TIME-SERIES ANALYSIS ON NEW TB CASES IN KAZAKHSTAN

Author contributions:
Zhussupov had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Zhussupov, Hermosilla, Muminov, Aifah, Terlikbayeva. Acquisition of data, critical review of intellectual content and final approval of the version to be published: Zhumadilov, Abildayev, Issayeva. Analysis and interpretation of data: Zhussupov, Hermosilla, Aifah, Tinglin. Drafting of the manuscript: Zhussupov, Hermosilla, Aifah, Terlikbayeva. Statistical analysis: Zhussupov, Hermosilla. Obtained funding: Terlikbayeva, Zhumadilov, Abildayev, Issayeva, Muminov.

Abstract. Objectives. To evaluate predictive national time series model for tuberculosis (TB) incidence constructed as the sum of the regional models in comparison with a model based only on national data.

Key words: Tuberculosis, ARIMA, incidence forecasting.

Study Design
We conducted a comparison of TB forecasting models based on Kazakh national health surveillance data from 2007 to 2013.

Methods
The autoregressive integrated moving average (ARIMA) models were constructed with the data on the monthly number of newly reported TB cases from 2007 to 2012 for all administrative regions and at the national level. The first national model was built based on national data only. The second national model was the sum of the regional models. Data from 2013 were used to test the performance of the models.

Results
Seasonal ARIMA(0,1,1)(1,0,1)$_2$ model demonstrated best fit to the national TB notification rates. Regional ARIMA models varied from region to region. Mean absolute percentage error (MAPE) of the sum of regional models was 7.3, whereas the model based only on national data had MAPE equaling 10.7.

Conclusions
The sum of the regional models is more accurate than the model based on national data only. The national ARIMA model and the regional models correctly reflect Kazakhstan’s downward trend in notification of new TB cases. Improving forecasting models at a national level will help stem the multidrug-resistant tuberculosis epidemic.

Introduction
In 2012, there were 8.6 million new cases of tuberculosis (TB) and 1.3 million deaths from the disease registered worldwide, continuing a decade-long decline in the global trajectory of the disease. 1 Although
the TB incidence rate in Kazakhstan is also experiencing a downward trend, now at 73.5 per 100,000 in 2013 compared to 165 per 100,000 in 2002, Kazakhstan continues to have high incidence rate of active TB and has one of the world’s highest proportions of multi-drug resistance TB (MDR-TB) among new and previously treated TB cases. The estimated proportion of new TB-cases that were MDR-TB was sixth highest in 2012 globally and Kazakhstan is considered as a high MDR-TB burden country.\textsuperscript{1,2}

The registration of new TB cases provides a good estimate of the actual TB incidence rate,\textsuperscript{3} which varies by season in many countries.\textsuperscript{4,7} The timely prognosis of the disease is crucial in terms of planning and evaluating the subsequent public health response.

One of the well-established methods of predicting incidence, including seasonal incidence, is the Autoregressive Integrated Moving Average (ARIMA) model.\textsuperscript{8,9} ARIMA uses national data to identify the optimal model for TB incidence, and then estimates its parameters to predict future cases of the disease. In addition to direct national estimation, another way to build a national model is through the summation of the constructed regional models. After the model is created, the final step is to assess its performance by comparing it against real data.\textsuperscript{8,9}

ARIMA models create point estimates and error terms. The errors of an ARIMA model must be stationary and normally distributed:

\[ Y(t) = \hat{Y}(t) + \varepsilon(t), \]

where \( Y(t) \) is the actual value of the series at time \( t \); \( \hat{Y}(t) \) is an estimate for the time \( t \), and \( \varepsilon(t) \) is a normally distributed stationary error. Therefore, after summing independent ARIMA models, we also have a model in the same form.

Kazakhstan is an ideal location to test this hypothesis because the current TB system is consistent and doesn’t fluctuate by region. The Kazakh National TB Center coordinates all TB activities including TB surveillance and TB case notification at the national level. Regional TB dispensaries work under the supervision of regional health departments and the National TB Center. TB treatment is free for all patients with legal residence, provided by local TB dispensaries, and funded by local or central government budgets. All TB cases, new and relapsed, are continually recorded in the National TB register.

Kazakhstan has 16 administrative regions, which consist of 14 oblasts and two cities-Almaty and Astana. In geographically large countries as Kazakhstan, regions differ in terms of geography, climate, population density, and level of economic development. Taking into account such heterogeneity we expect that regional ARIMA models predicting TB incidence rates may also vary from region to region, possibly leading to inconsistencies with the national optimal ARIMA model.

We hypothesize that the national model predicting TB incidence constructed as the sum of the regional models shows a better fit than the model that is based only on national data. To examine this hypothesis, we constructed three forecasting models after analyzing the seasonality of TB in Kazakhstan. The first forecasting model is a simple application of national monthly incidence of the previous year. This approach is intuitive and widely used as a prediction method in public health when other more sophisticated forecasting methods are not available. The second model is a model of the seasonal ARIMA model based on national data, and the third model is an aggregated national model comprised of multiple regional ARIMA models. To construct these models, we used new cases of TB occurring on a monthly basis from 2007 to 2012 and then tested their performance on National TB registry data from 2013.

Materials and Methods

Study design

We evaluated TB forecasting models based on Kazakh national health surveillance data from 2007 to 2013. Data on the monthly number of newly reported TB cases at the regional and national level were obtained from the National Center for Tuberculosis. To construct the ARIMA model, we used the data over six years from 2007 to 2012. Data from 2013 were used to test the performance of the models.

Determination of seasonality

To determine the seasonality of TB notification rates, we identified whether monthly rates differ from each other. To estimate the difference we used the analysis of variance of 12 groups of incidence rates, made up by the twelve months in a calendar year.
Model identification

A seasonal ARIMA model can be represented by ARIMA \((p, d, q)(p_{12}, d_{12}, q_{12})\). The main purpose of model identification is to determine \(p, d, q, p_{12}, d_{12}, q_{12}\) values, where \(p\) and \(p_{12}\) define the number of autoregressive and seasonal autoregressive terms; \(d\) and \(d_{12}\) are number of required differences, nonseasonal and seasonal; \(q\) and \(q_{12}\), the number of nonseasonal and seasonal moving average parameters. The optimal model should produce estimations which provide the best fit to the actual data with the lowest number of parameters and allows stationarizing a time series. Selection of optimal ARIMA models was based on the minimization of Akaike’s information criterion with a correction for finite sample sizes (AICc). Models were estimated in R using the package forecast.\(^9\)

Diagnostic testing for residuals

We checked the adequacy of fitted models to the data by auto-correlation functions (autocorrelation and partial autocorrelation functions) of residuals to ensure the presence of small correlations. Histograms and Q-Q plots of errors were constructed to be sure that errors have normal distribution.

Forecasting

We conducted forecasting using the prediction equation of a known ARIMA model for 12 months of 2013. The ‘forecast’ function from the R package forecast uses existing time series data in an ARIMA model equation to forecast results. Performance of forecasting was evaluated by three measures: mean absolute deviation (MAD), root-mean-square error (RMSE) and mean absolute percentage error (MAPE).\(^8\)

Results

Seasonality

Figure 1 presents data on newly registered TB cases by month from January 2007 to December 2012. The data demonstrate monthly variation. Figure 2 compares the average values by month for 6 years, the peak of case registration is in April (1778 cases) with minimums in September (1091 cases) and December (986 cases). Analysis of variance results indicate significant differences in the incidence of monthly TB cases: \(F_{11,60} = 5.752\) (\(p < 0.001\)), which necessitates the use of seasonal (monthly) ARIMA model - SARIMA\(_{12}\).

![Figure 1 - Number of new TB registered cases in Kazakhstan, per month (2007-2012)](provided in the separate file)

Models

The first model, repetition of monthly incidence from previous year, can be recorded as SARIMA\((0,0,0)(0,1,0)_{12}\) model. The second model constructed based on the national TB notification data is a SARIMA\((0,1,1)(1,0,1)_{12}\) model. To build the third model, summing of regional models, we identified optimal models for each region (Table 1). All models were checked for errors and showed low autocorrelation values (range: \(-0.312 - 0.283\)) and partial autocorrelation values (range: \(-0.318 - 0.261\)) without patterning, thus fulfilling the requirements for modeling.\(^11\)
Figure 2 - Monthly mean number of new TB registered cases in Kazakhstan in 2007-2012

Notes. Error bars represent one standard deviation above and below the mean. (provided in the separate file)

Table 1 - Optimal ARIMA models

<table>
<thead>
<tr>
<th>Region</th>
<th>Optimal ARIMA model</th>
<th>ACF*</th>
<th>PACF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akmola</td>
<td>SARIMA(2,1,0)(2,0,0)_12</td>
<td>0.283</td>
<td>-0.283</td>
</tr>
<tr>
<td>Aktobe</td>
<td>SARIMA(2,1,1)(1,0,1)_12</td>
<td>-0.156</td>
<td>-0.160</td>
</tr>
<tr>
<td>Almaty</td>
<td>SARIMA(2,0,2)(1,0,1)_12</td>
<td>0.184</td>
<td>0.178</td>
</tr>
<tr>
<td>Atyrau</td>
<td>SARIMA(1,1,1)(1,0,0)_12</td>
<td>-0.261</td>
<td>-0.210</td>
</tr>
<tr>
<td>West-Kazakhstan</td>
<td>SARIMA(2,1,0)(0,0,1)_12</td>
<td>-0.160</td>
<td>-0.174</td>
</tr>
<tr>
<td>Zhambyl</td>
<td>SARIMA(1,1,1)(2,0,0)_12</td>
<td>0.266</td>
<td>0.251</td>
</tr>
<tr>
<td>Karaganda</td>
<td>SARIMA(0,0,0)(1,1,0)_12</td>
<td>0.238</td>
<td>0.261</td>
</tr>
<tr>
<td>Kostanay</td>
<td>SARIMA(2,1,0)(1,0,0)_12</td>
<td>-0.235</td>
<td>-0.261</td>
</tr>
<tr>
<td>Kyzylorda</td>
<td>ARIMA(4,1,2)</td>
<td>-0.205</td>
<td>-0.186</td>
</tr>
<tr>
<td>Mangystau</td>
<td>SARIMA(1,1,1)(1,0,0)_12</td>
<td>-0.181</td>
<td>-0.187</td>
</tr>
<tr>
<td>South-Kazakhstan</td>
<td>SARIMA(2,1,1)(2,0,0)_12</td>
<td>-0.199</td>
<td>-0.223</td>
</tr>
<tr>
<td>Pavlodar</td>
<td>SARIMA(1,1,1)(1,0,0)_12</td>
<td>-0.271</td>
<td>-0.318</td>
</tr>
<tr>
<td>North-Kazakhstan</td>
<td>SARIMA(0,1,1)(1,0,1)_12</td>
<td>-0.280</td>
<td>-0.262</td>
</tr>
<tr>
<td>East-Kazakhstan</td>
<td>SARIMA(0,1,1)(2,0,0)_12</td>
<td>-0.312</td>
<td>-0.313</td>
</tr>
<tr>
<td>City of Astana</td>
<td>SARIMA(0,1,1)(1,1,1)_12</td>
<td>-0.266</td>
<td>-0.273</td>
</tr>
<tr>
<td>City of Almaty</td>
<td>SARIMA(1,0,0)(2,0,1)_12</td>
<td>-0.183</td>
<td>-0.197</td>
</tr>
<tr>
<td>Republic of Kazakhstan</td>
<td>SARIMA(0,1,1)(1,0,1)_12</td>
<td>-0.197</td>
<td>-0.214</td>
</tr>
</tbody>
</table>

Notes. ARIMA = autoregressive integrated moving average; SARIMA = seasonal autoregressive integrated moving average; ACF = autocorrelation function PACF = partial autocorrelation function

*Residual ACF and PACF values having maximum absolute values.
Performance of forecasting

The predicted and actual values of new registered cases are presented in Table 2. Based on a comparison of percentage errors, Model 1 has the best prediction in June (5.0% error) and the worst in November (22.6% error). Model 2 has the best prediction in September (3.7% error) and the worst in November (17.3% error). Model 3 has the best prediction in July (-1.3% error) and the worst in November (13.2% error). Models consistently overestimated the cases (as compared to actual 2013 case registry) except for July in Model 3. Table 3 shows the model performance assessment estimates. Model 3, the forecasting model built as the sum of regional models, showed the best performance (MAD = 70.3, RMSE = 80, MAPE = 7.3) in the comparison of forecasted and actual values (Table 3).

Table 2 - Predicted and actual number of new TB cases notified by month in 2013

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
<th>New TB cases registered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted cases</td>
<td>PE*</td>
<td>Predicted cases</td>
<td>PE*</td>
<td>Predicted cases</td>
<td>PE*</td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>1166</td>
<td>10.5</td>
<td>1183</td>
<td>12.1</td>
<td>1132</td>
<td>7.3</td>
<td>1055</td>
</tr>
<tr>
<td>February</td>
<td>1230</td>
<td>7.2</td>
<td>1239</td>
<td>8.0</td>
<td>1168</td>
<td>1.8</td>
<td>1147</td>
</tr>
<tr>
<td>March</td>
<td>1012</td>
<td>10.7</td>
<td>998</td>
<td>9.2</td>
<td>957</td>
<td>4.7</td>
<td>914</td>
</tr>
<tr>
<td>April</td>
<td>1480</td>
<td>13.8</td>
<td>1453</td>
<td>11.8</td>
<td>1317</td>
<td>1.3</td>
<td>1300</td>
</tr>
<tr>
<td>May</td>
<td>1247</td>
<td>10.3</td>
<td>1270</td>
<td>12.3</td>
<td>1189</td>
<td>5.1</td>
<td>1131</td>
</tr>
<tr>
<td>June</td>
<td>1086</td>
<td>5.0</td>
<td>1149</td>
<td>11.1</td>
<td>1139</td>
<td>10.2</td>
<td>1034</td>
</tr>
<tr>
<td>July</td>
<td>1262</td>
<td>8.8</td>
<td>1221</td>
<td>5.3</td>
<td>1145</td>
<td>-1.3</td>
<td>1160</td>
</tr>
<tr>
<td>August</td>
<td>1163</td>
<td>19.8</td>
<td>1123</td>
<td>15.7</td>
<td>1090</td>
<td>12.3</td>
<td>971</td>
</tr>
<tr>
<td>September</td>
<td>944</td>
<td>7.8</td>
<td>908</td>
<td>3.7</td>
<td>946</td>
<td>8.0</td>
<td>876</td>
</tr>
<tr>
<td>October</td>
<td>1128</td>
<td>17.5</td>
<td>1111</td>
<td>15.7</td>
<td>1068</td>
<td>11.3</td>
<td>960</td>
</tr>
<tr>
<td>November</td>
<td>1182</td>
<td>22.6**</td>
<td>1131</td>
<td>17.3**</td>
<td>1091</td>
<td>13.2**</td>
<td>964</td>
</tr>
<tr>
<td>December</td>
<td>863</td>
<td>12.2</td>
<td>820</td>
<td>6.6</td>
<td>852</td>
<td>10.8</td>
<td>769</td>
</tr>
<tr>
<td>Year total</td>
<td>13,763</td>
<td>11.2</td>
<td>13,606</td>
<td>10.1</td>
<td>13,094</td>
<td>6.5</td>
<td>12,281</td>
</tr>
<tr>
<td>Model to observed difference</td>
<td>1,482</td>
<td>1,325</td>
<td>813</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: ARIMA = autoregressive integrated moving average; SARIMA = seasonal autoregressive integrated moving average
Model 1 = Previous year data SARIMA (0,0,0)(0,1,0)_12.
Model 2 = National SARIMA model (0,1,1)(1,0,1)_12.
Model 3 = Sum of regional ARIMA models predictions.
*PE = percentage error
**largest PE

Table 3 - Forecasting measure error on number of new TB registered cases in Kazakhstan (2013, per month)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MAD</td>
<td>123.5</td>
<td></td>
<td>110.4</td>
<td></td>
<td>70.3</td>
<td></td>
</tr>
<tr>
<td>RMSE</td>
<td>133.5</td>
<td></td>
<td>118.7</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>MAPE</td>
<td>12.2</td>
<td></td>
<td>10.7</td>
<td></td>
<td>7.3</td>
<td></td>
</tr>
</tbody>
</table>

Notes: MAD = mean absolute deviation; RMSE = root-mean-square error; MAPE = mean absolute percentage error.
Model 1 = Previous year data SARIMA (0,0,0)(0,1,0)_12.
Model 2 = National SARIMA model (0,1,1)(1,0,1)_12.
Model 3 = Sum of regional ARIMA models predictions.
Discussion

The national ARIMA model and the regional models correctly reflect Kazakhstan’s downward trend in TB incidence and showed a better fit compared to the prediction based on historical data. The sum of the regional models is more accurate than the national model in this high MDR-TB burden country. This is expected because more data points were used for the regional models than were used for the national model only.

The national (model 2) and sum of regional models (model 3) predicted greater incidence in 2013 than was recorded in 2013 (2013 recorded - 12,281 cases, model 2 predicted 13,606 cases, model 3 predicted 13,094 cases). This divergence in the two models from the actual observed data may be due to new intensive efforts to combat tuberculosis in the country. One of the six target indicators of the State Program of Health Care Development "Salamatty Kazakhstan" for 2011-2015 was decreasing incidence of tuberculosis.12

A limitation of this study was that we used the TB case notification rate and not the actual incidence. However, we believe that there have been no significant change in the identification of cases, the quality of diagnosis, or the reporting of case, and trends in notification is largely reflects trends in incidence. In 2012 the case notification rate was 111 per 100,000 population while the WHO reported the incident rate as 137 per 100,000 population.1

The approach of summing the regional models is valid only if incidence rates are sufficiently high, i.e. the disease is not rare. In such cases we may achieve the underlying distributional assumptions of residuals. If the disease is rare, our prediction can include negative values for cases, which are meaningless, and ARIMA models may be inappropriate. In this situation other approaches should be considered.13

Despite the fact that univariate time series analysis doesn’t account covariates including demographical, economical, behavioral, epidemiological, health system variables and isn’t considered as a commonly used approach to justify TB control measures, it can be used as a practical tool in public health practice. First, it’s very important to plan drug procurement properly. Issues with drug stock-outs have occurred in many countries, with implications such as delaying treatment or choosing alternative treatment regimes. Treatment interruptions, including those due to drug stock-outs, are associated with poor outcomes.15,16 Second, mismatch between the predicted and actual numbers can be applied as a flag to revise, reinforce or keep up current TB control activities.

The forecasting approach to predict number of new cases using ARIMA models is being implemented in everyday practice of TB system in Kazakhstan for both drug-susceptible and MDR-TB new cases and should be considered for adoption in other high burden areas.

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Ethical Approval

This protocol was reviewed and approved by the Columbia University Institutional Review Board.

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Conflict of Interest: None to declare.

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АНАЛИЗ ВРЕМЕННЫХ РЯДОВ ПО НОВЫМ СЛУЧАЯМ ТУБЕРКУЛЕЗА В КАЗАХСТАНЕ

Аннотация. Оценить прогнозируемую национальную модель временных рядов по заболеваемости туберкулезом (TB), построенную как сумму региональных моделей по сравнению с моделию, основанной только на национальных данных.

Ключевые слова: туберкулез, АРИМА, прогнозирование заболеваемости.

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Туберкулез бойынша Қазақстан мемлекеттік құмандықыестьы

ҚАЗАҚСТАНДА ТУБЕРКУЛЕЗДІН ЖАНА ЖАГАЙДАЛЫРЫ БОЙЫНША УАҚИТТЫҚ ТÍЗБЕКТІ ТАЛДАУ

Аннотация. Ұлттық мәліметтерге сүйінген ұлттық салыстыра отырғын, өңірлік ұлт жынтығы ретінде тұзғыл туберкулезден науқастанудың ұақыттық тізбесін болмамды ұлттық моделін бағалу.

Тірек сәлі: туберкулез, ауырыды әрекет.