Original Article

# Epidemiological Trends and Seasonal Dynamics of Tuberculosis in Southeastern Turkey

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ABSTRACT

**Background:** Tuberculosis (TB) is an important public health issue. Determining TB trend and seasonal variability provides useful information for designing treatment strategies and control programs. **Aim:** The present study attempts to investigate the epidemiological trend and the seasonal variations. **Materials and Methods:** TB data containing 2450 cases were collected over a period of seven years in the province of Diyarbakir in southeast Turkey. Trend function and seasonal variability were investigated by statistical curve fitting, surface fitting, and autoregressive time series analysis. **Results:** The study revealed a gradually decreasing trend in the number of TB cases over a period of seven years. Total TB incidence had seasonal variations ($P = 0.04$); there was a greater number of TB cases between April and July, with a peak in June. There were significant monthly seasonal variations with June peaks among females ($P < 0.001$), in patients in the age groups of 0–15 ($P < 0.001$) and 36–45 years ($P < 0.001$), in new cases ($P < 0.001$) and in the patients with pulmonary TB ($P = 0.01$). The extra-pulmonary TB cases peak in May ($P = 0.01$). Pulmonary TB and TB patients in the 36–45 age group had summer peak, while the other groups peaked at spring. **Conclusions:** Spring and summer peaks detected in total TB cases and in many subgroups indicate that multicenter and comprehensive clinical studies are needed to explain these variations.

**Keywords:** *Curve fitting, seasonality, surface fitting, trend, tuberculosis*

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## Introduction

Tuberculosis (TB) is an aerosol-borne global condition with high rates of morbidity and mortality. According to 2021 data from the World Health Organization (WHO), one-fourth of the world's population is infected with TB bacillus; every year, approximately 10 million people contract this disease and 1.5 million die as a result.[1] According to the report published by the Turkish Tuberculosis Department in 2020 which contains the latest 2018 data, the incidence of TB was found to be 14.1 per hundred thousand for Turkey and 10.8 per hundred thousand for Diyarbakır. The total number of cases in Diyarbakır was also reported as 187 cases.[2]

Standard TB control programs, which have many regional variations, have been developed to combat this prevalent disease. The success of TB control programs in a given region depends on the level of knowledge of the characteristics of the TB epidemiology in that region.[3] The identification of epidemiological trends over the years and seasonal variations in the characteristics of TB cases within a year may be useful for the development of successful control programs and may clarify some of the previously unknown aspects of TB pathogenesis. Most epidemiological studies in the literature are surveillance studies (based on records) and indicate the control status up to their respective dates of submission. However, only a limited number of studies

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have investigated epidemiological trends and reviewed seasonal variability.[4-9]

MATLAB is an advanced piece of computer-based software with a highly developed graphical interface that is commonly used in many science and engineering fields.[10,11] To our knowledge, only a few previous studies have used MATLAB-based forecasting models for TB epidemiology.[12] The findings of this study may be useful in investigating TB epidemics and in providing reference information for TB control and intervention.

## Materials and Methods

### Subjects (data collection)

Data from a total of 2450 TB cases (37.5% of them are extra-pulmonary TB) diagnosed in Diyarbakır and notified to the Ministry of Health between January 2005 and December 2011 (84 months) were reviewed retrospectively through records from TB dispensaries. Based on the demographic (age, gender, date of diagnosis), clinical (TB involvement sites, case definitions), and microbiological data (AFB smears and cultures) of the patients, data for 84 months were documented. Since the HIV prevalence in Turkey is negligibly low and TB cases are not routinely studied, the HIV results of the patients were not documented.[13] Monthly number of cases was determined for each TB subgroup.

### Study design (construction of models)

The data were converted to a MATLAB-processable data (mat) format. Curve fitting tool, surface fitting tool, statistical toolbox, and time series regression analysis were used to determine trends and seasonal variations. The trend (incidence-time) graph representing the total number of cases over a period of 84 months was developed, and the residual function was extracted for total TB cases and for all subgroups.

A spectral intensity heat map was constructed according to the data by using surface fitting tools, linear interpolation method. According to this method, there are three dimensions on the map; one of these is the time (years), the second represents the months of a year, and the third is the color scale referring to the intensity, which represents the number of cases per month. Of the colors in the spectral scale, the yellow color was used to indicate the highest incidence values, and the blue color to indicate the lowest.

Autoregressive time series model was used to determine seasonal variations. Time series created from the data matrixes in MATLAB. Since the series appears to have a seasonal component with a trend that can be linear or quadratic, a log transform was applied to make seasonal variation more constant. Thus, a new time series was created with this log transformation. General seasonal variations (monthly variation within year and yearly trends within months) were calculated.

The fit of the model was calculated by Ljung Box Q Autocorrelation T-test, which shows the correlation between residuals across time. A typical cutoff for hypothesis tests is to decide that $P < 0.05$ was accepted as significant at 95% confidence interval.

## Results

The data of this study includes a total of 2450 TB cases, including monthly case numbers, for the 84 months period between January 2005 and December 2011. The average number of cases notified per month was 29.7 ± 7.88. The annual incidence varied over the period understudy, with a maximum of 34 cases per month in 2005 and a minimum of 24 per month in 2011. Overall, a decreasing trend was observed [Table 1].

Using the curve fitting linear interpolation method on the basis of the number of cases per month, the total TB

**Table 1: Total case numbers of tuberculosis diagnosed per month by years**

| Diagnosis month | 2005 | | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| January | 41 | 10 | 14 | 3 | 29 | 8 | 30 | 10 | 15 | 4 | 18 | 6 | 35 | 12 | 182 | 7 |
| February | 36 | 9 | 45 | 11 | 37 | 10 | 30 | 10 | 22 | 6 | 25 | 8 | 29 | 10 | 224 | 9 |
| March | 36 | 9 | 27 | 7 | 41 | 11 | 25 | 8 | 29 | 9 | 30 | 9 | 29 | 10 | 217 | 9 |
| April | 34 | 8 | 35 | 9 | 33 | 9 | 32 | 10 | 30 | 9 | 31 | 9 | 38 | 13 | 233 | 10 |
| May | 38 | 9 | 37 | 9 | 44 | 12 | 33 | 11 | 30 | 9 | 39 | 12 | 23 | 8 | 244 | 10 |
| June | 41 | 10 | 43 | 11 | 47 | 12 | 35 | 11 | 36 | 11 | 34 | 10 | 22 | 8 | 258 | 11 |
| July | 31 | 8 | 37 | 9 | 26 | 7 | 18 | 6 | 38 | 11 | 25 | 8 | 16 | 6 | 191 | 8 |
| August | 30 | 7 | 30 | 7 | 36 | 9 | 22 | 7 | 32 | 9 | 14 | 4 | 23 | 8 | 187 | 8 |
| September | 29 | 7 | 44 | 11 | 21 | 5 | 16 | 5 | 24 | 7 | 31 | 9 | 17 | 6 | 182 | 7 |
| October | 38 | 9 | 37 | 9 | 27 | 7 | 17 | 5 | 23 | 7 | 29 | 9 | 17 | 6 | 188 | 8 |
| November | 25 | 6 | 23 | 6 | 19 | 5 | 27 | 9 | 28 | 8 | 27 | 8 | 21 | 7 | 170 | 7 |
| December | 28 | 7 | 31 | 8 | 22 | 6 | 25 | 8 | 32 | 9 | 24 | 7 | 12 | 4 | 174 | 7 |
| Total | 407 | 100 | 403 | 100 | 382 | 100 | 310 | 100 | 339 | 100 | 327 | 100 | 282 | 100 | 2450 | 100 |

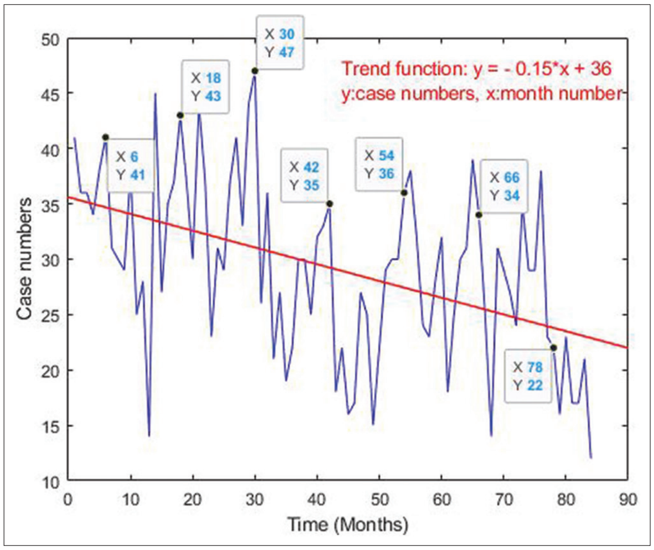


**Figure 1:** Trend function for total tuberculosis cases. The plot shows monthly number of TB cases/month over time. The decreasing of case number over time shown by linear interpolation method. Months which were marked by dots as June indicated higher case number

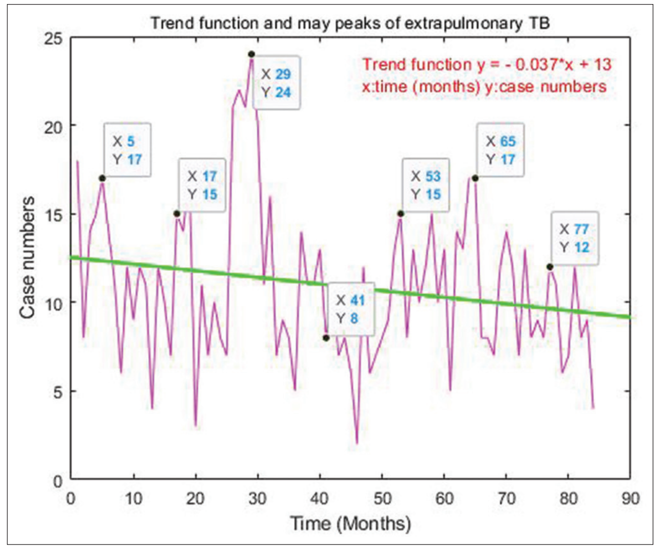


**Figure 2:** Trend function for extra-pulmonary tuberculosis cases. The plot shows monthly number of TB cases/month over time. The decreasing of case number over time shown by linear interpolation method. Months which were marked by dots as May indicated higher case number

**Table 2: Factors associated with monthly seasonal difference**

| Factors | *n* | Highest month - case ratio (%) | | Lowest month - case ratio (%) | | *P* |
|---|---|---|---|---|---|---|
| Female (gender) | 1111 | June | 11.30 | August | 6.40 | <0.001 |
| New cases | 2172 | June | 10.20 | September | 6.70 | <0.001 |
| Pulmonary TB | 1531 | June | 11.60 | August | 4.70 | 0.03 |
| Extra-pulmonary TB | 919 | May | 11.80 | August | 6.20 | 0.01 |
| Age: 0–15 years | 394 | June | 12.30 | January | 4.30 | <0.001 |
| Age: 36–45 years | 320 | June | 14.40 | December | 4.40 | <0.001 |
| Total case number | 2450 | June | 10.50 | November | 6.90 | 0.04 |

**Table 3: Factors associated with seasonal differences**

| Factors | Winter | | Spring | | Summer | | Autumn | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | |
| Female gender | 250 | 22,50 | 329 | 29,6 | 294 | 26,5 | 238 | 21,4 | 0.40 |
| New cases | 512 | 23,57 | 632 | 29,1 | 563 | 25,9 | 465 | 21,4 | 0.02 |
| Pulmonary TB | 376 | 24,56 | 404 | 26,4 | 420 | 27,4 | 331 | 21,6 | 0.01 |
| Extra-pulmonary TB | 204 | 22,20 | 290 | 31,6 | 216 | 23,5 | 209 | 22,7 | 0.01 |
| Age: 0–15 years | 88 | 22,34 | 122 | 31,0 | 113 | 28,7 | 71 | 18,0 | 0.10 |
| Age: 36–45 years | 61 | 19,06 | 88 | 27,5 | 100 | 31,3 | 71 | 22,2 | 0.01 |
| Total cases | 580 | 23,70 | 694 | 28,3 | 636 | 26,0 | 540 | 22,0 | 0.04 |

incidence trend function was identified in the form of equation [Figures 1 and 2] as y = p1*x + p2 (Coefficients: p1= -0. 15, p2 = 36 for Figure 1 and p1= -0. 037, p2 = 13 for Figure 2), where y represents number of cases and x for time. The number of TB cases per month showed a downward trend over the time. Month, which marked by dots shown in Figures 1 and 2, indicated June peaks for total cases and May peaks for extra-pulmonary TB cases with higher case numbers.

As shown on the spectral map (created by surface fitting interpolation method), every year there were a larger number of cases between April and July [Figures 3 and 4]. Within the context of the distinctly observed seasonal variations in the map, the intensity of cases in June in almost all of the years is striking TB cases (yellow-orange areas). Goodness of fit; SSE: 2.84, R-square: 0.9 and goodness of validation; SSE: 2.83, RMSE: 4.81 were calculated for total TB cases.

According to the time series autoregressive model analysis (ARIMA 1:1:2), there was a periodicity in the number of cases during 12-month periods ($P$ = 0.04 and Durbin Watson (DW) values calculated as 0.61 obtained for residues. Here the small $P$- value gives evidence that the residuals are correlated for time series plot which indicates seasonal variation [Figure 5].

The maximum percentage of cases by season had been observed in the spring (28.3%), while the minimum percentage of cases was in autumn for total TB cases (22%). When the curve was examined for each year separately, all but one exhibited a similar pattern (peak in spring/summer); however, some years were more pronounced than others. The highest monthly case numbers was found in June for every year. The maximum percentage of cases was identified in June (10.5%), and the minimum percentage of cases was in November (6.9%, $P$ = 0.041) [Tables 2 and 3, Figures 1 and 3].

When taking gender into consideration, we found that male TB patients did not have seasonal variations, while female patients had a significantly higher number of

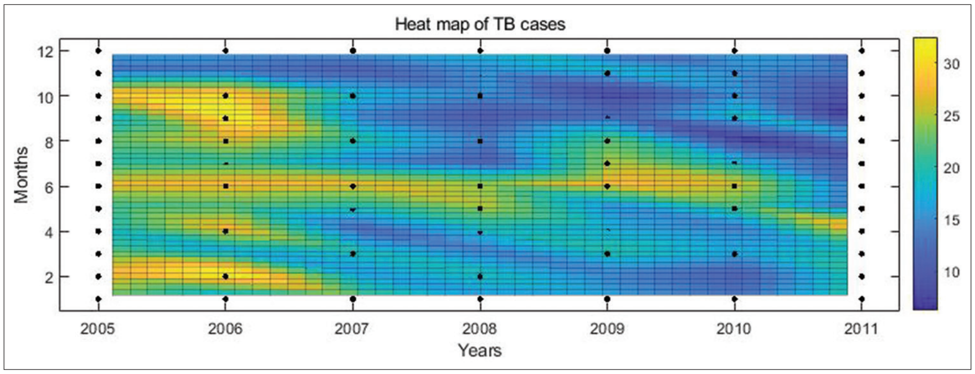


**Figure 3:** Seasonal variation heat map for total tuberculosis cases. Model constructed by surface fitting-linear interpolation method (x = years, y = months and color represents case number/month). In this spectral illustration, yellow color represents higher case number, and blue indicates lower. Condensed case number (yellow scale) seen between April and July months

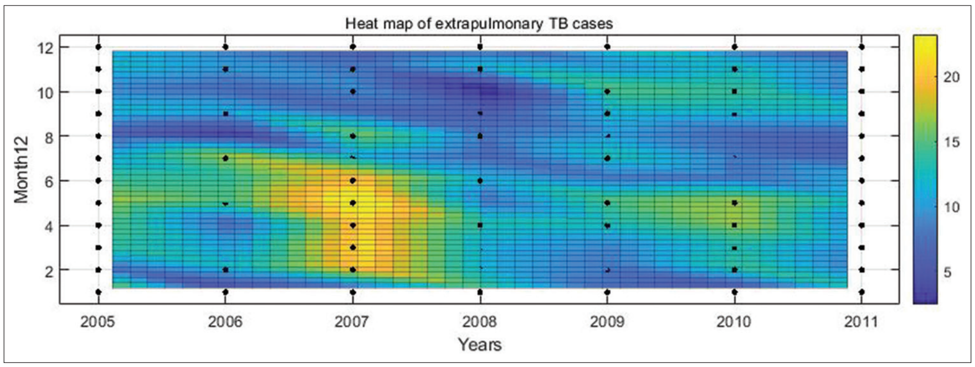


**Figure 4:** Seasonal variation heat map for extra-pulmonary tuberculosis cases. Model constructed by surface fitting-linear interpolation method (x = years, y = months and color represents case number/month). In this spectral illustration, yellow color represents higher case number, and blue indicates lower. Condensed case number (yellow scale) seen between April and June months

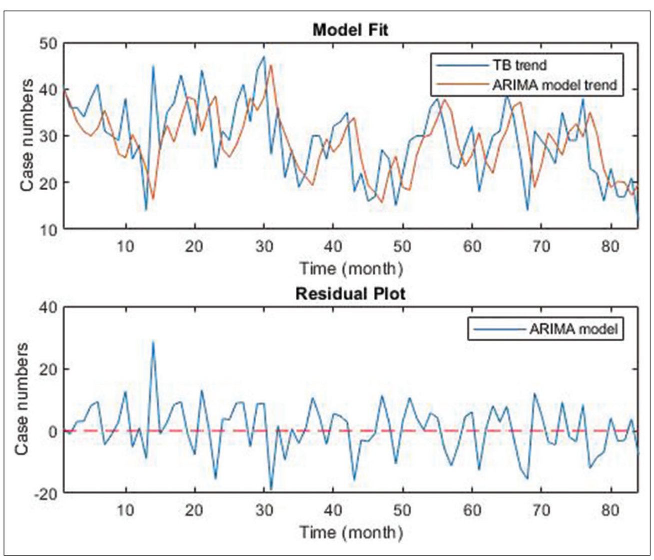


**Figure 5:** Time series autoregressive model plots. The autoregressive mean average (ARIMA 1:1:2) model to forecast optimal prediction observed data over the time (the red line represents the model plot and the blue represents the actual data curve)

cases in the spring ($P = 0.04$) and in June ($P < 0.001$) when compared to other seasons and months [Tables 2 and 3].

With regard to age, the number of cases in those patients aged 0–15 years was significantly higher in the spring ($P = 0.01$) and in June ($P < 0.001$) when compared with other times, while those aged between 36 and 45 years had a higher number of cases in the summer ($P = 0.01$) and in June ($P < 0.001$) when compared with other times. However, such seasonal variations were not present in the other age groups [Tables 2 and 3].

Considering case definitions, the peak number of new cases was observed in the spring ($P = 0.02$) and in June ($P < 0.001$); there was no seasonal variation for relapsed cases [Table 2].

With regard to TB localization, there were seasonal variations in both pulmonary TB and extra-pulmonary TB. For pulmonary TB cases, the peak number was observed in the summer ($P = 0.01$) and in June ($P = 0.03$), and for extra-pulmonary TB cases, the peak was observed in the spring ($P = 0.01$) and in May ($P = 0.01$) [Tables 2 and 3].

## Discussion

Identifying the trend of TB is very important issue for TB control strategies. A decreasing trend in cases over time is the intended goal in demonstrating good TB control. The incidence of TB in the WHO European Region has decreased by approximately 5% per year between 2000 and 2011.[14] In our study, the number of total TB cases was found in decreasing trend approximately 5.11% per year. This result, which is acceptable for WHO TB control targets, indicates that the regional TB control program is functioning properly in the population in which the present study was conducted.

Published studies have shown that TB cases peak in the spring and summer months in most countries; however, the cause of the seasonal variations in TB is not known. One theory explaining the seasonal variations is that; TB bacillus is known to be transmitted in crowded and closed spaces during the winter months and emerges as a disease in the spring and summer months following an incubation period of two to three months.[15-17] In a study conducted in New York City, the incidence of TB was at its highest in the spring and at its lowest in the autumn; this finding was attributed to the diagnostic delays in TB.[17] The fact that both pulmonary and extra-pulmonary TB forms peak in the spring and summer months, both in our study and in the different studies mentioned, shows that seasonal variability cannot be attributed only to the delay in diagnosis, and that this situation may be caused by season-specific social, climatological, or biological factors those have not yet been discovered. However, the late peak of pulmonary TB compared to extra-pulmonary tuberculosis in this study may be attributed to the fact that the diagnosis of pulmonary tuberculosis is delayed because the non-specific symptoms of pulmonary TB can be confused with many pulmonary infections and non-infectious diseases.

Furthermore, another study suggested that low post-winter trough levels of vitamin D (which are known to affect macrophage function and cell-mediated immunity) lead to impaired cellular immunity, thereby inducing, following a latent period, reactivation of dormant mycobacterial infection.[15] However, Fares[18] attributed the seasonal variations in TB to the warm clothing preferred during the winter months, reduced vitamin-D synthesis due to lower exposure to sunlight, or seasonal variations in immune competency in a year. A study conducted in Australia reported a lower level of seasonal variations in TB cases in the northern parts of the country, where the ultraviolet (UV) index never dropped below 4, even in the winter months, when compared to regions where the UV index values fall below 3.[16] In a study performed in India, TB diagnoses peaked between April and June and reached a rare between October and December in Northern India; however, no seasonal variation was observed in Southern India.[19] In the aforementioned study, two different regions of India were compared. However, since our study was conducted in a single province, it is not possible to make a regional comparison.

On the other hand, a study performed in the United States reported a significantly higher disease incidence in March when compared to November; however, they reported no difference arising from variations in altitude.[20] As mentioned before, we cannot make any inferences about altitude and seasonality, since the present study is local and does not contain data from different altitudes.

A study conducted in the USA has shown that seasonal changes are especially detected in the age group younger than 15 years.[20] Likewise, in the present study, seasonal and monthly variations were significantly higher in the age groups of 0–15 years and additionally in the age between 36 and 45 years and female population.

In our region, female and pediatric population have a more sedentary lifestyle compared to men and other age groups. They may be exposed to the bacillus, probably due to longer close contact with active TB patients in closed environments. Furthermore, indoor lifestyle may affect the vitamin D synthesis negatively which is necessary for macrophage function regulation.

In a seven-year immunological study performed with healthy individuals to consider the rise in TB in the spring and summer seasons, no significant seasonal variations were specified in the total number of white cells or total lymphocyte counts. However, the absolute number of CD4+ T lymphocytes was the lowest in the summer, which also had the highest CD8+ T lymphocytes. One may speculate that seasonal variations in the absolute numbers and ratios of T-helper and -suppressor cells could cause changes in cell-mediated immunity, which is a crucial element in the host response for controlling infection with Mycobacterium TB.[21] Nevertheless, the factors regulating the seasonal variations in T-cell subset numbers or functions remain undetermined.

The important limitation of our study is the inability to measure the effect of populations with different regional, altitude, geographical, and sociodemographic characteristics, since it is a single-center study. Another limitation of our study is that, rather than finding the direct cause of seasonal variability such as vitamin D and immune mechanisms, it is a retrospective study with an epidemiological nature, trying to find the trend and focusing on investigating whether there are seasonal variations.

## Conclusions

In the present study, remarkable seasonal differences were detected with spring and summer peaks in many subgroups of TB cases. It seems that multicenter and comprehensive clinical studies are needed to elucidate these variations, the cause of which is still unknown.

### Ethical statements

The study was prepared, conducted, and written within the framework of ethical standards.

### Author contributions

Mahsuk Taylan, Sibel Dogru, Cengizhan Sezgi, and Sureyya Yılmaz had the same contribution to this paper. Study conception and design: Mahsuk Taylan. Acquisition of data: Mahsuk Taylan, Sureyya Yılmaz, Sibel Dogru. Analysis and interpretation of data: Mahsuk Taylan, Sureyya Yılmaz. Drafting of the manuscript: Sureyya Yılmaz, Sibel Dogru, Mahsuk Taylan. Critical revision: Cengizhan Sezgi. Approval of the final manuscript: all authors.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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