The Relationship Between Seasonality, Latitude and Tuberculosis Notifications in Pakistan

Mohsin F. Butt (m.butt@qmul.ac.uk)
Queen Mary University of London https://orcid.org/0000-0003-0859-6470
Sidra Younis
National University of Medical Sciences, Rawalpindi, Pakistan
Zhenqiang Wu
University of Auckland
Syed H. Hadi
National TB Programme
Abdullah Latif
National TB Programme
Adrian R. Martineau
Queen Mary University of London

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Abstract

Background

Pakistan is amongst the top 20 highest burden tuberculosis (TB) countries in the world. Approximately 369,548 cases of TB (all forms) were notified in 2018, with an estimated incidence of 265 per 100,000 people per year. In other settings, TB has been shown to demonstrate seasonal variation, with higher incidence in the spring/summer months and lower incidence in the autumn/winter; the amplitude of seasonal variation has also been reported to be higher with increasing distance from the equator.

Methods

Notifications of newly-diagnosed pulmonary and extrapulmonary TB cases were obtained for 139 districts in Pakistan from 2011–2017. Data were provided by the Pakistan National TB Control Programme, Islamabad, Pakistan. Statistical analyses were performed to determine whether there was seasonal variation in TB notifications in Pakistan; whether the amplitude of seasonal variation in TB notifications varied according to latitude; whether the amplitude of seasonal variation of TB in Pakistan differed between extrapulmonary TB vs. pulmonary TB. To assess the quarterly seasonality of TB, we used the X-13-ARIMA-SEATS seasonal adjustment programme from the United States Census Bureau. The mean difference and corresponding 95% confidence intervals of seasonal amplitudes between different latitudes and type of TB were estimated using linear regression.

Results

TB notifications were highest in quarter 2, and lowest in quarter 4. The mean amplitude of seasonal variation was 25.5% (95% CI 25.0–25.9%). The mean seasonal amplitude of TB notifications from latitude 24.5ºN-<26.5ºN was 29.5% (95% CI 29.3–29.7%) whilst the mean seasonal amplitude of TB notifications from latitude 34.5ºN -<36.5ºN was 21.7% (95% CI 19.6–23.9%). The mean seasonal amplitude of TB notifications across Pakistan between latitudes 24.5ºN to 36.5ºN reached statistically significant difference ($p < 0.001$). The amplitude of seasonal variation was greater for extrapulmonary TB (mean seasonal amplitude: 21.6%, 95% CI 32.1–33.1%) vs. smear positive pulmonary TB (mean seasonal amplitude 32.6%, 95% CI 21.4–21.8%), $p < 0.001$.

Conclusion

TB notifications in Pakistan exhibit seasonal variation with a peak in quarter 2 (April-June) and trough in quarter 4 (October-December). The amplitude of seasonality decreases with increasing latitude, and is more pronounced for extrapulmonary TB than for pulmonary TB.

Background

Tuberculosis (TB) is an infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex, which can spread by small airborne droplets (1). TB was the leading cause of death from a single infectious pathogen in 2016 (2) and is highly epidemic in Pakistan. According to 2018 figures from the World Health Organisation, Pakistan is amongst the top 20 highest burden TB countries in the world, with an estimated incidence of 265 per 100,000 people per year (3).

Studies conducted in various countries in the northern hemisphere have identified peak months of TB notification in spring (March to May) (4-10), late spring and early summer (April to June) (7, 11, 12), or summer (June to August) (13-16). Trough months have been noted in the fall (September to November) (5), late fall and early winter (October to December) (4, 6, 11, 12), or winter (January to February) (15). TB notifications have been shown to peak in October in Australia (22) and South Africa (19), but this is the month of local spring in the southern hemisphere. To our knowledge, Khaliq et al. (17) have been the only group to explore the seasonality of TB in Pakistan. The group studied the seasonal variation in newly diagnosed pulmonary TB cases notified to the directly observed therapy short course of the national TB programme in a single district (Lahore) from 2006-2013. In this study, the seasonal adjusted factor showed peak TB notifications in the second quarter of the year (April to June) in Lahore, Pakistan (17).

Several hypotheses have been put forward to explain the relationship between TB and seasonality, one of which implicates seasonal variation in vitamin D (18). In a cross-sectional study conducted in South Africa over eight-years, we reported a reciprocal seasonal relationship between reduced serum vitamin D concentration and increased TB notifications (19). We have also shown that *in vivo* vitamin D supplementation enhances immunity to mycobacteria both in healthy people (20) and in a genetically defined subgroup of patients with active TB (21). If the vitamin D hypothesis is true, latitude should be correlated to TB seasonality. Indeed, at the extreme latitude, there is insufficient ultraviolet B-ray (UVB) intensity in the autumn and winter months for adequate synthesis of vitamin D, thus the seasonal amplitude of TB notification may be greater (9). This hypothesis is supported by studies conducted in Australia (22) and India (12), which show a more pronounced amplitude of seasonal variability in regions with less UVB exposure.

We hypothesise greater seasonal variation in the number of notifications of extrapulmonary TB compared to pulmonary TB. In India, extrapulmonary TB has been reported to have greater seasonal variation compared to pulmonary TB (12). A study (23) investigating the relationship between vitamin D and disease phenotype reported a specific association between vitamin D deficiency and development of extrapulmonary tuberculosis, raising the possibility that amplitude of seasonal variation might be greater for extrapulmonary TB than for pulmonary TB.

Hitherto, no study has investigated the relationship between seasonality, latitude and TB notifications in Pakistan, which could guide public health interventions and policy decision making. We therefore conducted the current study, with three aims: to determine whether there is seasonal variation in the notifications of active TB in Pakistan; to determine whether the amplitude of seasonal variation of active TB varies according to latitude; and to determine whether the amplitude of seasonal variation of TB in Pakistan differs between extrapulmonary TB vs. pulmonary TB.

Methods

Data for newly diagnosed smear positive pulmonary and extrapulmonary TB cases were obtained for 139 districts (see supplementary table 1) in Pakistan from 2011-2017. Data were provided by the Pakistan National TB Control Programme, Islamabad, Pakistan. Data were provided quarterly: quarter 1 (January-March), quarter 2 (April-June), quarter 3 (July-September), quarter 4 (October-December). In the Pakistan National TB Control Programme, smear positive pulmonary TB is diagnosed using sputum smear microscopy, whereby two sputum samples are collected under a microscope for the presence of acid fast bacilli, whilst extrapulmonary TB is diagnosed using clinical methods or histopathology (24). The latitudes of each of the 139 districts were obtained from the following website: https://latitude.to/ .

To assess the quarterly seasonality of TB, we used the X-13-ARIMA-SEATS seasonal adjustment software from the United States Census Bureau, which is widely considered as one of the best seasonal adjustment methods (9). The quarterly time series was decomposed into (a) the trend component that reflects the long-term progression of the series, (b) the seasonal component that reflects seasonal variation, and (c) the irregular component (or “noise”) that describes random, irregular influences (R package: ‘seas’). A decomposition of monthly notification was conducted for extrapulmonary and pulmonary TB. The mean peak month, trough month and annual seasonal amplitude with 95% confidence intervals (CIs) were calculated if identifiable seasonality was assessed by WO-test (25). The annual seasonal amplitude was calculated from isolated seasonal factor and defined as the fraction with the numerator representing the peak-to-trough different between the months with the highest and the lowest case counts and the denominator as the mean case counts for that year. The mean difference and corresponding 95% confidence intervals of seasonal amplitudes between different latitudes and type of TB were estimated using linear regression. Statistical analyses were performed using R version 3.6.3. A p value<0.05 was considered statistically significant.

Data from the Pakistan National TB Control Programme were aggregated without any personal information, hence informed consent was not required. The study was approved by the Institutional Review Board of the National University of Medical Sciences, Rawalpindi, Pakistan (reference number: NUMS/PVC-19/R&D/ORIC/IRB&EC).

Results

A total of 12,295,88newly diagnosed pulmonary and extrapulmonary TB cases were notified to the Pakistan National TB Programme for 139 districts from 2011 – 2017. The notification of newly diagnosed pulmonary and extrapulmonary TB cases are presented in **figure 1.** The original time series of monthly notifications of active TB cases displays consistent annual periodicity and seasonal fluctuation. The X-13-ARIMA-SEATS seasonal adjustment method was then used to decompose the original time series into three components: trend cycle **(figure 2A)**, seasonal component **(figure 2B)**, and remainder component **(figure 2C)**. The trend cycle reflects the long-term progression of the time series where the high frequency fluctuations have been filtered out. Our trend cycle shows a general upward trend of TB notifications from 2011 to 2017. The seasonal component (referred to as the seasonality of the time series) is that part of the variations in a time series representing intra-year fluctuations that are more or less stable year after year with respect to timing, direction and magnitude. Our seasonal component did not change over time. The remainder (irregular) component includes random fluctuations, abnormal values, and other irregular factors. Of note in our remainder component is the marked reduction in the notifications of TB in quarter 2 of 2018, but the reasons for this are unclear. Analysis of the isolated seasonal component revealed that the annual seasonal amplitude for TB notifications was 25.5% (95% CI 25% to 25.9%), suggesting an annual mean of 25.5% additional cases of TB diagnosed in the quarter two (April – June) compared to quarter four (October – December).

Table 1 shows the effect of latitude on the seasonal variation of tuberculosis notifications and the difference in the mean seasonal amplitude of extrapulmonary and pulmonary TB.Increasing distance from the equator was associated with a reduction in mean seasonal amplitude of TB notifications ($p<0.001$). At districts closer to the equator (latitude range 24.5ºN - <26.5ºN), the mean seasonal variation of TB was 25.5% (95% CI 25.0% to 25.9%) whilst districts further away from the equator (latitude range 34.5ºN - <36.5ºN) had a mean seasonal variation of TB of 21.7% (95% CI 19.6% to 23.9%). The mean seasonal amplitude for extrapulmonary TB notifications was 11% (95% CI 10.6% to 11.5%) higher than for pulmonary TB, $p < 0.001$. The mean seasonal amplitude of TB notifications across Pakistan (latitude ranges 24.5ºN - 36.5ºN) is graphically illustrated in **figure 3.**

Discussion

To our knowledge, we are the first group to investigate the seasonality of tuberculosis across the whole of Pakistan and the effect of latitude on this relationship. We report seasonal variation of TB notification across 139 districts in Pakistan, with a peak in TB notifications in quarter two (April-June) and trough in quarter four (October-December). The amplitude of seasonal variation in TB notifications was greater in regions closer to the equator. Seasonal variation in notifications was also more pronounced for extrapulmonary TB than for pulmonary TB.

The results of our study are consistent with those of a smaller study looking at the seasonality of TB in a single district, Lahore, Pakistan, in which the investigators showed a peak in pulmonary TB cases in the second quarter of the year (17). Several studies (6, 9, 12, 22) have explored the relationship between distance from the equator and seasonal variation of TB, and it is plausible that the seasonality of TB is more pronounced in areas where UV exposure is reduced and dermal vitamin D synthesis is low (12, 22). Contrary to a study published in India (12), which showed Northern areas to have greater seasonal variation than those in central southern regions, our study shows reduced seasonal variation in regions further from the equator. Our results are consistent with a study looking at the seasonality of TB in Xinjiang, in which greater seasonality was noted in southern Xinjiang (34ºN-42ºN) than eastern and northern regions (43ºN-48ºN); however, the difference was not statistically significant (9). In the USA, the amplitude of TB seasonality has not been shown to vary according to latitude (6).

Several hypotheses have put forward to explain the relationship between seasonality and tuberculosis, including winter indoor crowding, the seasonal variation of other respiratory infectious diseases, dietary nutrient intake and dermal synthesis of vitamin D. During the winter season, indoor activities are more common than in a warm climate, which exposes people to tubercle bacilli expelledfrom infected people in a room with closed windows (26-28). Several other respiratory infectious diseases, both viral and bacterial, peak during the winter (29), which may suppress host immunologic capacity and make people more vulnerable to primary infection or activation of latent TB (6). Seasonal variations in the dietary intake and meal patterns of humans may also affect immune system functions, which may be linked with seasonal variability of TB (26). Vitamin D plays a putative role in the pathogenesis of a variety of respiratory infections (30-32), and it is possible that reduced exposure to sunlight during the winter months (and the consequential reduction in cutaneous vitamin D synthesis) can make a host more susceptible to infection with *Mycobacterium tuberculosis* (33-35).

Key strengths of this study are that we have pooled outcomes of pulmonary TB and extrapulmonary TB to maximise power. Moreover, we studied the seasonality of pulmonary TB and extrapulmonary TB separately and demonstrated that seasonal variation of extrapulmonary TB was more marked than for pulmonary TB. Data were analysed on a district level, which maximized their granularity. Our analysis also has limitations. Data were not collected on a monthly basis; hence it was not possible for us to identify the specific month/s of the year in which TB peaked or nadired. Data on sex and age were not available for each year, hence we were not able to study whether these variables affected the amplitude of seasonal variation (6) nor if different age groups or sexes had a different peak/trough of TB notifications (10). Other important confounding variables that have been shown to affect the seasonality of TB in other settings include air pollution (37), HIV status (38) and climate parameters, such as rainfall and temperature (26). We were also unable to collect data on the rural or urban nature of the different district. This would be important given a significant body of evidence demonstrates greater UV exposure in rural compared to urban areas (39-41), hence the seasonality of TB might be more pronounced in rural regions. Lastly, we only included smear-positive pulmonary TB patients in this study, hence the results are not applicable to all forms of pulmonary TB.

In conclusion, TB notifications in Pakistan exhibit seasonal variation with a peak in quarter 2 (April-June) and trough in quarter 4 (October-December). The amplitude of seasonality decreases with increasing latitude, and is more pronounced for extrapulmonary TB than for pulmonary TB. The exact cause of the seasonal variation of TB notifications is unknown, but winter indoor crowding, poor UV exposure in winter, seasonal variation in immune function and coinfection with other seasonal pathogens may be responsible. This study may help to shape future public health responses, ensuring that governments can target public health interventions at specific times of the year to reduce TB transmission. Future analyses should ensure confounding variables, such as age, sex, air pollution, temperature and HIV status are controlled for.

Abbreviations

TB Tuberculosis

UVB Ultraviolet B rays

Declarations

Ethics approval and consent to participate

Data from the Pakistan National TB Control Programme were aggregated without any personal information, hence informed consent was not required. The study was approved by the Institutional Review Board of the National University of Medical Sciences, Rawalpindi, Pakistan (reference number: NUMS/PVC-19/R&D/ORIC/IRB&EC).

Consent to publish

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the Pakistan National TB Programme, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Pakistan National TB Programme.

Competing interests

Not applicable

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MFB was supported by a Queen Mary University of London Medical Student Travel Vacation Scholarship to visit Pakistan and co-ordinate this study. No other author was in receipt of any funds related to this study.

Authors' contributions

MFB: Helped conceive idea, accessed and cleaned data, helped with data analysis and interpretation of data, wrote the manuscript.

SY: Accessed data, helped conceive the idea, critically revised the manuscript for important scientific content.

ZW: Performed the statistical analysis on the data, analysis and interpretation of data.

SHH: Project administration, resources and data collection from the National TB Programme, Pakistan.
AL: Project administration, resources and data collection from the National TB Programme, Pakistan.

ARM: Pioneered study design, overall supervision for the project and edited the manuscript for important scientific content.

All authors reviewed the manuscript and contributed comments.

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Tables

Table 1. The relationship between seasonality, latitude and tuberculosis phenotype in Pakistan.Original table. No permissions required.

	Peak /Trough quarter	**Mean seasonal amplitude (%), 95% CI**	**Mean difference (%), 95% CI, p**	**Type III test for group difference**
Overall	Q2/Q4	25.5 (25.0-25.9)	NA	
Latitude				**<0.001**
24.5-<26.5	Q2/Q4	29.5 (29.3-29.7)	7.7 (6.3, 9.2), <0.001	
26.5-<28.5	Q2/Q4	24.3 (23.7-24.8)	2.5 (1.1, 4.0), <0.001	
28.5-<30.5	Q2/Q4	23.9 (23.4-24.3)	2.1 (0.7, 3.6), 0.004	
30.5-<32.5	Q2/Q4	24.3 (23.0-25.5)	2.5 (1.1, 4.0), <0.001	
32.5-<34.5	Q2/Q4	24.6 (23.2-25.9)	2.8 (1.4, 4.3), <0.001	
34.5-<36.5	Q2/Q4	21.7 (19.6-23.9)	0.0 (reference)	
Type of TB				**<0.001**
PTB	Q2/Q4	21.6 (21.4-21.8)	0.0 (reference)	
EPTB	Q2/Q4	32.6 (32.1-33.1)	11.0 (10.6, 11.5), <0.001	

Notes, the mean annual seasonal amplitude was calculated from the seasonal component as the annual difference between the peak and trough as a proportion of the annual mean case count.

Figures

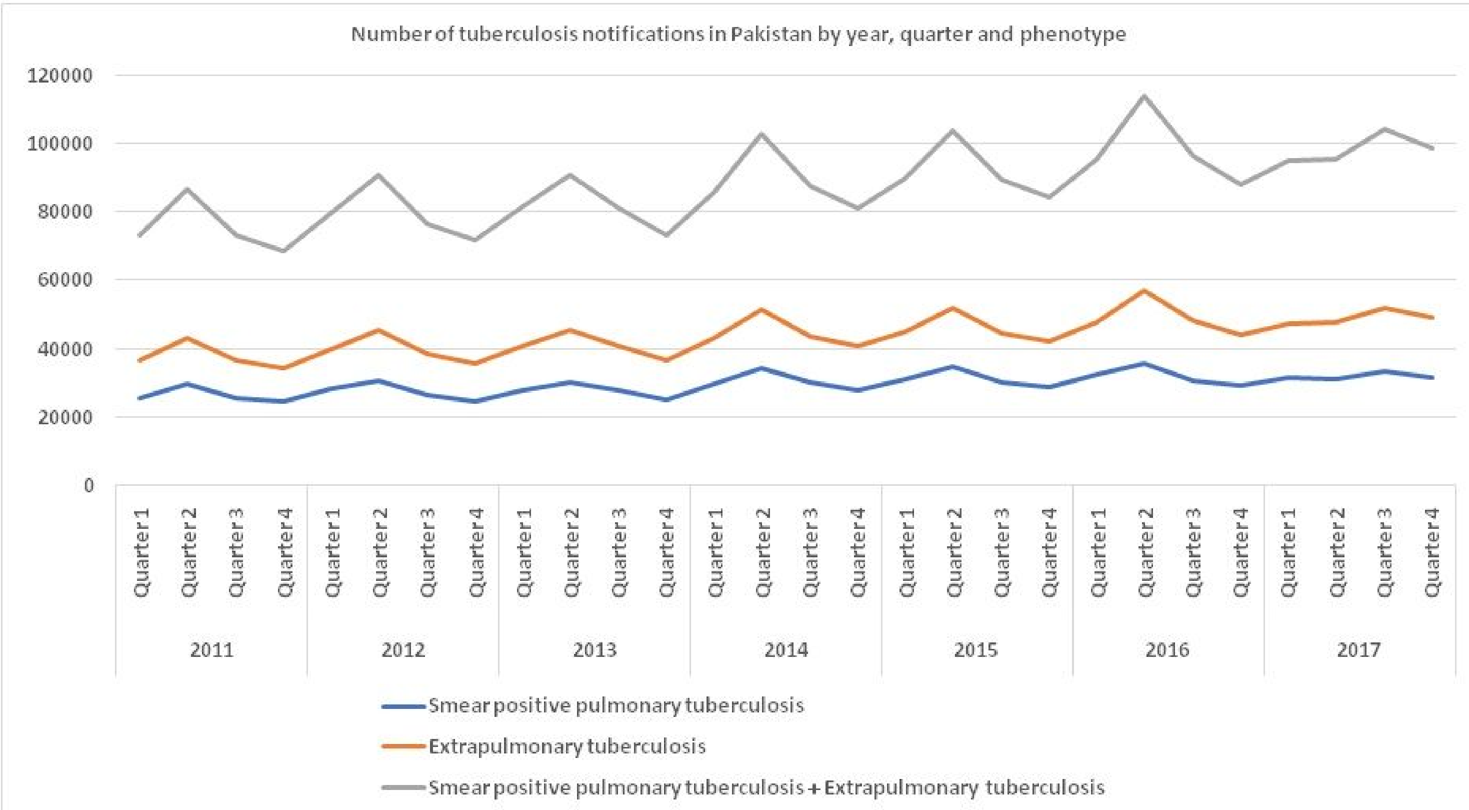

Figure 1

Number of tuberculosis notifications in Pakistan by quarter, year and phenotype. Original figure. No permissions required.

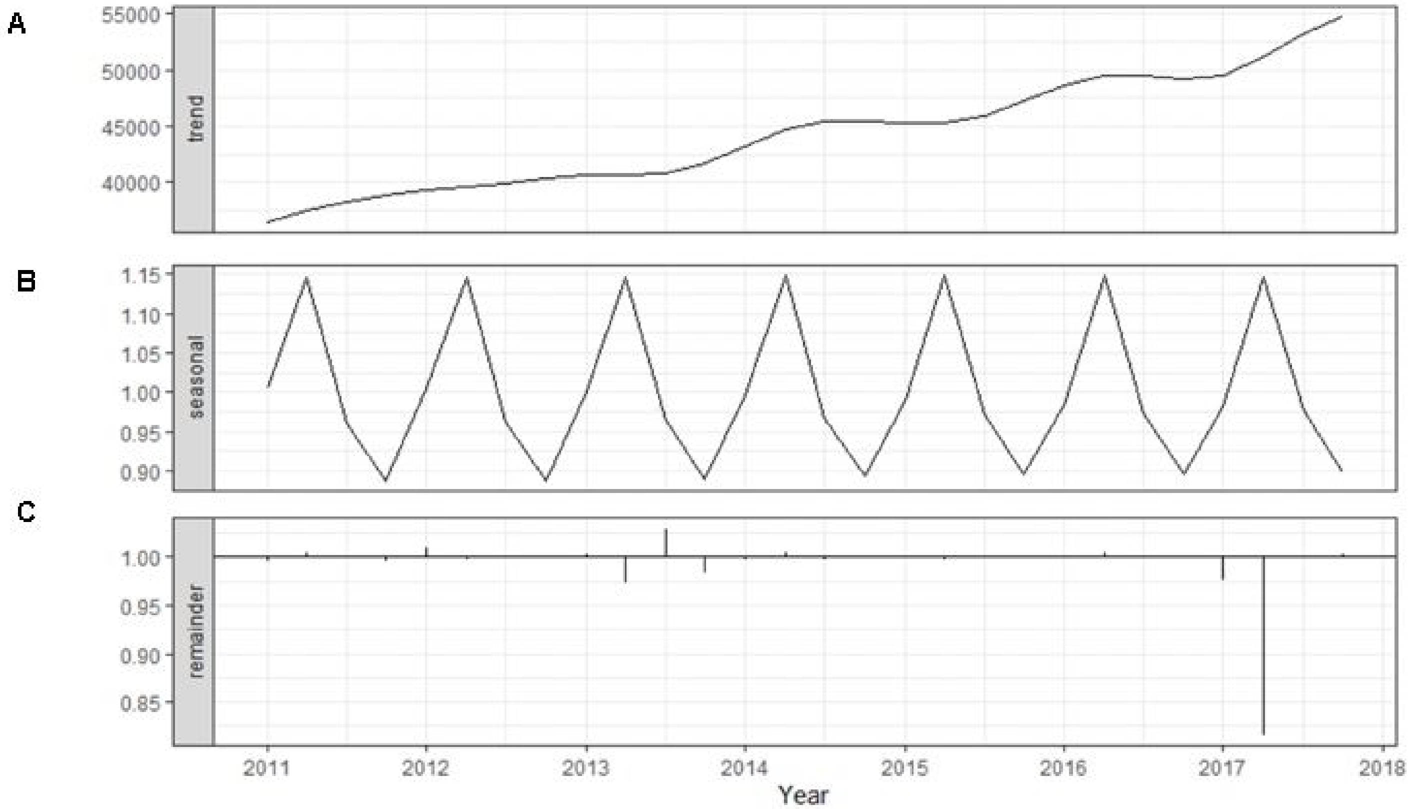

Figure 2

X-13-ARIMA seasonal decomposition of monthly notifications of active tuberculosis (extrapulmonary and smear positive pulmonary TB, see figure 1) in Pakistan from 2011-2017: trend cycle (A), seasonal component (B) and remainder component (C). Definitions: trend cycle - the component that represents variations of low frequency in a time series, the high frequency fluctuations having been filtered out; seasonal component - that part of the variations in a time series representing intra-year fluctuations that are more or less stable year after year with respect to timing, direction and magnitude; remainder component - the residual time series after the trend-cycle and the seasonal components (including calendar effects) have been removed. It corresponds to the high frequency fluctuations of the series. Original figure. No permissions required.

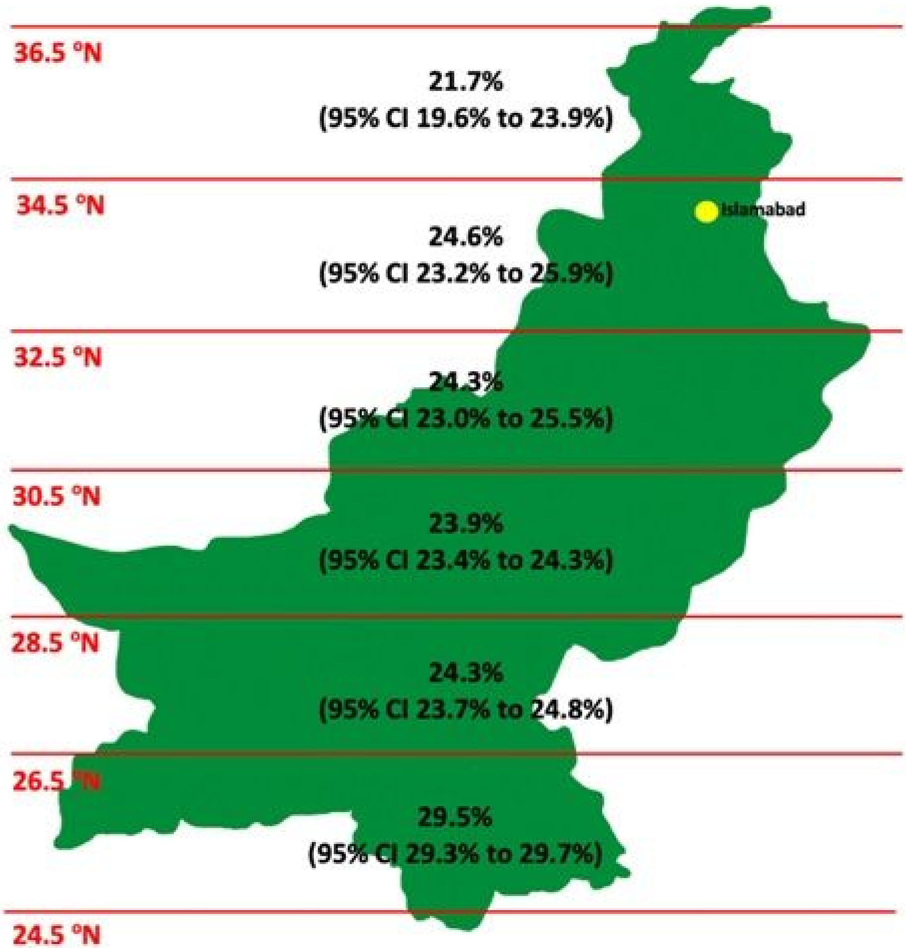

Figure 3

The mean seasonal amplitude of TB notifications from 24.5ºN to 36.5ºN across Pakistan. The 95% confidence interval (CI) is described. The location of Islamabad – the capital city of Pakistan – is highlighted in yellow. Original figure. No permissions required.

Supplementary Files

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- Supplementarydata.docx