampen et al revealed an additional advantage of the XPERT MTB/Rif in terms of a shorter turnaround time, this is pivotal in linkage to care (Kampen *et al.*, 2015),(Malone *et al.*, 2017). With increasing rollout of the XPERTMTB/Rif Assay, one can expect more cases of DR-TB to be detected and reported, especially in lieu of the disruptions in TB services due to the COVID-19 pandemic, especially affecting access to anti-medicine and non- adherence to treatment because in person observation of TB treatment was not possible during the COVID 19 pandemic.

The increase in TB related mortality shown in this study is due to delayed detection of TB inevitably leading to progression and dissemination of the infection. A study by Muchemwa et al brings into sight factors driving TB mortality. They established a 34.8% prevalence of TB bacteremia in patients with severe sepsis (Muchemwa *et al.*, 2017). Arguably, TB bacteremia suggests delayed diagnosis.

In addition to our findings of an increase in annual percentage of TB related deaths despite a decrease in numbers of active TB being reported, recent data from forensic autopsy examination of sudden or unexpected deaths in the community revealed incidental undiagnosed active TB antemortem (Muchelenganga AL 2022 et al, IJID-under review). Other autopsy studies have shown incidental TB co-morbidity in COVID-19 related deaths in Zambia (Mucheleng'anga *et al.*, 2021). This indicates that many people with TB may remain undiagnosed and untreated and a proactive TB screening programme needs to be re-invigorated.

Other studies have shown that in low resource and high TB burden settings, the Bandim TBscore, a clinical score that predicts treatment outcome in TB patients may be useful as an indicator of which healthcare-seeking adults to refer for sputum smear microcopy. Rudolph and colleagues showed in a trial that use of the TB score for triage before smear microscopy may improve case detection and decrease mortality if there is sufficient laboratory capacity to increase sputum smears testing (Rudolf *et al.*, 2021). Health-related quality of life (HRQoL) in patients with pulmonary TB may be useful in prediction disease outcome. Bohlbro et al (2022) suggest that a simple single-item self-rated health (SRH) score could correlate with TBscore/TBscoreII and could be used in clinical decision-making to identify TB patients at high risk of death (Bohlbro *et al.*, 2022). It could thus identify patients in need of intensified follow-up during treatment provision.

While Zambia recorded a negative AAPC in TB notification. From 2018 through to 2020 this evaluation showed a positive trajectory in TB notifications. There are various reasons attributed to increase in notifications observed between 2018 and 2020. The plausible explanations for the recovery include: expansion of the TB diag-

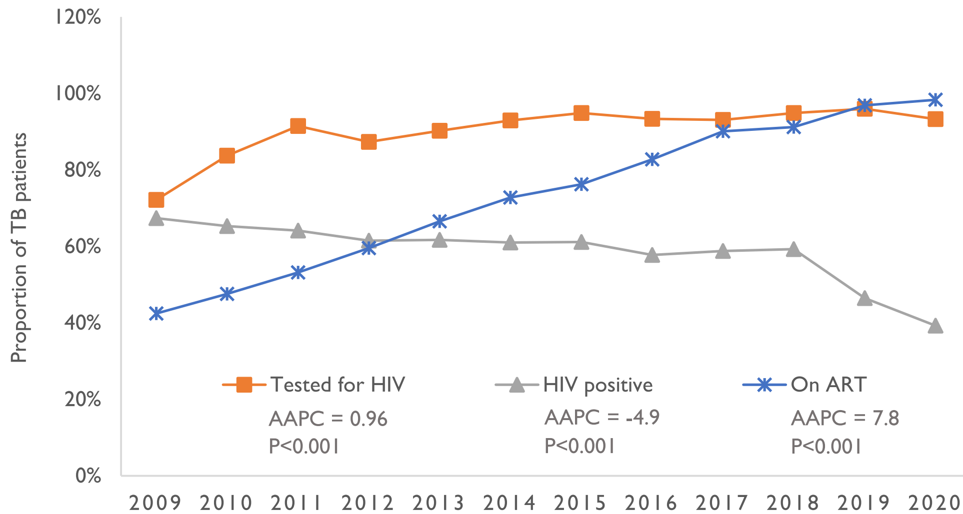


Figure 10. Graph showing trends in the proportion of TB patients tested for HIV and initiated on ART.

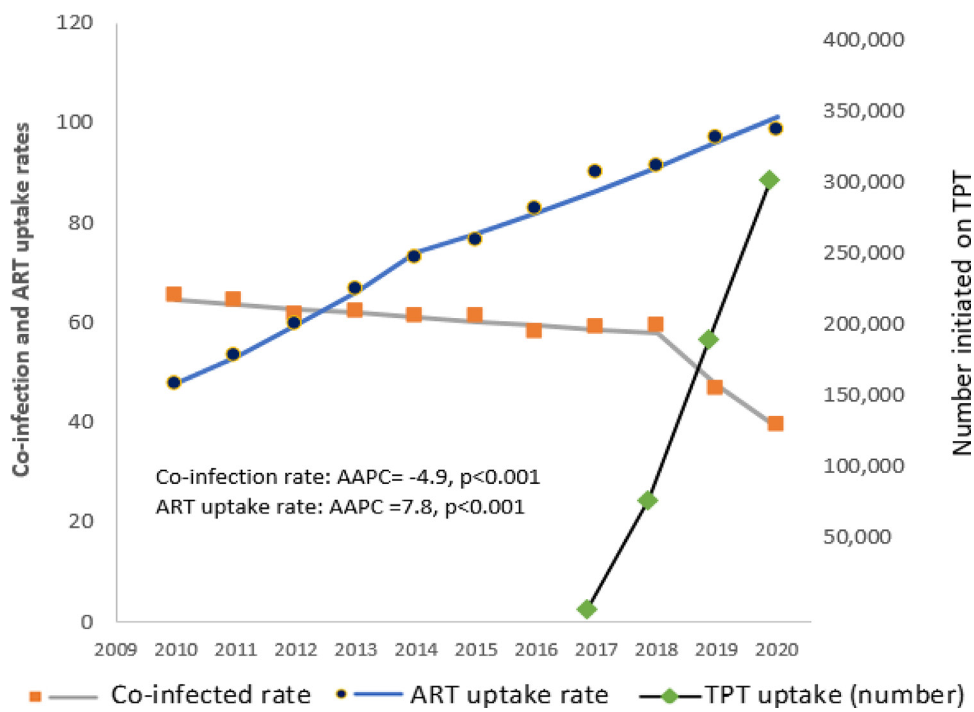


Figure 11. Graph showing an increasing trend of annual percentage change rates in the proportion of HIV co-infected TB patients on ART and a decreasing trend in the proportion of TB patients testing HIV positive (HIV positivity rate).

nostic network from only four sites in 2010 to 315 sites in 2020 that are using the rapid molecular TB diagnostic tools such as the Xpert MTB/Rif. Additionally, the quick adoption of the WHO recommendation of the inclusion of the Xpert MTB/Rif the digital CXR, Urine LAM in the TB evaluation algorithms as part of the first line tools for TB diagnosis has certainly brought in efficiency and thus catalysed TB case finding in Zambia. In response to the findings of the data quality assessment of 2019, the TB program established weekly reporting as part of the surveillance for TB and used this platform put in corrective measures addressing the factors driving under-notifications. Lungu et al showed that at about one-month post notifying the first two cases of Covid-19 and as a result of the restrictive Covid-19 measures, the TB control program experienced an 18% drop in weekly notifications. This compelled program to establish a virtual platform to oversee the TB response amidst Covid-19 outbreak. This platform uses data for decisions making and actions. Using this mechanism, the program has been able to sustain the TB interventions modeled to suit the covid-19 situation (Lungu *et al.*, 2022).

A review of the WHO Annual global TB 2021 report on financing of the TB programs, reveals a great improvement in funding of the annual TB budgets from only 26% of the funded needs in 2014 to 83% 2020. Further, reveals a significant increment in both domestic and international funding of the TB program in Zambia (Baddeley *et al.*, 2014),(WHO, 2021). To sustain gains made so far in increasing treatment coverage and reducing TB patients who die of

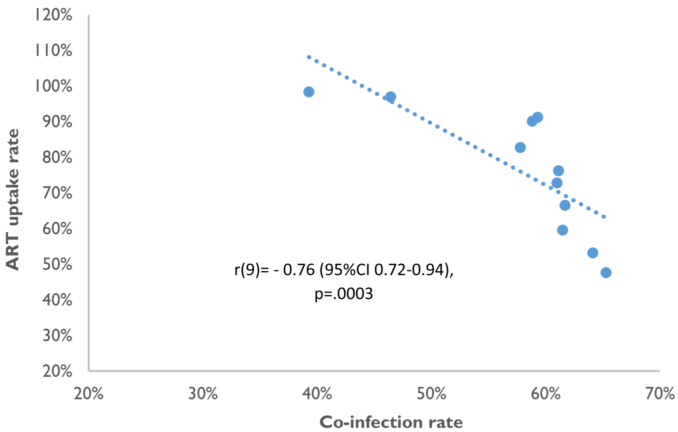


Figure 12. Shows the correlation between the proportion of TB patients tested HIV positive and the HIV co-infected TB patients on ART.

TB, there urgent need to increase both domestic and international funding to TB services. Actualising the Multi-Sectoral Accountability at national level will catalyse the achievement of the 2030 End TB Strategy Milestones.

Conclusion

Our study has illustrated the importance of reviewing and analyzing routinely collected TB data by national programs. The review of TB data for a period of 10 years and analyzing notification and mortality trends revealed areas of improvement in terms of TB control and underscores the need for increased and sustained investment in case detection, diagnostics as well as skills transfer to health care providers. There is need for more resources to be apportioned to strengthening systems to be able to address not only the TB burden but also drug-resistant TB, TB/HIV and COVID-19 co-infections.

Figs. 3, 5, 6 and 9

Declaration of Competing Interest

The authors declare no conflicts of interest

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Ethical Approval Statement

The Study did not involve any human subjects, we used the data that the national TB program shares is its report

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