Supplementary Material

Content:

Supplementary Methods:

Laboratory Diagnosis of the TB Cases

The laboratory diagnostic algorithm for suspected TB cases involves several tests and is composed of the following steps: (I) Sample Collection: Clinical samples are collected, preserved, and transported to the designated laboratory for further analysis; (II) RMT-TB or Microscopy: The initial diagnosis is preferably performed using the Xpert MTB/RIF. If unavailable, smear microscopy can be used as an alternative. (III) MTB Culture: Samples processed for RMT-TB, with a positive result, or microscopy, regardless of the results, undergo culture to facilitate the growth of mycobacteria. In addition, culture is also recommended for treatment monitoring in cases with positive microscopy in the second month, for children, individuals living with HIV, extrapulmonary TB, retreatment cases regardless of TRM-TB results, and suspected drug resistance, treatment failure, or non-tuberculous mycobacteria (MNT) infection; (IV) Preliminary Species Identification and First-Line DS Test: If the culture yields positive results, the sample is subjected to preliminary species identification. If it belongs to the MTB complex, first-line phenotypic DS testing is conducted to determine the appropriate treatment regimen[1].

Anomaly detection test:

The *tsoutliers* package from R version 4·3·1 was used following the procedure proposed by Chen & Liu et al. (1993) for automatic anomaly detection in a time-series that identifies significant shifts in our time-series data that could indicate the impact of the intervention[2,3]. This method is particularly suited for detecting points where there are significant and sudden changes that cause large fluctuations in the data, classified as anomalies. We chose this method for its robustness in identifying meaningful changes in time-series data, crucial for accurately pinpointing intervention impacts. The test specifically looks for three types of anomalies: Level Shift, Additive Outlier, and Temporary Change. A Level Shift indicates a sudden and permanent change in the series level, suggesting an intervention or structural break. While Additive Outliers represent sudden spikes or drops in the series and Temporary Changes denote short-term deviations that revert to the original pattern in later observations[4,5]. The package also provided information on the year, estimated coefficient value, and t-statistic for each detected anomaly, as well as determining the anomaly type. P-values were calculated based on the model's t-statistic and degrees of freedom, with significance set at $p < 0{\cdot}05$.

Intervention time-series analysis

Next, the calendar year classified as the anomaly with highest impact on the model was denoted as the intervention year, which we used to segment the time series into pre- and post-intervention phases. Afterwards, different forecasting models were employed to identify patterns and create a forecasting algorithm to predict the counterfactual values of the time-series under the assumption that the intervention had not occurred. Given the constraints posed by the limited size of our dataset, we selected two prominent models highlighted by Cruz-Nájera et al's study for accurately forecasting short-sized time-series data: ARIMA (AutoRegressive Integrated Moving Average) and ForecastHybrid and models.

The ARIMA modelling was performed using the 'auto.arima' function from the *forecast* package in R version 4·3·1[6,7]. This function automates the process of identifying the most suitable ARIMA model for a given time series. It performs this by conducting a detailed search over possible model specifications and the selecting the ARIMA formula that minimizes the AICc (Corrected Akaike Information Criterion) value. The AICc is a measure used to compare the goodness-of-fit of different models while adjusting for sample size. The formula for the ARIMA model is represented as ARIMA(p,d,q)(P,D,Q)[s], where: where p and P are the orders of the autoregressive components, d and D are the others of differencing, q and Q are the orders of the moving average component, and s checks for a possible seasonal period in the time-series[6,7]. Importantly, when the model identifies

the absence of a significant trend, seasonality, or sufficient temporal dynamics in the data, the formula can be represented as ARIMA (0,0,0). This model, indicative of a random walk, projects future values to equal the last observed value, yielding a flat forecast with prediction intervals widening over time to reflect increasing uncertainty. By evaluating the AICc value in different combinations of these parameters, the function determines the most accurate possible model and ensures that the chosen model is well-suited for the data[6,7].

On the other hand, the ForecastHybrid model combines the strengths of multiple forecasting techniques, including ARIMA[7], Exponential Smoothing State Space Models (ETS)[8], TBATS[9] and the Theta Model[10], to enhance prediction accuracy. To do this, the *forecastHybrid* R package[11] automatically combines the forecast results of each model by either assigning an equal weight to each model or determining the weighting based on in-sample accuracy measures such as Mean Absolute Error (MAE), Mean Absolute Scaled Error (MASE) or Root-Mean-Square Error (RMSE). Due to the small-size of our time-series, the feed-forward neural network model (nnetar) was excluded from the ForecastHybrid modelling.

To ensure a rigorous evaluation of our models, we partitioned our data into two distinct sets. Observations from the pre-intervention phase served as our in-sample testing data, providing the foundation upon which our models were trained and fitted. In contrast, data from the post-intervention phase was reserved as a test set, allowing us to assess the models' predictive capabilities in real-world, out-of-sample scenarios. Therefore, to select the model with highest accuracy we used the Mean Absolute Percentage Error (MAPE) calculated using the out-sample data. MAPE is a measure that captures the average discrepancy between observed and forecasted values, expressed as a percentage[7.] Upon evaluating the models, those with the lowest MAPEs were chosen as our primary forecasting tools to predict the counterfactual values. The detailed accuracy results for all models, including those not selected, are reported in Supplementary Table 2.

Of note, for the phenotypic DS testing model, our analysis revealed a Level Shift in 2013, which we attribute to the launch of the Site-TB platform for special treatment TB case notifications[12]. Interestingly, while an additive outlier was detected in 2014, suggesting the initial impact of Xpert, the most significant anomaly was identified in 2015, aligning with the Xpert implementation. Given these findings, we reasoned that selecting 2015 as the intervention year might not accurately capture the pre-Xpert scenario, as ITSA influence seemingly began in 2014. Thus, to better represent the scenario without Xpert's influence and to account for the potential early impact of Xpert in 2014, we designated 2014 as the intervention year for this model.

Todo-Yamamoto Procedure for Granger Causality

To determine if observations from Xpert MTB/RIF testing could be used to improve prediction models of the future values in our time-series models depicting yearly TB and DR-TB case notification and testing, we used the concept of Granger Causality. Granger Causality is a statistical hypothesis test that evaluates whether past values of one time series can provide information that aids in predicting another time series[13,14]. For example, if time series X's historical values improve the predictability of time series Y beyond Y's past values alone, X is deemed to "Granger-cause" Y, which is represented by a p value lower than 0·05[14]. Furthermore, given the non-stationary nature of our time-series models, as confirmed by the Augmented Dickey–Fuller test, we adopted the Toda-Yamamoto procedure tailored for bivariate Granger Causality tests on non-stationary data[15]. To perform this procedure adhered to the following steps: (1) The maximal order of integration (d) was determined for all series using Augmented Dickey-Fuller (ADF) unit root tests34. (2) Constructing six vector autoregressive model (VAR) models, each incorporating the Xpert MTB/RIF testing coverage and one of the time-series data sets. The

Akaike information criterion (AIC) determined the optimal lag order (k) for these VAR models. (3) To ensure the robustness of our VAR models, we examined residual serial correlation with the Lagrange multiplier (LM)-test. (4) A Granger causality test was conducted on a new augmented VAR model, which incorporated the sum of the maximal order of integration and optimal lag order (k + d)[15].

Dynamic Regression Forecast Models

In order to perform the dynamic regression forecast models, our methodology hinged once again on the two primary models highlighted by Cruz-Nájera et al 2022: the ARIMA with external regressors (ARIMAX) and the ForecastHybrid models with external regressors[16]. In addition to fitting these models with external regressions, we also create univariate models for each time-series data and compared their out-of-sample accuracy to the dynamic regression versions. To do this, we segmented the time-series into training data (in-sample: 2011-2020) and test data (out-of-sample: from 2021-2022). The model boasting the lowest MAPE for each outcome time-series was then chosen for a 6-year forecast. For those time-series where the dynamic regression model with external regressors emerged superior, we incorporated historical Xpert MTB-RIF testing data from 2019-2022 and forecasted data for 2023-2024. Through this approach, we could validate the results of the Granger Causality test on whether Xpert MTB/RIF annual testing values can be used to better predict the future values of each outcome variable, as well as forecasts of a possible scenario on the next 6-years of TB and DR-TB notification in Brazil. However, it is critical to acknowledge that to more accurately project the future burden of TB, given its complex and multifactorial nature, necessitates the consideration of a broad array of determinants. These include comorbidities, transmission dynamics, socio-epidemiological influences, and preventative measures, each playing a role in shaping the prevalence of TB.

Moreover, after producing the 6-year forecasts for each time-series data, we also performed a Mann-Kendall (MK) test to perceive statistically significant decreasing or increasing trends on our data. To do this, we sectioned each time-series into two datasets, one including only data from the historical values and another with both the historical and forecasted values. In addition, Sen's slope estimates, including linear rate of change and 95% confidence levels, were calculated to determine the magnitude of the trend in our temporal data, quantifying the time change. A significant advantage of the Sen's Slope estimator is its resistance to outliers in the data, thus fitting well with the nature of our time-series data.

Notification of TB cases

Confirmation of TB cases, whether by laboratory analysis or clinical evaluation, is a prerequisite for notification; (II) Notification: Healthcare professionals are responsible for notifying SINAN-TB about all TB cases, which includes the submission of detailed clinical and epidemiological information about the patient, including which tests were used for diagnosis, as well as their results; (III) Treatment Accessibility: The Unified Health System (Sistema Único de Saúde - SUS) ensures that TB treatment is accessible nationwide at no cost. The standard treatment for DS-TB usually consists of a two-month intensive phase with four drugs (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol), followed by a continuation phase of at least four months with Isoniazid and Rifampicin. Treatment for DR-TB varies according to resistance type; (IV) Update Notification: data on the treatment outcome is mandatorily updated in SINAN-TB9.

Supplementary Table 1. Packages used for the statistical analyses.

Type of Analysis	R package	Version	Reference
Anomaly Detection Test	tsOutliers[5]	**8·21.1**	5
Intervention Time-Series - ARIMA Model	Forecast[17]	**8·21.1**	17
Intervention Time-Series - Hybrid Model	Forecast[17]	**5·0.19**	17
Plot graphs	ggplot[18]	**3·4·4**	18
Cross-Correlation Function	stats[19]	**4·3.1**	19
Spearman Correlation	pspearman[20]	**0·3.1**	20
Granger Causality Test	vars[21]	**1·5-9**	21
Geographical Distribution	geobr[22]	**1·8.1**	22

Supplementary Table 2. Anomaly detection test on all time-series included in the analysis.

Time-Series Data	Anomaly Type	Anomaly Detection Year	Anomaly Estimated Coefficient	t-Statistic	p-value
Total TB Cases	LS	2017	8435·00	5·83	< **0·001**
DR-TB Cases	LS	2014	908·33	5·96	< **0·001**
DS-TB Cases	LS	2014	15028·33	6·45	< **0·001**
Phenotypic DS Test	LS	2015	5887·00	14·64	< **0·001**
MTB Culture Test	LS	2015	3190.11	70.18	< **0·001**
Smear Microscopy Test	LS	2015	-3732·74	-44.17	< **0·001**

Table note: Data represents results of anomaly detection test on all time-series included in the analysis. The anomaly Type indicates the type of anomaly detected, the test specifically searched for three types of anomaly: Level Shifts, Additive Outliers, and Temporary Changes. The "**Anomaly** Detection Year" column specifies the year in which the impact initiated. Anomaly Estimated Coefficient represents the estimated coefficient for the anomaly, indicating ITSA magnitude. The "t-Statistic" column displays the calculated t-statistic value for the anomaly, which assesses the significance of ITSA effect. P-values lower than 0·05 were considered significant and are outlined in bold. Notably, all anomalies detected in this analysis demonstrated a significant impact.

Abbreviations: LS: Level Shift; TB: Tuberculosis, DR-TB: Drug-resistant tuberculosis; DS-TB: Drug-sensitivity tuberculosis; DS: Drug-sensitivity; MTB: *Mycobacterium tuberculosis*.

Supplementary Table 3. Accuracy Measures of different forecasting models for ITSA analysis

Time-Series Data	Forecast Accuracy Measures	ARIMA Model	Hybrid Model - Equal Weights	Hybrid Model - MASE Weights	Hybrid Model - MAE Weights	Hybrid Model - RMSE Weights
Total TB Cases	In-sample - MAPE (%)	**0·79%**	6·70%	6·60%	6·60%	6·50%
	Out-of-sample - MAPE (%)	**9·55%**	9·99%	10.13%	10.13%	10.19%
	Best Model	✓	-	-	-	-
Total DR-TB Cases	In-sample - MAPE (%)	9·22	5·28	1·87	1·87	**1·72**
	Out-of-sample - MAPE (%)	74·25	65·63	62·27	62·27	**62.13**
	Best Model	-	-	-	-	✓
Total DS-TB Cases	In-sample - MAPE (%)	24·80	24·49	24·47	**24·47**	24·50
	Out-of-sample - MAPE	89·86	89·54	89·51	**89·51**	89·56
	Best Model	-	-	-	✓	-
Phenotypic DS Testing	In-sample - MAPE (%)	29·32	14·80	11·31	11·31	**11·33**
	Out-of-sample - MAPE (%)	72·43	50·65	44·92	44·92	**44·75**
	Best Model	-	-	-	-	✓
MTB Culture Testing	In-sample - MAPE (%)	1·93	**1·90**	1·89	1·89	1·91
	Out-of-sample - MAPE (%)	18·82	**17·28**	17·48	17·48	17·42
	Best Model	-	✓	-	-	-
Smear Microscopy Testing	In-sample - MAPE (%)	1·27	**1·31**	1·31	1·31	1·31
	Out-of-sample - MAPE (%)	7·58	**6·75**	6·77	6·77	6·85
	Best Model	-	✓	-	-	-

Table note: Data represents MAPE accuracy values of all tested time-series models, and the best chosen to perform the forecast. The “In-sample - MAPE” row represents the accuracy measures calculated based on the observed historical used to construct the model, while the " Out-of-sample - MAPE" row presents the accuracy measure estimated on the un-seen data not included in the model creation process. Accuracy measures for the ARIMA modelling technique, in addition to different variations of the Forecast Hybrid model were included.

Abbreviations: TB: Tuberculosis, DR-TB: Drug-resistant tuberculosis; DS-TB: Drug-susceptible tuberculosis; MTB: *Mycobacterium tuberculosis*, ARIMA: Autoregressive Integrated Moving Average, MASE: Mean Absolute Squared Error, MAE: Mean Absolute Error, RMSE: Root Mean Squared Error, MAPE: Mean Absolute Percentage Error.

Supplementary Table 4. Assessment of Forecasting Model Accuracy Using In-Sample and Out-of-Sample MAPE

Time-Series Data	Best Model (Without External Regressor)	In-sample MAPE Value	Out-of-sample MAPE Value	Best Model (With External Regressor)	In-sample MAPE Value	Out-of-sample MAPE Value	Overall Best Model
Total TB Cases	ARIMA	3·03%	10.19%	Hybrid (Equal Weights)	3·09%	**4·71%**	With External Regressor
Total DR-TB Cases	Hybrid (Equal Weights)	16·37%	17.13%	Hybrid (RMSE Weights)	18.14%	**6.10%**	With External Regressor
Total DS-TB Cases	ARIMA	63·38%	3·36%	Hybrid (RMSE Weights)	27·48%	**2·08%**	With External Regressor
Phenotypic DS Testing	Hybrid (Equal Weights)	21·57%	**3·51%**	Hybrid (Equal Weights)	23·57%	6·89%	No External Regressor
MTB Culture Testing	Hybrid (MASE Weights)	4·68%	10·80%	ARIMA	3.19%	**9·02%**	With External Regressor
Smear Microscopy Testing	Hybrid (RMSE Weights)	2·95%	10·69%	ARIMA	2·88%	**6·80%**	With External Regressor

Table note: This table showcases the comparative performance of primary models used for the forecast analysis using MAPE accuracy values calculated for both in-sample (2011-2020) and out-of-sample (2021-2022) data sets. Models were evaluated based on their out-of-sample MAPE values, with the lowest MAPE indicating optimal performance. Dynamic regression model with external regressors incorporated historical Xpert MTB-RIF testing data from 2011-2019 in their construction, while univariate models did not include external regressors and relied solely on historical data from the outcome series. The models with lowest MAPE values in each category were compared in table, with the most accurate model being chosen for the 6-year forecasts.

Supplementary Table 5. Correlation and Causality Analysis Between Xpert MTB-RIF Testing and Anomaly Time-Series Data (Spearman Correlation)

Time-Series Data	Spearman-Correlation	
Target	**rho**	**p-value**
Total TB Cases	0·75	**0·007**
DR-TB Cases	0·89	**< 0·001**
DS-TB Cases	0·82	**0·003**
Phenotypic DS Testing	0·95	**< 0·001**
MTB Culture Testing	0·89	**< 0·001**
Smear Microscopy Testing	-0·63	**0·033**

Table note: This table represents results from three analyses: Spearman's rank correlation test, Cross-Correlation Function, and Toda-Yamamoto Procedure for Granger Causality. For Spearman's rank correlation, we reported both Spearman's rho and the associated p-value calculated using exact null distribution. In the Cross-Correlation analysis, we showed the correlation coefficients and the respective lag of highest correlation. All displayed cross-correlation coefficients were deemed significant based on ACF plots with a p-value less than 0·05. The Granger Causality analysis employed the Toda-Yamamoto procedure, presenting both the F-statistic and p-values. P-values lower than 0·05 are considered statistically significant and are highlighted in bold.

Supplementary Table 6. Regional Analysis of TB and DR-TB Testing and Notification Case Counts in Brazil

Characteristics	North (n = 118,438)	Northeast (n = 281,539)	Midwest (n = 51,523)	Southeast (n = 476,772)	South (n = 133,50
Xpert MTB/RIF testing					
No. of Cases	31637	54077	11596	129596	29589
Pop. Density per 100 cases	34	26	30	36	29
Total TB Cases (2014-2022)	92905	211804	39122	362595	100329
Total DR-TB Cases					
No. of Cases	1435	2998	659	7641	2566
Pop. Density per 100 cases	1·21	1·06	1·28	1·60	1·92
Total DS-TB Cases					
No. of Cases	24742	42726	9706	130475	27921
Pop. Density per 100 cases	21	15	19	27	21
Phenotypic DS testing					
No. of Cases	7475	11470	4799	81036	15589
Pop. Density per 100 cases	6	4	9	17	12
MTB Culture testing					
No. of Cases	33580	61727	17792	187354	53701
Pop. Density per 100 cases	28	22	35	39	40
Smear microscopy testing					
No. of Cases	90356	196573	35330	342295	97382
Pop. Density per 100 cases	76	70	69	72	73

Table Note: Regional analysis of TB and DR-TB testing and notification case counts in Brazil. The table includes the total TB cases notified for each region, as well as the number of cases and population density per 100 cases for various testing and notification categories, which indicates the number of notified cases for each testing category per 100 TB cases in each region. For Xpert MTB/RIF testing, data from 2014-2022 post-implementation is analysed, contrasting with other testing categories that consider data from 2011-2022 to include pre-implementation trends. The Total TB cases from 2014-2022 row is highlighted to emphasize its reference value. **Abbreviations:** MTB**:** *Mycobacterium tuberculosis;* TB: Tuberculosis, Pop: Population; 'n': the total TB cases notified for each region

Supplementary Table 7. Drug-Sensitivity Status of Total TB-Infected Population

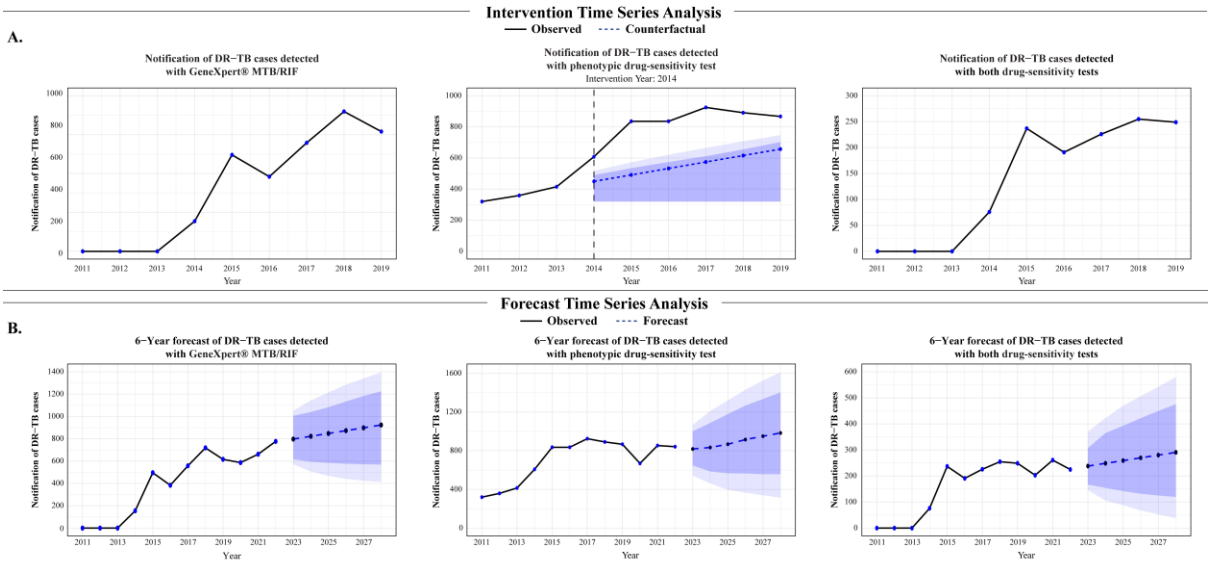
Characteristics	Total TB-Infected Population (n = 1061776)
MTB-Sensitivity Status, n (%):	
Known	250869 (23·6%)
Unknown	810907 (76·4%)

Table note: This table depicts the proportion of the total TB population with known and unknown drug-sensitivity results, with 24% of cases having known drug-sensitivity results. Abbreviations: **MTB:** Mycobacterium tuberculosis; **TB:** Tuberculosis.

Supplementary Table 8. Drug-Sensitivity Status of Total TB-Infected Population

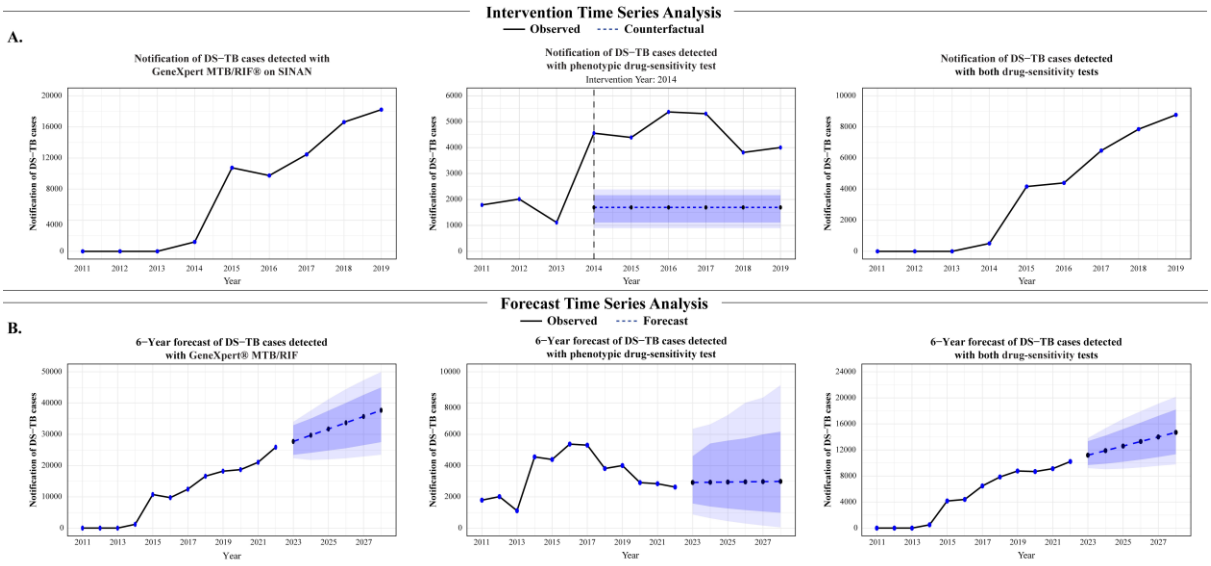
Characteristics	Total DR-TB Cases (n = 15299)	Total DS-TB Cases (n = 235570)
Resistance Screening Method, n (%):		
Phenotypic DST	8422 (55·0%)	40741 (17·3%)
Xpert MTB/RIF	4954 (32·4%)	134621 (57·1%)
Both methods	1923(12·6%)	60208 (25·6%)

Table note: This table provides a detailed breakdown of TB cases with known sensitivity results, further categorized into Drug-Resistant TB (DR-TB) and Drug-Susceptible TB (DS-TB), with the respective detection methods used, including solely Phenotypic DS test or Xpert MTB/RIF, and cases detected by both tests. **Abbreviations: TB:** Tuberculosis; **DR-TB:** Drug-resistant Tuberculosis; **DS-TB:** Drug-susceptible Tuberculosis; **DST:** Drug-Sensitivity Test.



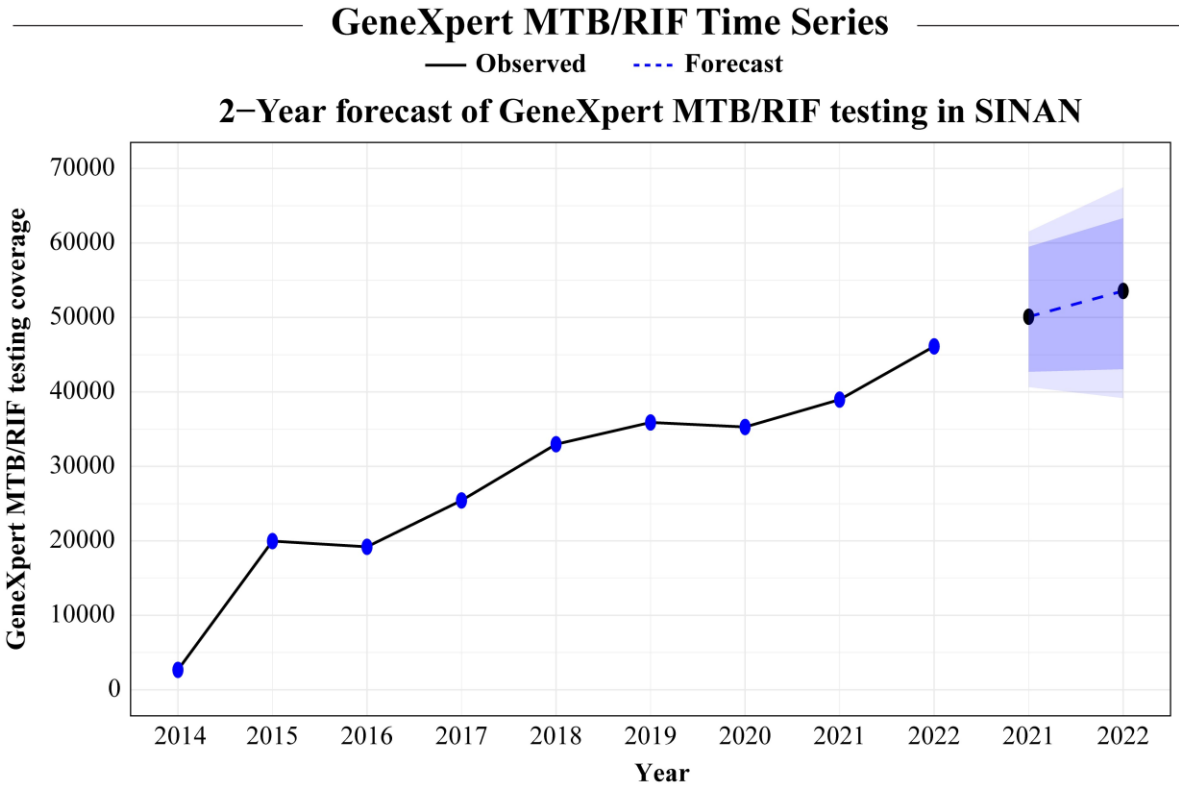
Supplementary Figure 1. Time-series analysis on DR-TB case notification categorized based on the resistance detection method. Firstly, the impact of Xpert implementation on the notification of DR-TB cases solely diagnosed via the phenotypic method, and as well as the reporting rate of cases exclusively identified solely through genotypic (Xpert) method and those diagnosed by both approaches are displayed in **Supplementary Figure 1A**. Secondly, the forecasted values are displayed from 2023-2028 in **Supplementary Figure 1B**.

Abbreviations: TB: Tuberculosis; DR-TB: Drug-resistant Tuberculosis.

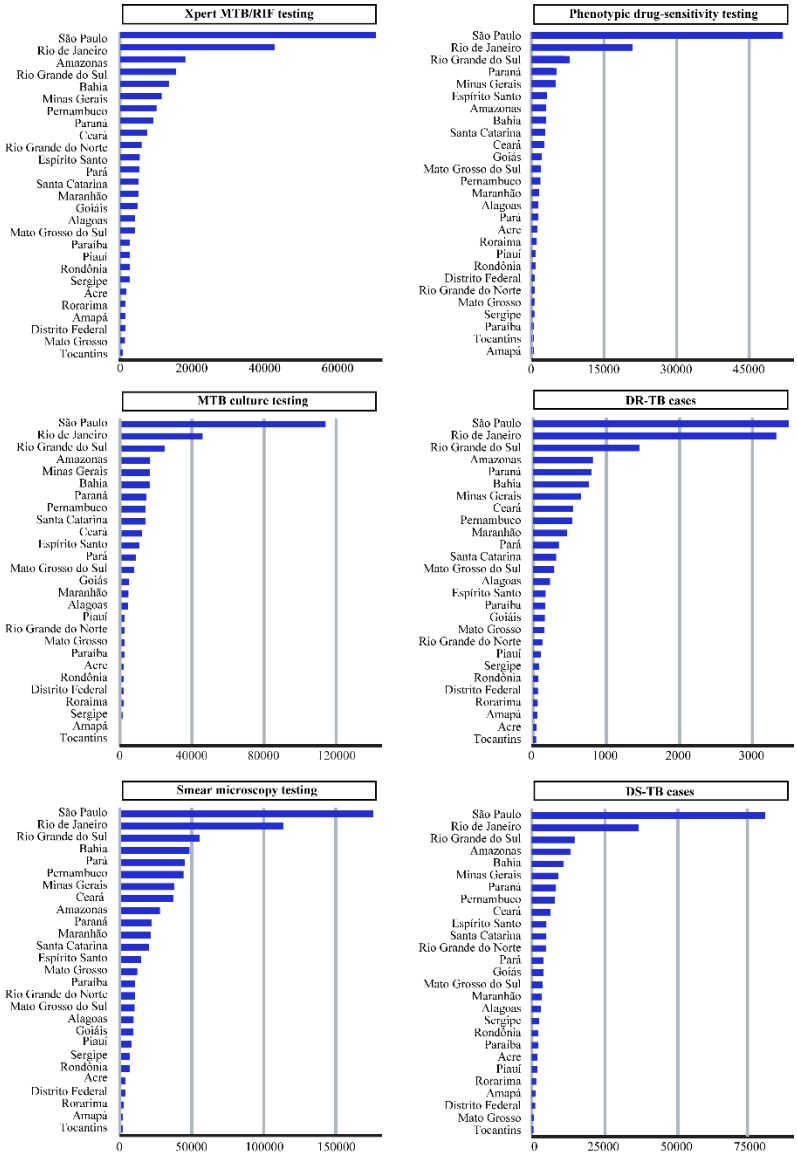


Supplementary Figure 2. Time-series analysis on DS-TB case notification categorized based on the resistance detection method. Firstly, the impact of Xpert implementation on the notification of DS -TB cases solely diagnosed via the phenotypic method, and as well as the reporting rate of cases exclusively identified solely through genotypic (Xpert) method and those diagnosed by both approaches are displayed in **Supplementary Figure 2A**. Secondly, the forecasted values are displayed from 2023-2028 in **Supplementary Figure 2B**.

Abbreviations: TB: Tuberculosis; DS -TB: Drug-susceptible Tuberculosis.



Supplementary Figure 3. 2-Year Forecast of Xpert MTB/RIF testing coverage on SINAN. This figure represents a 2-year forecast of annual Xpert testing with an out-of-sample MAPE accuracy measure of 5·04%. Prediction intervals are presented at two confidence levels: 80% and 95%. These intervals are visually differentiated by two distinct shades of blue, with the lighter shade representing the broader 95% interval.



Supplementary Figure 4. Bar graphs depicting the TB and DR-TB case notification and diagnostic testing coverage stratified by state. The figure represents the total number of notified numbers of TB cases, DR-TB and DS-TB cases and, as well as testing coverage for Xpert MTB/RIF, phenotypic drug-sensitivity, MTB culture and smear microscopy testing on SINAN between 2011-2022, are depicted in blue.

Abbreviations: TB: Tuberculosis, DR-TB: Drug-resistant tuberculosis; DS-TB: Drug-susceptible tuberculosis, MTB: Mycobacterium tuberculosis.

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