Original Research Article

Evaluating the impact of the GeneXpert technique on casedetection and management of Tuberculosis in Ghana

Abstract

Background

Rapid and more sensitive diagnostic assayshave seen substantial investment globally intending to improve Tuberculosis (TB) diagnosis towards treatment. This study evaluated the impact of the GeneXpert interventionon TB case detection and management in Ghana.

Methods

The study made use of an interrupted time series design. Data from Ghana's District Health Information Management System (DHIMS II) was used to evaluate the impact of the intervention. A cross-section of DHIMS II data was analyzed repeatedly using 2017 and 2022 as baseline and end lines, respectively. Descriptive analysis and interrupted time series models were used.

Results

No immediate impact was observed on bacteriologically confirmed TB, however, 5 years following the intervention, the number of bacteriologically confirmed TB cases increased by an average of 562 cases per year (step and ramp (coefficients of pre- and post-intervention) variables being -278.5 (95% (CI): -1118.3, 561.3) and 561.9 (95% CI: 352.3, 771.6), respectively. The cure rate decreased on average by 32.8% at the onset (step coefficient of -32.8 (95% CI: 40.5 – 25.0), however, there were no significant changes in the pre-and post-intervention cure rates (ramp coefficient = 1.5 (95% CI: -4.0, 7.0). Subsequently, the treatment completed rate increased sharply in the year of implementation but did not significantly differ from the pre-and post-intervention period (step and ramp coefficients were 29.4% (95% CI: 27.0, 31.9) and 1.5% (95% CI: -1.8, 0.4). Moreover, the intervention did not have a significant sudden or gradual impact on adverse treatment outcomes; step and ramp coefficients were 3.0% (95% CI: -4.5, 10.6) and 0.2% (95% CI: -5.1, 5.5)

Conclusions

While bacteriologically diagnosed TB casesimproved during the implementation period, clinical outcomes were not significantly impacted. To achieve recommended global targets, there is a

need to address treatment follow-up challenges and enhance monitoring as part of addressing implementation challenges.

Keywords: Tuberculosis, GeneXpert, Intervention, interrupted time series,impact

Introduction

Tuberculosis remains a global public health concern, specifically in low and middle-income countries (Biermann et al., 2019). An estimated 10.6 million people were infected with TB worldwide in 2021(WHO, 2022).Without effective treatment strategies and improvement in diagnostic techniques, the goal to achieve a 90% and 95% reduction in TB incidence and mortality by 2035 will not be possible(García-Basteiro et al., 2017; Uplekar et al., 2015).Given that barely two-thirds of the expected number of TB cases are diagnosed or reported to health authorities, diagnostic improvement is of the utmost importance(García-Basteiro et al., 2017).

The aim of tuberculosis control is early detection and management. The gold standard for tuberculosis testing is sputum culture, but its turnaround time is too long and thus delays the treatment of patients infected with TB (Parsons et al., 2011). Sputum smear microscopy, the most widely used diagnostic tool has been shown to have low sensitivity ranging from 30-70 %(Ejeta et al., 2018; Pinyopornpanish et al., 2015; Steingart et al., 2014). Rapid and more sensitive diagnostic assays, including GeneXpert MTB/RIF®, have seen substantial worldwide and national investment to improve the diagnostic cascade of treatment for patients. There has been a significant global scale-up of the GeneXpert technique since the World Health Organization (WHO) endorsed it in 2010. The advent of GeneXpert epitomizes a paradigm shift in the diagnosis of TB and drug-resistant as well as simplified molecular testing worldwide (Pinyopornpanish et al., 2015). The GeneXpert assay has shown improved sensitivity (77-99%) than sputum smear microscopy and is comparable to sputum culture and produces results in less than 2 hours making it a better diagnostic tool (Ejeta et al., 2018; Moussa et al., 2016;

Pinyopornpanish et al., 2015; Sorsa&Kaso, 2021). Rapid and accurate diagnosis of TB and timely initiation of appropriate treatment and management are key to curbing the spread and elimination of the disease (Dravid et al., 2019).

Previous studies have shown that Ghana has made progress in its quest to eliminate TB and achieve the global target by 2035 but poor health infrastructure, and low TB case detection and management have hampered its progress over the years (Ahorlu & Bonsu, 2013). The disease remains a significant public health problem in the country despite the several efforts that have been made over the years to curb its incidence.In the last quarter of 2017, the NTP adopted the GeneXpert as the initial diagnostic tool for TB testing across the country(GHS, 2021).The introduction of the GeneXpert showed a significant improvement in the coverage of testing among all notified cases in 2018 at 58% and 20% coverage in 2017.The number of GeneXpert testing facilities over the years has increased from 126 sites to 143 GeneXpert testing sites at the close of 2021. These facilities have been linked to over a thousand TB requesting sites through the spoke and hub system of sputum sample transportation(GHS, 2021). However, very little information is available to ascertain the impact of this strategy in improving case detection and management of TB in Ghana. The current study seeks to understand what impact GeneXpert interventionis having on case detection and management of TB and help inform future decisions regarding improvement as well as further rollout.

Methods

Study Design and Setting

The study made use of an interrupted time series design, in which the same group is observed repeatedly across time, both before and after the intervention(Govender, 2018). Interrupted time series is robust and regarded as one of the best designs for determining causality when

randomized controlled trials (RCTs) are not possible(Bernal et al., 2018; Schaffer et al., 2021). Administrative and clinically generated data collected routinely using Ghana's District Health Information Management System (DHIMS II) was usedto evaluate the impact of the intervention. A cross-section of the DHIMS data was analyzed repeatedly using 2017 and 2022 as baseline and end lines, respectively.

The Ghanaian health system is made up of three levels namely; national, regional, and district, however, service delivery is carried out at the zonal level: national, regional, district, sub-district, and Community Health Planning and Services (CHPS). The NTP is a Public Health Division's Disease Control and Prevention Department programme. The National Tuberculosis Control Programme's major activities are coordinated through Ghana's five-tier health system.

The Ghana Health Service, as well as the Ministry of Health and its agencies, have a nationwide network of health facilities (hospitals, health centres, clinics, and maternity homes) spread over the country's sixteen regions and 261districts (as of 2022). There are currently 405 hospitals, 822 health centres, 1006 clinics, and 601 medical laboratories in operation in Ghana, accounting for 83 per cent of all health facilities, 9% of faith-based institutions, and 7% of the commercial sector. The National Tuberculosis Control Program operates within the Ministry's structures.

Data Analysis

Data were extracted in an Excel file(Microsoft Excel 16) double-checked and analyzed using STATA and R statistical soft wares. The years 1997-2017 were selected to study trends before, and 2018–2022 after, the rollout of GeneXpert as a routine tuberculosis diagnostic test. Different indicators such as the number of bacteriologically confirmed cases, cure rate, treatment completion rate and adverse outcome rates were retained for analysis.

For time series analysis to be properly specified, the model assumes the data to be stationary, meaning it has a constant mean and variance; without seasonal variation, and is not correlated with its values (autocorrelation). To be sure these assumptions are not violated, we chose the autoregressive integrated moving average (ARIMA) model using the Box-Jenkins method to select the model parameters. ARIMA models an outcome variable as a function of past values of the outcome variable and the error term. It consists of an autoregressive (AR) model, a moving average (MA) model and a part that integrates the two by inducing stationarity through differencing. Differencing means computing the difference between adjacent values of the observed data. The AR model has the outcome variable predicted by lagged values of the outcome (values of the outcome shifted forward by one or more time points) whereas the MA models the outcome by lagged values of the error term. Thus, an ARIMA model is characterized by *p*, the number of lags of the AR model, *q*, the number of lags of the MA model, and *d*, the order of differencing required to inducestationarity. This is typically written as ARIMA (*p*,*d*,*q*) (Schaffer et al., 2021).

In our analysis of the data, we assessed for the violation or otherwise of the assumptions. For stationarity, we plotted the trend line for visual assessment and confirmed using the augmented Dickey-fuller test. The plot was considered stationary at $p<0.05$. If not stationary, the first or second-order differencing was done to induce stationarity. We cross-checked visually and statistically as discussed above for stationarity. For autocorrelation, we used the autocorrelation function (ACF) and partial autocorrelation (PACF) plots for visual assessment. The plots suggested autocorrelation if the lags in the ACF plot exceeded the upper bound or lower bound of the confidence interval. After- fitting the ARIMA models, we checked for autocorrelation using the Box-Ljung test. A p-value great than or equal to 0.05 was considered insufficient

evidence against autocorrelation. The above procedures are presented for only the impact of GeneXpert on the number of bacteriologically confirmed cases but were followed for all other outcomes.

To fit the ARIMA models, we used the "auto.arima()" command in the R package "forecast" to determine the parameters for the best model with the Akaike Information Criteria as the basis for model selection. We sought to evaluate the effect of GeneXpert on the following outcomes: the number of bacteriologically confirmed cases and the treatment outcome rates (the cure rate, the rate of treatment completion, the successful outcome rate, and the adverse outcome rate). We did this by forecasting (using an ARIMA model) each outcome from 2017 to 2021 (2017 to 2022 for the number bacteriologically confirmed) based on the prevailing trend before the national implementation of GeneXpert for TB diagnosis (before 2017). This forecast, being the counterfactual is compared with the observed data to provide an eyeball assessment of GeneXpert's impact. We fit the ARIMA model with a covariate that predicts a sudden and sustained change at implementation (step) and another that predicts a change in slope that occurs after the implementation of the intervention (ramp). These two were used to show statistically, the impact of GeneXpert on the outcomes. The model fitness based on the procedures described was assessed using plots of the residuals.

Results

Descriptive summary

The median number of bacteriologically confirmed TB cases from 1997 to 2022 was 7713 (interquartile range 7400.8-8006.8), the minimum (6877) number of bacteriologically confirmed cases was observed in 1999 and the maximumnumber (11713) was observed in 2022.

Similarly,the median cure rate was 63.6 %(IQR 45.9-74.8), the lowest (36.7%) and the highest (79.1%) cure rate was recorded in 1997 and 2009 respectively. On the other hand, the median treatment completed rate was 7.8 %(IQR 6.4 -13.1), the minimum (5.3) was recorded in 2005 and the maximum (41.9) was recorded in 2017. The median adverse outcome was 15.6%, the highest (55.3%) was observed in 1997 and the lowest (11.9%) was observed in 2014(table 1).

Table 1Summary statistics of various tuberculosis indicators used in the study

Variable	Median	IQR	Minimum	Maximum
Number bacteriologically confirmed	7713	7400.8 – 8006.8	6877	11713
Cure rate	63.6	45.9 - 74.8	36.7	79.1
Treatment completed	7.8%	6.4 – 13.1	5.3	41.9
Adverse outcomes	15.6	13.5 – 38.5	11.9	55.3

Impact on the number of bacteriologically diagnosed TB cases

We postulate that the introduction of the GeneXpert to diagnose TB in Ghana will not result in an immediate increase in bacteriologically confirmed numbers since its availability was staggered across the country. Over time, we expect to see a gradual increase after the intervention.

The plot of the data is shown in Figure 1. The plot shows an uptrend, particularly noticeable at the start of the trend and after the implementation of the intervention. This suggests non-stationarity in the data, a violation of a key assumption for time series data analysis. A confirmation using the augmented Dickey-fuller test yielded p = 0.99, indicating insufficient evidence against non-stationarity.

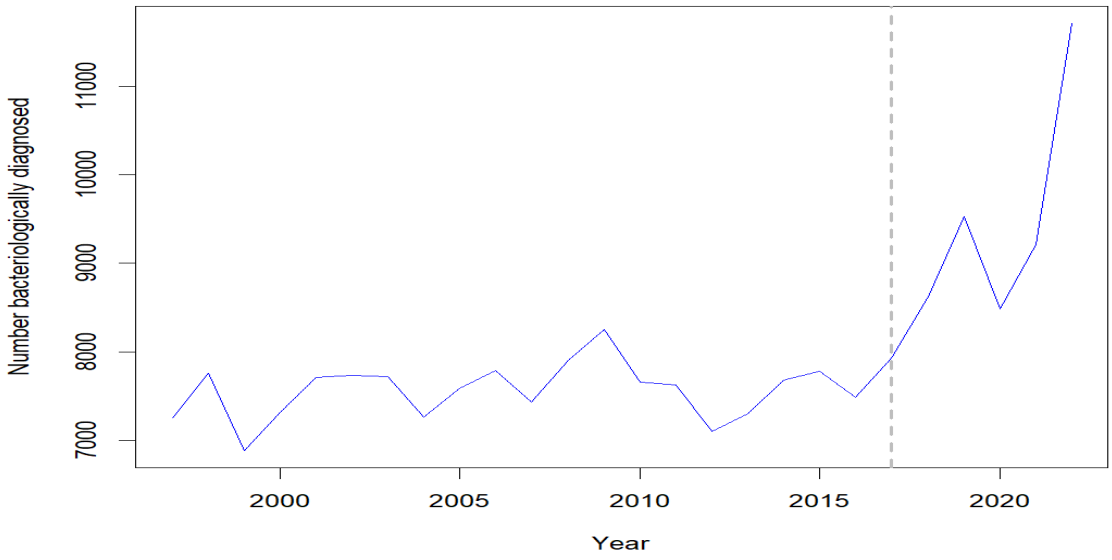

Figure 1 Trend of the annual number of bacteriologically confirmed TB cases in Ghana from 1997 to 2021

We determined the second difference as being necessary to induce stationarity. The plot is presented in Figure 2. This was statistically confirmed with the augmented Dickey-fuller test with $p < 0.01$.

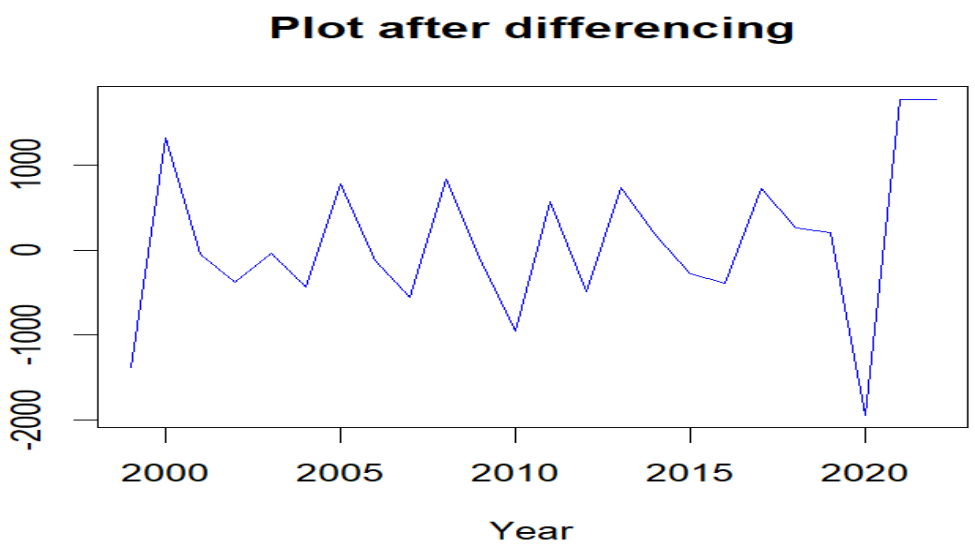

Figure 2 Trend of the annual number of bacteriologically confirmed TB cases in Ghana after second-order differencing

Figure 3 presents a chart of the autocorrelation function (ACF) and partial autocorrelation (PACF) plots before (plot 1) and after (plot 2) differencing to enable visual assessment of autocorrelation in the data. The first 2 lags exceeded the upper bound for the ACF as well as the first for the PACF in the plots before differencing, suggesting autocorrelation in the data. After differencing, only the first lag in the ACF plot exceeded the upper bound and none in the PACF plot.

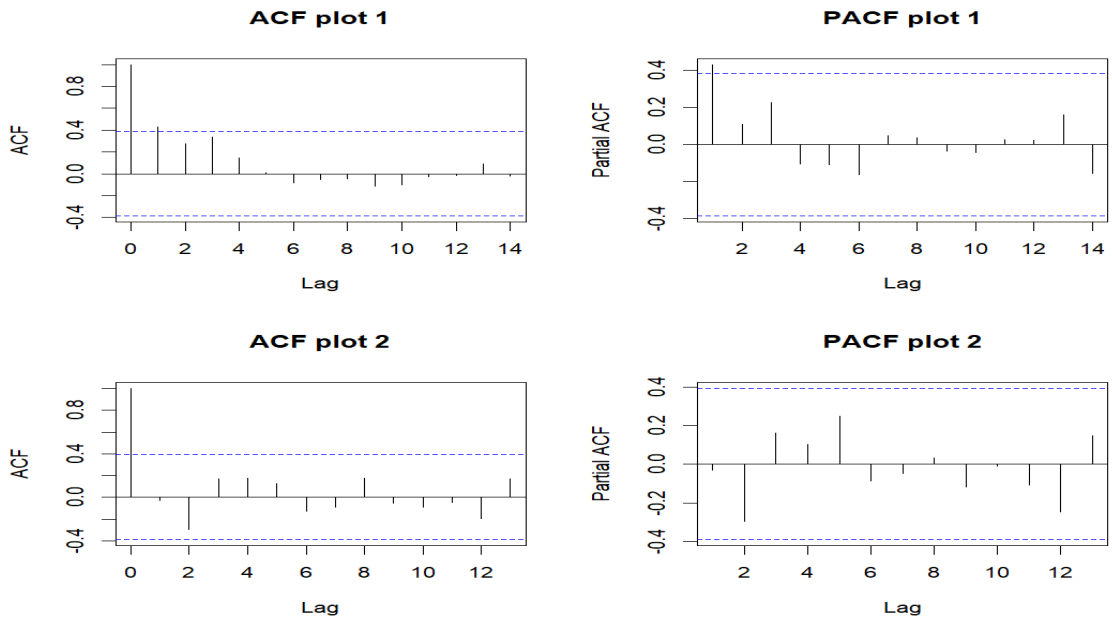

Figure 3 autocorrelation function (ACF) and partial autocorrelation function (PACF) plots before differencing (plot1) and after differencing (plot2)

Using the "auto.arima()" command in the R package "forecast" to determine the best ARIMA model the resulting model was a regression with ARIMA(0,0,0) errors. Plots of the residuals are presented in Figure 4. The residuals are normally distributed with a reasonably equal variance around the mean. Also, there is no autocorrelation in the residuals from the ACF plot. The Box-Ljung test for the residuals was p = 0.490, meaning insufficient evidence for autocorrelation.

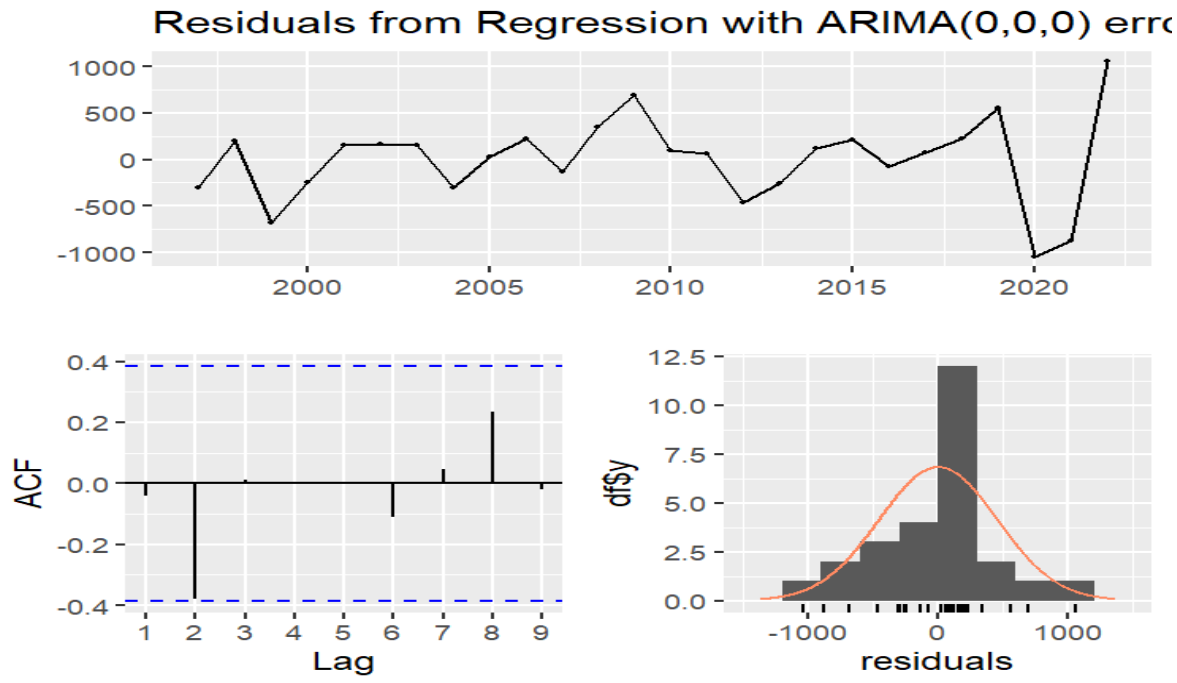

Figure 4 Residual plots of the best ARIMA model (regression with ARIMA (0, 0, 0) errors) for the number of bacteriologically confirmed.

The coefficients of the step and ramp variables were -278.5 (95% confidence interval (CI): -1118.3, 561.3) and 561.9 (95% CI: 352.3, 771.6), respectively. These indicate that there was no immediate impact on the number of bacteriologically confirmed cases of TB at the time of implementation. However, over the 5 years following its implementation the number of bacteriologically confirmed cases increased by an average of 562 cases per year.

A trend of the annual number of bacteriologically confirmed TB cases in Ghana from 1997 to 2021 with an overlay of the counterfactual (red line) after GeneXpert implementation is presented in Figure 5. Our model predicts 7559.7 (95% CI: 6947.1, 8172.3) as the number of bacteriologically confirmed cases for each of the years following the implementation of the GeneXpert. The sharp increase in observed value of 11713 in 2021 owes to the GeneXpert implementation for the diagnosis of TB in Ghana.

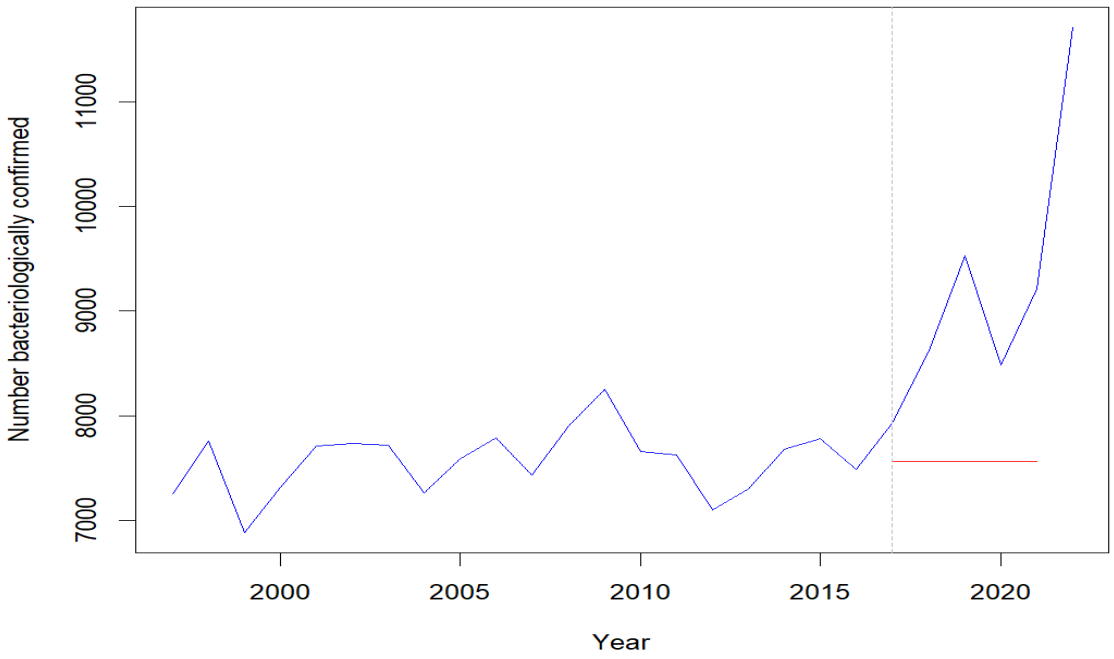

Figure 5 Trend of the annual number of bacteriologically confirmed TB cases in Ghana from 1997 to 2021 with an overlay of the counterfactual (red line) after gen expert implementation

Impact on cure rate

We postulate that the introduction of the GeneXpert to diagnose TB in Ghana will increase the cure rate. This is based on the knowledge that GeneXpert is more sensitive than sputum microscopy which was mainly used for diagnosis(Rimal et al., 2022; Tang et al., 2017). Having fewer people likely to be misdiagnosed will lead to improvement in the cure rate.

The trend plot is shown in Figure 6. The plot shows an uptrend in the cure rate until the year before the implementation of the intervention. The cure rate fell sharply in the year of the implementation and then resumed the uptrend thereafter. The plot appears non-stationary. This was confirmed with the augmented Dickey-fuller test with p = 0.93. The second difference

induced stationarity with an augmented Dickey-fuller test showing evidence of stationarity (p = 0.028).

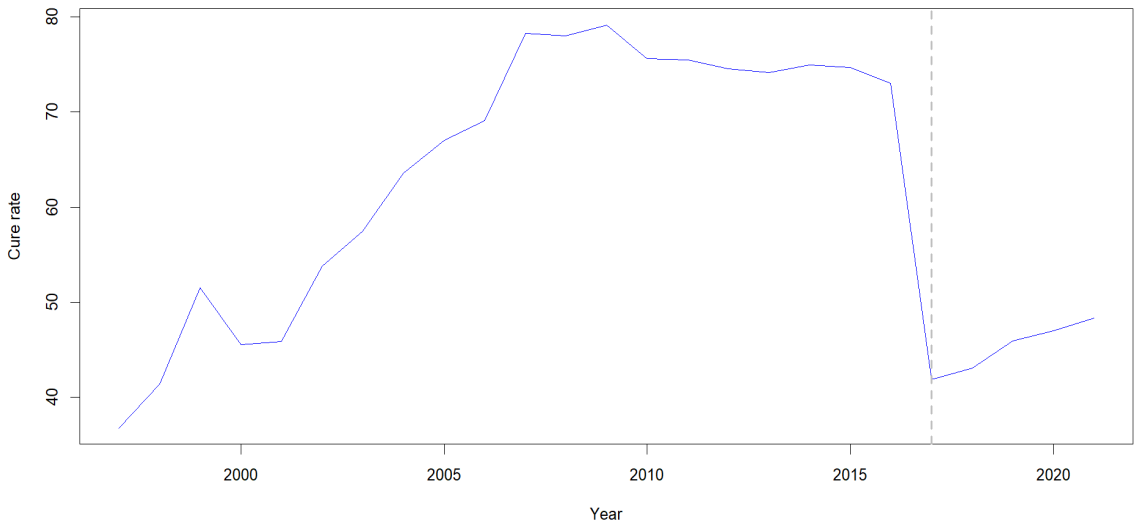

Figure 6 Trend of the annual cure rate of TB cases in Ghana from 1997 to 2021

Using the "auto.arima()" command in the R package "forecast" we determined the best ARIMA model with the information criteria as the basis for model selection. The resulting model was a regression with ARIMA (0, 2, and 1) errors. The Box-Ljung test of the residuals confirmed the goodness of fit at p = 0.670.

The step coefficient of -32.8 (95% CI: 40.5 – 25.0) indicates that the implementation of the GeneXpert had an immediate effect of reducing the cure rate by an average of 32.8%. The period after the implementation (2018 – 2021) did not see a change in trend different than that before the implementation (ramp coefficient = 1.5 (95% CI: -4.0, 7.0). The observed drop in cure rate to 41.9% in 2017 owes to the implementation of GeneXpert.

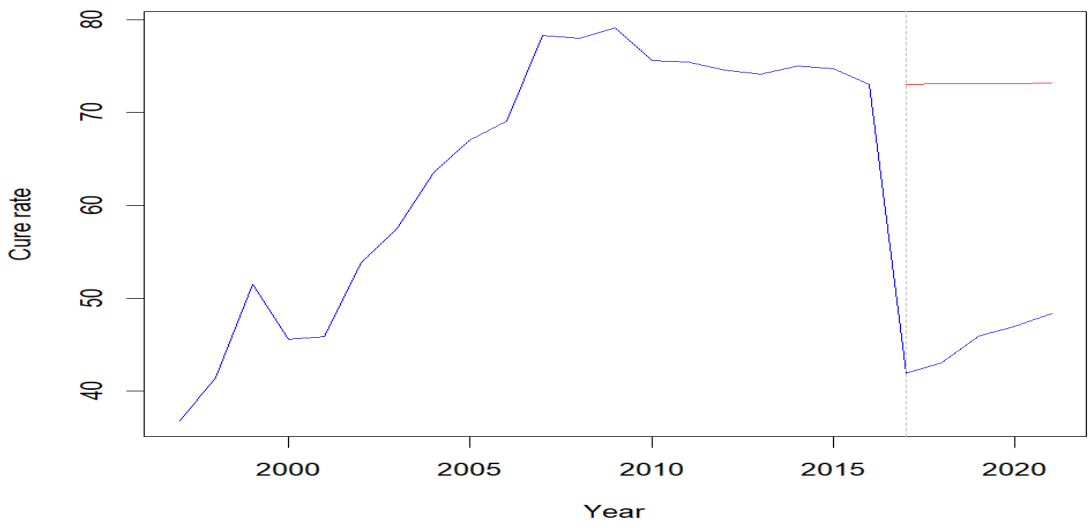

Figure 7:Trend of annual TB cure rate in Ghana from 1997 to 2021 with an overlay of the counterfactual (red line) after GeneXpert implementation.

Impact on treatment completed

We postulate that the introduction of the GeneXpert to diagnose TB in Ghana will reduce the proportion of treatment completed. This is based on the knowledge that GeneXpert is more sensitive than sputum microscopy which was mainly used for diagnosis (Rimal et al., 2022). Assuming no change in the general rate of success, an improvement in the cure rate will mean fewer people being categorized as treatment completed.

Figure 8 presents the treatment completed trend plot from 1997 to 2021. A gradual up trend is observed up to 2016 after which a sharp rise is seen. The trend shows a mild decline from 2017. The trend is non-stationary. The augmented Dickey-fuller test confirmed this $p = 0.780$ and second order differencing induced stationarity (augmented Dickey-fuller test $p = 0.018$).

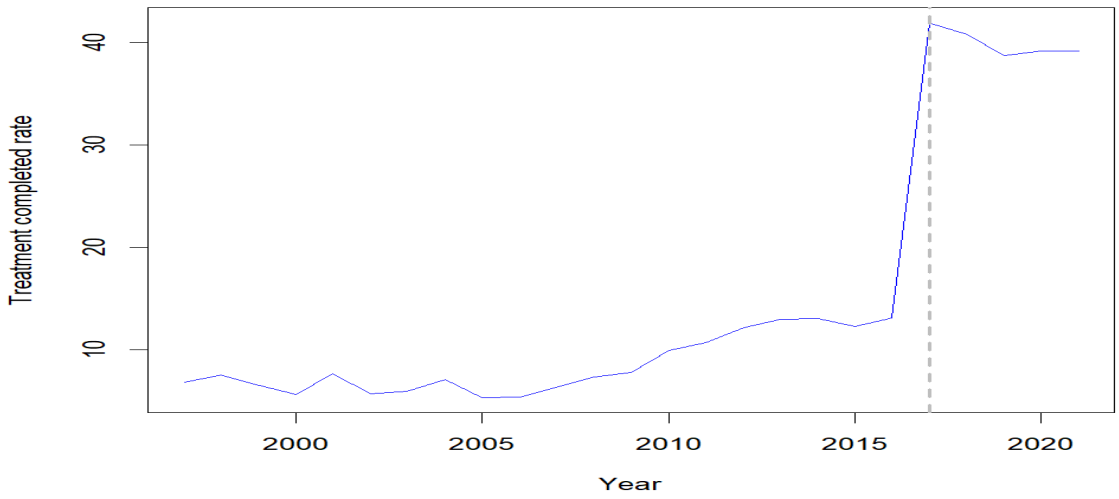

Figure 8: Trend of annual treatment completed rate of TB cases in Ghana from 1997 to 2021

The "auto.arima()" command in the R package "forecast" determined regression with ARIMA(0,1,0) errors as the best ARIMA model using the information criteria for model selection. The step and ramp coefficients were 29.4% (95% CI: 27.0, 31.9) and 1.5% (95% CI:-1.8, 0.4), respectively.

The findings show that the treatment completed rate increased sharply in the year of implementation but did not significantly differ in trend afterwards in comparison with the trend before. The observed increase in treatment completed rate from 13.2% to 41.9% is due to the intervention.

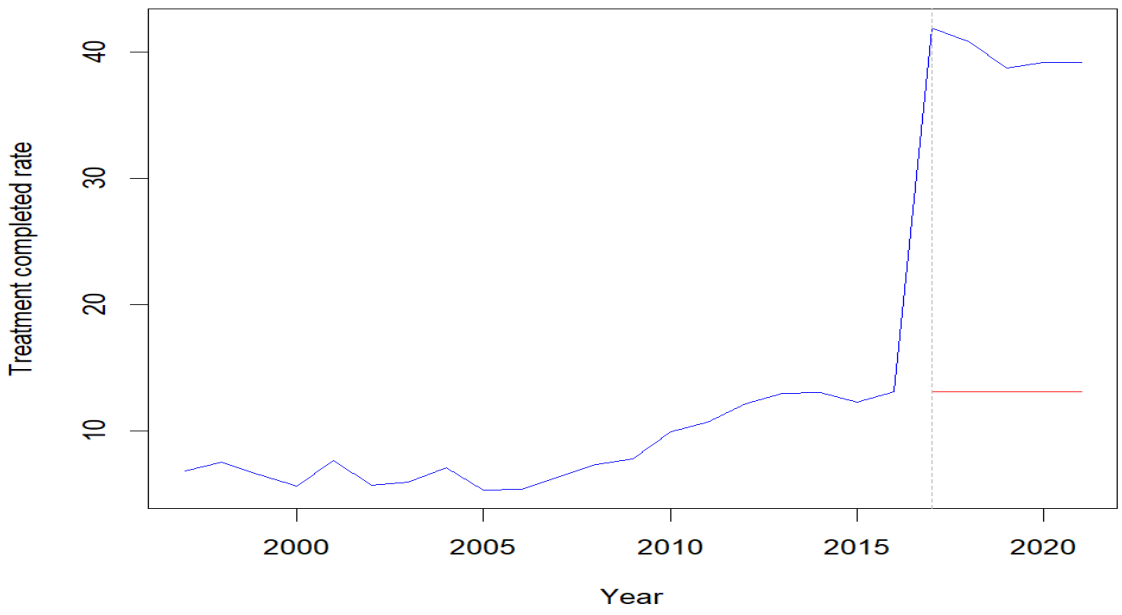

Figure 9:Trend of annual treatment completed rate in Ghana from 1997 to 2021 with an overlay of the counterfactual (red line) after GeneXpert implementation.

Impact on the rate of adverse outcomes

We postulate that the introduction of the GeneXpert to diagnose TB in Ghana will improve adverse outcomes. The plot of the trend of the adverse outcomes rate from 1997 to 2021 shows a steady drop from 1997 to 2007 after which it plateaued until 2021. The sharp fall in the rate makes the trend non-stationary (augmented Dickey-fuller test p = 0.973).

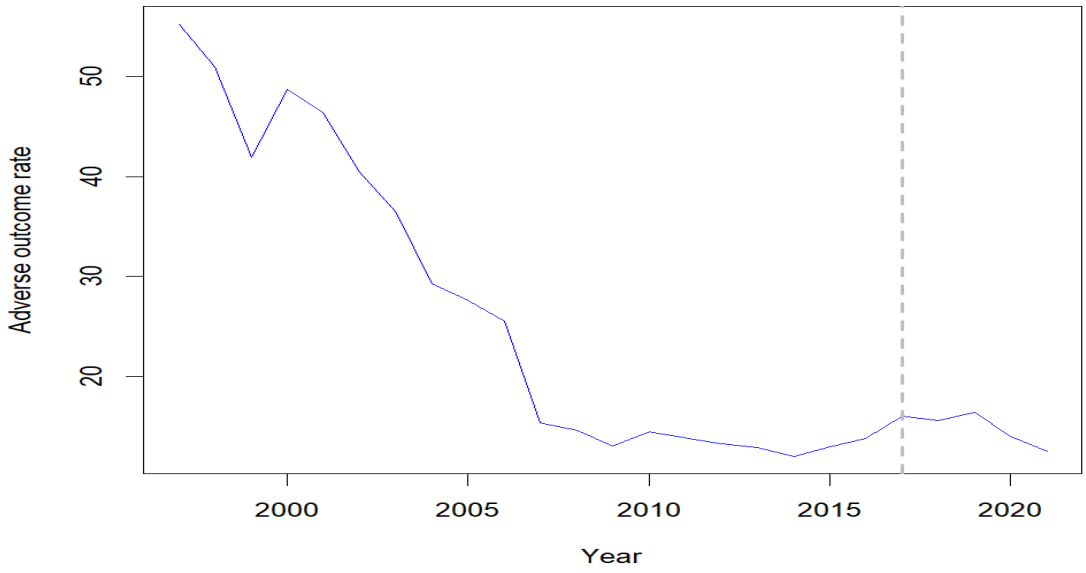

Figure 10: Trend of annual adverse outcomes rate of TB cases in Ghana from 1997 to 2021

Regression with ARIMA(0,2,1) errors was the best model and it was selected using the "auto.arima()" command in the R package "forecast" based on having the smallest Akaike Information Criterion value of all the potential models. The step and ramp coefficients were determined using this model as 3.0% (95% CI: -4.5, 10.6) and 0.2% (95% CI: -5.1, 5.5), respectively.

From the findings, the implementation of GeneXpert as the diagnostic mechanism for TB in Ghana did not have a significant sudden or gradual impact on adverse treatment outcomes.

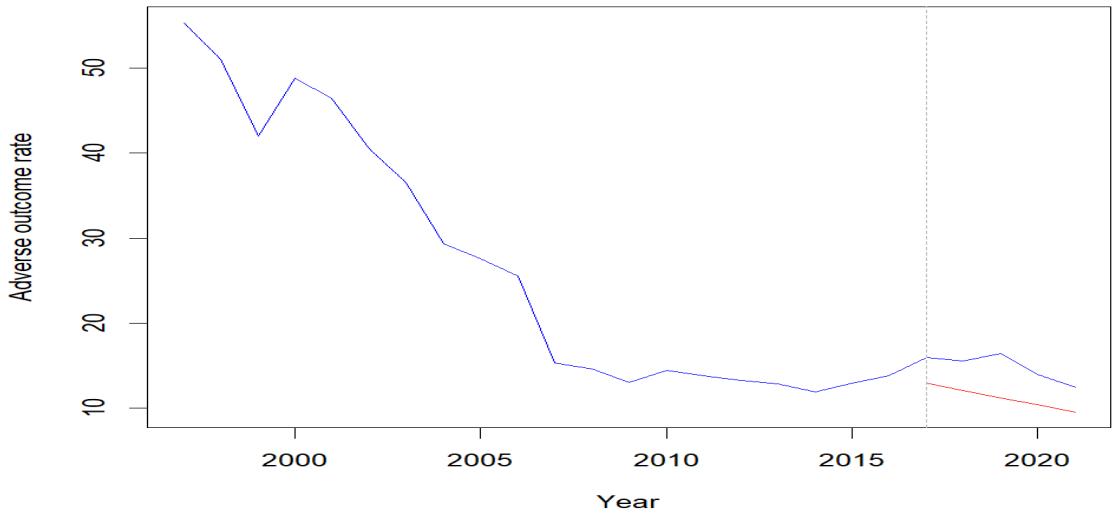

Figure 11:Trend of annual adverse TB outcomes rates in Ghana from 1997 to 2021 with an overlay of the counterfactual (red line) after GeneXpert implementation.

Discussion

Generally, the number of bacteriologically confirmed TB cases improved over time between 2017 and 2021 following the implementation of the GeneXpert intervention. However, there was no significant change in the cure rate during the implementation of the GeneXpert intervention (2018 -2021). Similarly, the findings show that the implementation of the intervention did not have a significant impact on the treatment completionrate and adverse treatment outcomes.

Previous studies showed that GeneXpert has superior sensitivity compared with the conventional sputum smear microscopy in the diagnosis of TB (Rimal et al., 2022; Sorsa & Kaso, 2021; Tang et al., 2017). It is therefore not surprising that the bacteriologically confirmed cases increasedover time during the implementation of the intervention. Our model predicts that if the intervention is implemented optimally, the number of bacteriologically confirmed tuberculosis cases per year would increase by 7559.7. Similar findings have been reported showing that

GeneXpert's technique is a game changer in the diagnosis and control of TB globally (Agizew et al., 2019; Brown et al., 2021; Habte et al., 2016; Joshi et al., 2018; Williams et al., 2022).The microbiological detection of TB is critical because it enables accurate diagnosis and ensuresthat the most effective treatment regimen is administeredas soon as possible(WHO, 2022).

While TB cases increased significantly with the implementation of the intervention, cure rates reduced by an average of 32.2% in the year of implementation (2017) and there was no difference in the cure rate before implementation. The highest (79.1%) cure rate was observed in 2009, implying that the cure rate worsened with the implementation of the intervention, falling below the internationalrecommended benchmark of 85%(Hayibor et al., 2020). This could be attributable to challenges with the sputum smear microscopy which is used for monitory treatment outcomes.Prior studies have also shown that the GeneXpert intervention did not have any impact on treatment outcomes compared with microscopy except for reduced time to diagnosis andtreatment as well as empirical treatment, corroborating what was found in this study(Agizew et al., 2019). Similarly, other studies have attributed the lack of public health impact of the GeneXpert to implementation barriers(Brown et al., 2021). It is therefore imperative to improve and strengthen laboratory capacity and infrastructure to improve TB treatment outcomes.The minor impact of the GeneXpertclinical outcomes seen in this study and previous studies is a major concern and could have dire consequences for TB control globally (Brown et al., 2021; Luca & Tanna, 2019). It is imperative for TB control programmesto institute innovative approaches to deal with barriers to the implementation of the technique.

Conclusion

Our findings indicate that, although case detection increased significantly with the rollout of the GeneXpert intervention, clinical outcomes had no impact. There is a need to address implementation challenges that could be accounting for this trend.

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