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# **Temporal Trend Analysis of Tuberculosis in Turkey Between 2005** and 2019

2005-2019 Yılları Arasında Türkiye'de Tüberkülozun Zamansal Eğilim Analizi

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# Abstract

Introduction: Although the incidence rates of tuberculosis (TB) are declining, Turkey continues to be a high-priority country in Europe. We analyzed the trend in TB notification rates in Turkey between 2005 and 2019.

Materials and Methods: In this ecological study we obtained surveillance data and mid-year population estimates from the annual reports of the Turkish General Directorate of Public Health's Tuberculosis Department and Turkish Statistics Institute between 2005 and 2019. To evaluate the trends in TB rates, calculate the annual percent changes (APCs) for successive periods, and calculate the average APCs (AAPCs) for the entire period, piecewise log-linear Poisson regression models were used.

Results: The TB incidence decreased significantly from 2005 to 2019 in Turkey, with an AAPC of -5.7% [95% confidence interval (CI) -5.83%-(-5.61%)]. However, the TB notification rates in foreign-born individuals increased (AAPC: 23.5%; 95% CI: 22.6-24.5) during the same period. An increasing trend in TB notification rates was observed in the 0-4 years age group after 2013, with an APC of 5.6% (95% CI: 0.9-10.5).

Conclusion: TB remains an important health concern in Turkey. Healthcare executives and decision-makers should take necessary precautions to reduce the TB burden among foreign-born individuals and those aged 0-4 years.

Keywords: Tuberculosis, incidence, epidemiology, regression analysis

# Öz

Giris: Tüberküloz (TB) insidans hızı azalmakla birlikte Türkiye, Avrupa'da hala TB için öncelikli ülkelerden biridir. Bu çalışma, 2005 ile 2019 yılları arasında Türkiye'de TB bildirim hızlarının eğilimini ve kırılma noktalarını analiz etmeyi amaçlamıştır.

Gereç ve Yöntem: Türkiye'deki TB insidansını değerlendirmek için yapılan bu ekolojik çalışmada, 2005 ile 2019 yılları arasındaki gözetim verileri ve yıl ortası nüfus tahminleri, Halk Sağlığı Genel Müdürlüğü, Tüberküloz Dairesi Başkanlığı ve Türkiye İstatistik Kurumu'nun yıllık raporlarından elde edilmiştir. Ardışık dönemler için TB eğilimlerini değerlendirmek ve yıllık yüzde değişimleri (YYD) ile tüm dönem için ortalama yıllık yüzde değişimleri (OYYD) hesaplamak için piecewise log-lineer Poisson regresyon modelleri kullanılmıştır.

Bulgular: Türkiye'de 2005 ile 2019 arasında TB insidansı [OYYD: -%5,7, %95 güven aralığı (GA): -%5,83-(-%5,61)] belirgin bir şekilde azalmıştır. Ancak, aynı dönemde yabancı doğumlu bireylerde TB bildirim hızı artmıştır (OYYD: %23,5, %95 GA: %22,6-%24,5). Tüberküloz olgularını yaş gruplarına göre sınıflandırdığımızda, 2013'ten sonra 0-4 yaş grubunda artan bir trend gözlenmiştir ve YYD değeri %5,6 (%95 GA: %0,9-10,5) olarak belirlenmistir.

Sonuç: Tüberküloz, Türkiye için günümüzde de önemli bir halk sağlığı sorunudur. Başta yabancı doğumlu bireyler ve 0-4 yaş grubu olmak üzere insidansın artma eğiliminde olduğu gruplara yönelik önlemler alınmalıdır.

Anahtar Kelimeler: Tüberküloz, insidans, epidemiyoloji, regresyon analizi

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# Introduction

Tuberculosis (TB) is an airborne bacterial infection caused by an acid-fast aerobic bacillus called *Mycobacterium tuberculosis*, which can be transmitted via air droplets<sup>[1]</sup>. Tuberculosis, which is the 13<sup>th</sup> leading cause of death worldwide and the second leading cause of a single infectious agent, remains a public health concern. Approximately 9.9 million new TB cases were detected globally in 2020, and 98% of these were detected in low- and middle-income countries<sup>[2]</sup>.

All Member States of the World Health Organization (WHO) and the United Nations adopted the End TB Strategy and Sustainable Development Goals (SDGs) for reducing the TB burden<sup>[3]</sup>. Although the cumulative reduction of TB incidence was 11% worldwide from 2015 to 2020, the End TB Strategy's first milestone was not achieved<sup>[2]</sup>. The strategy includes targets to reduce the incidence and mortality rate (90% and 95% respectively) by 2035<sup>[3]</sup>. The SDGs aim to achieve universal health coverage and end the TB epidemic by 2030. According to the SDGs, countries should tackle poverty and malnutrition, invest in public health, ensure transparency and equality to successfully achieve the health goals<sup>[4]</sup>. The increase in public health expenditure per capita and improved wealth, education, and social protection are significantly associated with the reduction in TB incidence<sup>[5]</sup>. The early diagnosis and treatment of TB have also reduced disease transmission and incidence in most countries[6].

Turkey is one of the 18 high-priority countries for TB in the WHO European Region, where the incidence rates are declining<sup>[7]</sup>. Tuberculosis has been a notifiable infectious disease in Turkey since 1930 (Public Health Law no. 1593), and the treatment is free of charge. In the nationwide Directly Observed Treatment Strategy frame, the TB Surveillance System in Turkey adopted a case-based registration after 2005. Prior to 2005, the overall statistics from the TB dispensaries were registered at the tuberculosis department on a monthly basis. In 2012, laboratory-confirmed TB cases were reported through the laboratory-based surveillance system, in addition to the country-level drug resistance data. Since 2014, Turkey has actively surveilled for TB. The Turkish General Directorate of Public Health's Tuberculosis Department publishes data on the TB cases each year. According to the national TB surveillance data, the number of TB cases has declined from 20,535 in 2005 to 11,401 in 2019. The notification rate (per 100,000) had fallen from 29.8 in 2005 to 13.7 in 2019<sup>[7,8]</sup>.

Monitoring the incidence trends over time with appropriate statistical methods is a core practice of infectious disease surveillance systems. Temporal trend analysis of infectious diseases contributes to health administrators and policymakers evaluating the health system's performance during different time periods. Furthermore, it is a useful method for assessing the effect of health control programs, performance of healthcare workers, and decision-making concerning public health. Herein, we aimed to analyze the trend of TB notification rates in Turkey between 2005 and 2019 and estimate the breakpoints, with the goal of providing critical information to healthcare managers and policymakers.

# Materials and Methods

#### Data Source and Case Definitions

This ecological study included 15 years of case-based national TB surveillance data from 2005 to 2019. A total of 230,739 TB cases were notified between 2005 and 2019. In this study, we analyzed all the notified TB cases. All data were obtained from the Turkish Statistics Institute (https://www.tuik.gov.tr), Turkish General Directorate of Public Health's Tuberculosis Department, and WHO Regional Office for Europe's TB surveillance and monitoring report<sup>[7,8]</sup>. Data used in this study is publicly available. The study was approved by the Ethics Committee of the Dokuz Eylül University, İzmir, Turkey (no: 2022/13-13, date: 06.04.2022). Informed consent was not obtained as this was an ecological study.

The Turkish General Directorate of Public Health's Tuberculosis Department follows the WHO's standard case definitions for TB<sup>[9]</sup>. All notified TB cases are classified based on the history of previous TB treatment, anatomical site of the disease [pulmonary TB (PTB) or extrapulmonary TB (ETB)], origin of patients (Turkey or foreign born), gender, and age. The age groups were defined as 0-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64 and  $\geq$ 65 years.

#### **Statistical Analysis**

The total number of TB cases, new and relapse cases, PTB and ETB cases, and cases by country of birth were analyzed for the 2005-2019 period. The number of TB cases according to the age group and sex was available only from 2005 to 2018 in the surveillance reports; therefore, these data were analyzed only until 2018. The age-adjusted TB notification rates were calculated based on the European Standard Population. The rates were reported per 100,000 persons.

To evaluate the trends in TB rates, we constructed piecewise loglinear Poisson regression models. First, we fitted the generalized linear models with a Poisson distribution using the number of TB cases as a dependent variable, years as independent variables, and the population at risk as an offset variable. Subsequently, we investigated the segmented relationships within the models and estimated the breakpoints<sup>[10]</sup>. The existence of breakpoint(s) was evaluated using the Score test. The trend over specific periods before and after the breakpoint was summarized as the annual percent change (APC). The average APC (AAPC) was used as a summary measure for all the study periods. All statistical analyses were performed and visualizations were obtained using R version 4.1.2 (a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org) and the package "segmented." Statistical significance was set at p<0.05 and 95% confidence intervals (CI) of the slopes.

### Results

The TB notification rate decreased significantly by 6.44% [95% Cl: -6.60-(-6.29)] annually from 2005 to 2014 and by 4.26% [95% CI: -4.80-(-3.72)] annually from 2014 to 2019. The TB incidence showed a significant decline in the trend for the periods 2005-2014 and 2014-2019, with APCs of -6.45% and -4.18%, respectively. The TB notification rate of new cases also demonstrated a decreasing trend [AAPC: -5.53: 95% CI: -5.64-(-5.41)]. The decreasing trends were significantly observed for both PTB and ETB cases. In 2013, the trend change was determined in the notification rate of PTB. Between 2005 and 2013, the APC was -8.19% [95% CI: -8.44-(-7.93)]. Subsequently, between 2013 and 2019, the reduction in notification slowed down [APC: -3.92; 95% CI: -4.32-(-3.53)]. The notification rate of ETB decreased with an accelerated downward trend (AAPC: -4.28). The model of the TB notification rate in foreign-born individuals was broken into two segments in 2015, when a change in the trend line occurred. The increasing trend in APC was significant for all the time segments. The APCs for the first and second segments were 27.93% (95% CI: 26.32-29.57) and 13.11% (95 Cl: 10.24-16.06), respectively. While the TB notification rate increased in foreign-born individuals, it decreased in Turkeyborn individuals (Table 1, Figure 1).

Classification of the TB cases based on age groups revealed that the increasing trend in TB notification rate was observed only in the 0-4 years age group (Figure 1). The APC of the TB notification rate in this group was -7.49% [95% CI: -9.07-(-5.88)] from 2005 to 2013. Subsequently, a breakpoint was observed in 2013. Thereafter, from 2013 to 2018, the rate increased significantly by 5.63% (95% CI: 0.97-10.50) annually. In all the other age groups, the rates decreased. The trend of notification rates declined significantly in the 5-14 and 15-24 years age groups with a breakpoint in 2014. After 2014, the decreasing trend in notification rates was slower in both groups. The annual number of notified TB cases from among people aged  $\geq$ 65 years declined rapidly from 2014 to 2018. A reduction of 1.91% annually for the period 2005-2014 and 4.29% annually for the period 2014-2018 was determined to be significant. The age-adjusted TB notification rate decreased by an average of 5.02% during the entire study period. The AAPCs showed significant



**Figure 1.** Trend analysis of the TB notification rates TB: Tuberculosis

Table 1.	. Piecewise	regression	analysis	of the	<b>TB</b> notification	n rates in	Turkey	between	2005 and 2019

	First period		Second period	Entire period			
	Year	APC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)		
Overall*	2005-2014	-6.44 (-6.60, -6.29)	2014-2019	-4.26 (-4.80, -3.72)	-5.72 (-5.83, -5.61)		
New cases*	2005-2014	-6.27 (-6.43, -6.11)	2014-2019	-3.95 (-4.51, -3.39)	-5.53 (-5.64, -5.41)		
Incidence*	2005-2014	-6.45 (-6.60, -6.29)	2014-2019	-4.18 (-4.73, -3.64)	-5.70 (-5.81, -5.59)		
Country of birth							
TR-born	-	-	-	-	-6.52 (-6.63, -6.41)		
Non-TR-born*	2005-2015	27.93 (26.32, 29.57)	2015-2019	13.11 (10.24, 16.06)	23.51 (22.56, 24.47)		
Anatomical site of the disease							
PTB*	2005-2013	-8.19 (-8.44, -7.93)	2013-2019	-3.92 (-4.32, -3.53)	-6.35 (-6.48, -6.23)		
ETB*	2005-2010	-0.49 (-1.30, 0.33)	2010-2019	-6.15 (-6.44, -5.85)	-4.28 (-4.47, -4.10)		

\*Change in the slope parameter differs from zero with one breakpoint (score test, p<0.05).

APC: Annual percent change, AAPC: Average APC, CI: Confidence interval, TR: Turkey, PTB: Pulmonary tuberculosis, ETB: Extrapulmonary tuberculosis

declining trends in females [4.27%; 95% Cl: -4.48-(-4.06)] and males [6.87%; 95% Cl: -7.05-(-6.70)] between 2005 and 2018 (Table 2).

# Discussion

This study analyzed the temporal trend of TB cases in Turkey from 2005 to 2019, using piecewise regression models. A decreasing trend in TB incidence was identified until 2019, which is in line with the End TB Strategy milestones for 2020. However, the TB notification rates in foreign-born individuals and the 0-4 years age group increased.

The TB notification rate is reportedly the highest in the 25-44 years age group worldwide<sup>[2]</sup>. The TB notification rate in Turkey increased with increasing age, reaching a peak among people aged  $\geq$ 65 years. Our study determined that the TB notification rate decreased rapidly after the age of 65 years. However, there was an increasing trend in the 0-4 years age group after 2014 (APC=5.63%). The decreasing trend in TB incidence, new case rate, and TB notification rate also slowed down from 2014 to 2019. According to the Turkey Demographic and Health Survey, the Bacille Calmette-Guérin (BCG) vaccination coverage in Turkey declined from 94.4% in 2013 to 90.6% in 2018 in children aged 12-23 months<sup>[11,12]</sup>. Thus, screening activities and BCG vaccination coverage in the 0-4 years age group in Turkey should be increased and continued. Other studies have shown a decreasing trend in TB incidence across all age groups in India, China, Japan, and Northeastern Brazil<sup>[13-16]</sup>. An increasing trend of TB cases was reported in patients aged <20 years and 20-39 years in Tunisia<sup>[17]</sup>. In our analysis of the trend in TB notification rates among different age groups, we observed that the decrease

in the AAPC was significantly lower in  $\geq 65$  years age group than in the other age groups. Various factors, such as latent TB reactivation, age-related immunosuppression, and difficulties in accessing healthcare services may contribute to the lower reduction in AAPC observed in this age group.

Immigrants, especially those departing from countries with a high incidence of TB, are at risk of contracting TB for various reasons, such as the significant infection rates in their country of birth, poor travel conditions, health vulnerabilities created by pre-migration events, and poverty. The United States of America, Canada, United Kingdom (UK), Australia, and New Zealand conduct health screenings for TB before immigrants enter from countries with a high TB incidence<sup>[18]</sup>. Immigrants diagnosed with TB are not allowed to enter these countries until TB has been treated. According to the UK Security Agency's report, the TB reporting rate tended to decline for non-UK-born individuals; however, it remained 15 times higher than that for UK-born individuals<sup>[19]</sup>. With the decreasing trend in TB notification rates, foreign-born individuals account for 69.3% of the TB cases in Northern Italy<sup>[20]</sup>. Although several people from Syria, Afghanistan, and Africa have migrated to Turkey recently, Turkey does not screen for TB during immigration. Tuberculosis cases among foreign-born individuals are gradually increasing in Turkey. We observed an average annual increase of 23.51% in the TB notification rate among foreign-born individuals until 2019. In order to prevent and control TB among immigrants, social and economic policies focusing on health and socioeconomic issues should be developed<sup>[21]</sup>. Furthermore, screening programs should be implemented.

	First period		Second period		Entire period				
	Year	APC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)				
AAR	-	-	-	-	-5.02 (-5.3, -4.7)				
Sex									
Male*	2005-2014	-7.74 (-7.93, -7.54)	2014-2018	-3.64 (-4.64, -2.62)	-6.87 (-7.05, -6.70)				
Female*	2005-2007	0.49 (-2.73, 3.82)	2007-2018	-4.89 (-5.09, -4.69)	-4.27 (-4.48, -4.06)				
Age group (years)									
0-4*	2005-2013	-7.49 (-9.07, -5.88)	2013-2018	5.63 (0.97, 10.50)	-2.92 (-3.92, -1.92)				
5-14*	2005-2014	-8.41 (-9.30, -7.51)	2014-2018	-2.96 (-5.89, 0.07)	-7.01 (-7.67, -6.33)				
15-24*	2005-2014	-9.48 (-9.81, -9.14)	2014-2018	-5.16 (-7.04, -3.25)	-8.55 (-8.87, -8.23)				
25-34	-	-	-	-	-8.05 (-8.34, -7.76)				
35-44	-	-	-	-	-7.24 (-7.60, -6.87)				
45-54	-	-	-	-	-6.32 (-6.66, -5.98)				
55-64	-	-	-	-	-4.39 (-4.78, -3.99)				
≥65*	2005-2014	-1.91 (-2.45, -1.37)	2014-2018	-4.29 (-5.54, -3.03)	-2.69 (-3.01, -2.36)				

 Table 2. Piecewise regression analysis of the TB notification rates according to sex and age group in Turkey between 2005 and 2018

\*Change in the slope parameter differs with one breakpoint (score test, p<0.05).

AAR: Age-adjusted rate, APC: Annual percent change, AAPC: Average APC, CI: Confidence interval

Reports from developed countries have indicated a decreasing trend in PTB and ETB cases<sup>[19,22]</sup>. The TB notification rate for PTB and ETB in Turkey has also declined. This declining trend in PTB began to decelerate in 2013. According to the TB Surveillance Report in Turkey, smear positivity in PTB cases was 60.7% in 2013 and 52.3% in 2018<sup>[8]</sup>. Smear positivity is a marker of a more advanced disease and infectivity. This reduction may have resulted in a more rapid decrease in PTB transmission.

#### **Study Limitations**

A strength of our study is that it is a temporal trend analysis of nationwide data. Tuberculosis cases must be notified by all the health services in Turkey, and all these notified TB cases from 2005 to 2019 were analyzed in our study. However, our study had some limitations. First, this was an ecological study. Ecological studies examine exposure to the disease in populations, not individuals. Thus, these studies may cause ecological fallacy. Second, due to the lack of clinical data, we could not analyze the trend of TB notification rate based on human immunodeficiency virus status in the study. Third, because of missing data in the surveillance report, we could not identify the origin of some foreign-born individuals.

### Conclusion

TB remains an important health concern in Turkey. We determined that an increasing trend in the TB notification rate in the 0-4 years age group and foreign-born individuals. Healthcare executives and decision-makers should take necessary precautions to reduce the TB burden among foreign-born individuals and those aged 0-4 years.

#### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of the Dokuz Eylül University, İzmir, Turkey (no: 2022/13-13, date: 06.04.2022).

**Informed Consent:** Informed consent was not obtained as this was an ecological study.

Peer-review: Externally peer-reviewed.

#### **Authorship Contributions**

Concept: P.K., A.N.E., D.Ç., Design: P.K., A.N.E., D.Ç., Data Collection or Processing: P.K., A.N.E., Analysis or Interpretation: P.K., A.N.E., Literature Search: P.K., D.Ç., Writing: P.K., A.N.E., D.Ç.

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