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Drivers of seasonal variation in tuberculosis incidence: insights from a systematic review and mathematical model

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Abstract

Background—Seasonality in tuberculosis incidence has been widely observed across countries and populations; however, its drivers are poorly understood. We conducted a systematic review of studies reporting seasonal patterns in tuberculosis to identify demographic and ecologic factors associated with timing and magnitude of seasonal variation.

Methods—We identified studies reporting seasonal variation in tuberculosis incidence through PubMed and EMBASE and extracted incidence data and population metadata. We described key factors relating to seasonality and, when data permitted, quantified seasonal variation and its association with metadata. We developed a dynamic tuberculosis natural history and transmission model incorporating seasonal differences in disease progression and/or transmission rates to examine magnitude of variation required to produce observed seasonality in incidence.

Results—Fifty-seven studies met inclusion criteria. In the majority of studies (n=49), tuberculosis incidence peaked in spring or summer and reached a trough in late fall or winter. A standardized seasonal amplitude was calculated for 34 of the studies, resulting in a mean of 17.1% (range: 2.7–85.5%) after weighting by sample size. Across multiple studies, stronger seasonality was associated with younger patients, extrapulmonary disease, and latitudes farther from the Equator. The mathematical model was generally able to reproduce observed levels of seasonal case variation; however, substantial variation in transmission and/or disease progression risk was required to replicate several extreme values.

Conclusions—We observed seasonal variation in tuberculosis, with consistent peaks occurring in spring, across countries with varying tuberculosis burden. Future research is needed to explore

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and quantify potential gains from strategically conducting mass screening interventions in the spring.

Keywords

Tuberculosis; seasonality; seasonal variation; review

INTRODUCTION

Seasonal variation in tuberculosis (TB) incidence has been reported since as early as the 1930s, in the pre-chemotherapeutic era,¹ and across numerous populations and countries of varying incidence levels, including China,² the UK,³ Peru,⁴ and the Sudan.⁵ Seasonal respiratory diseases, most notably influenza, tend to display peaks of incidence in winter, while the peak of TB incidence seems to appear mostly in spring or summer.⁶ Additionally, while most respiratory illnesses progress from infection to symptomatic disease to diagnosis in a matter of days, the incubation period of TB can last decades, though the majority of patients who develop disease will do so within the first 2 years.⁷ This is often followed by a delay before diagnosis, with the median delay time variably estimated from 31 days to just under 5 months.⁸ Therefore, while the incidence of most respiratory diseases would respond immediately to any seasonal drivers, the nature and timing of the forces underlying TB seasonality are far more complex.

A number of mechanisms to explain seasonal variation in tuberculosis incidence have been hypothesized. These include: host immune response influenced by variation in vitamin D^{4,9–13} or melatonin levels;^{14–16} co-infection with seasonal respiratory viruses;^{17–20} increased indoor exposures during winter months;^{4,15,21–25} and seasonal differences in humidity or temperature that could influence *Mycobacterium tuberculosis* survival in droplet nuclei.^{20,26–29} Whether seasonal factors related to disease progression risks or transmission differences are the predominant forces of seasonal patterns remains unclear.

This paper aims to provide a comprehensive review of TB seasonality in peer-reviewed literature. In this review, we qualitatively examine associations between the timing and magnitude of seasonal variation and related attributes, including patient age, geographic location, and TB localization site. Next, we quantitatively compare magnitudes of seasonality between studies using a standardized measure of seasonal amplitude and statistically evaluate associations between seasonality and variables with sufficient data. Previous reviews were published prior to the publication of the majority (32 of 57) of studies included in this review and did not quantify seasonal variation.^{6,30} Finally, this review is the first to incorporate a tuberculosis natural history and transmission model in order to replicate observed patterns of seasonality and to explore the influence of disease progression and transmission variation on seasonal trends.

METHODS

Search strategy and inclusion criteria

We identified studies through PubMed and Embase searches on January 28th, 2017, using the search terms ‘tuberculosis’ AND (‘seasonality’ OR ‘seasonal’). Relevant publications from the reference lists of these studies were also included. All papers were assessed with the following inclusion criteria: studies must (i) report original data regarding seasonal variation of tuberculosis incidence in human subjects; (ii) be published in a peer-reviewed journal; (iii) be written in English; (iv) explicitly cite data sources; and (v) state sample size and report findings from a time period longer than or equal to 2 years. Few papers quantitatively assessed seasonality and/or annual periodicity through methods such as the Freedman test, the Edwards test³¹ or spectral analysis; therefore, we included all studies reporting on seasonal trends, irrespective of whether formal statistical evidence of seasonality was reported.

Data abstraction and definitions

We abstracted data on the location of the study population; years of study; tuberculosis incidence; ages included; forms of tuberculosis (e.g. pulmonary, extrapulmonary, smear status); data source; and sample size. We classified studies regionally according to World Health Organization regions. We utilized tuberculosis case definitions as reported by the studies; seasonal events were variable, including ‘diagnoses’, ‘presentations’, ‘registrations’ or ‘notifications’, and were analyzed here as incident cases. Separate reporting of events (e.g. ‘diagnoses’ versus ‘notifications’) did not occur within the same study. To obtain data on tuberculosis cases by month, we utilized data reported in tables or text, when available. When not reported, we extracted data from figures using PlotDigitizer software (Huwaldt, v2.6.8).³² Seasonal amplitude was defined as half the difference in TB incidence during the period (e.g. month) with the greatest incidence (peak) and the period with the lowest incidence (trough), and was expressed as a percent of the mean incidence over the given time period.

Data Analysis

We calculated the percent deviation in monthly incidence from mean incidence for each study in which monthly data could be obtained. Using linear regression, we estimated the effects of annual tuberculosis incidence on the normalized seasonal amplitude.

Mathematical model development

We developed a compartmental model of tuberculosis natural history and transmission to examine the magnitude of seasonal variation in progression and/or transmission rates that would be required to reproduce the observed magnitude and timing of seasonality in diagnoses. The basic model structure and parameters were derived from previously published models,^{33–37} with a few key modifications. First, while most published models generate exponential distributions of waiting times from infection to disease, carefully described observations demonstrated an approximately normally-distributed waiting time from infection to primary TB.⁷ Such a delay is more biologically plausible, given the slow

replication of *M. tuberculosis*, which requires weeks to months to grow to a level capable of causing clinical disease and being detected. By contrast, the assumption of an exponential distribution of the time period between infection and disease implies a mode of zero— instantaneous disease following infection—which is implausible. Based on this finding, we assumed that the time spent in the early disease stage is normally distributed and implemented this modification by use of 10 consecutive “holding” compartments (E_1 through E_{10}) having equal progression rates.³⁸ Second, re-infection was incorporated with a scaling factor to account for the protective effect of latent infection on developing active disease upon re-exposure.³⁶ We calibrated this baseline model without seasonality to an annual TB incidence just under 150 per 100,000 individuals, approximately the global average in 2015,³⁹ by varying the transmission parameter (β); baseline incidence then varied in sensitivity analysis. Finally, seasonal forcing was introduced in transmission, primary progression, and reactivation parameters through a cosine function with an annual period and variable amplitude, described by the following equation:

$$x_t = x_0 \alpha^{\cos(2\pi t/12)}$$

In the equation above, x is the parameter being forced, x_0 is the baseline value of the parameter, α is the seasonal forcing factor, and t is the time step. We varied the forcing factor for primary progression, reactivation and transmission rates both separately and simultaneously. For this example we simulated the Northern Hemisphere, with all seasonal forcing variables (i.e. transmission, reactivation, and progression rates) assumed to peak in December. The model was run to equilibrium, and then seasonality behavior was examined. Detailed model schematic and parameters are provided in Figure 2 and Table 1.

RESULTS

Systematic review

We identified a total of 733 papers through initial PubMed and Embase searches and review of corresponding reference lists. After initial screening, we reviewed 84 full texts, including two reviews on the topic of TB seasonality,^{6,30} and 57 papers were included in the qualitative analysis. Among these, 34 papers reported sufficient data to calculate a normalized seasonal amplitude using our standard formula. The studies represented 24 countries across six continents. Seventeen studies were from the Western Pacific Region, thirteen from the European Region, twelve from the African Region, four from the Southeast Asian Region, seven from the Eastern Mediterranean Region, and four studies from the Region of the Americas (see eTable 1). Only 11 out of 57 studies were from the Southern Hemisphere, with seven of these being from South Africa.

While three papers focused specifically on children and four papers focused specifically on adults, the majority of studies analyzed TB cases across all ages. In addition, 21 studies specifically reported cases of pulmonary tuberculosis, and one study reported only extrapulmonary TB results. Two papers reported results among HIV-infected adults.

The vast majority of studies (n=49) reported peaks in spring and summer and troughs in late fall or winter, with exceptions including three studies without clear peaks,^{13,40,41} as well as results from South Africa⁴² and China.⁴³ In the Northern Hemisphere, TB incidence generally peaked in March through August and came to a nadir in October through February. In the Southern Hemisphere, peaks appeared in August through December and troughs in March through July. In addition, several studies displayed multiple distinct peaks. For example, a Spanish study noted a dominant peak in June and a lesser peak in March.⁴⁴ A spring and a summer peak were similarly observed in Wuhan, China.¹⁹ Timing and magnitude of seasonality are shown in Table 2 for studies where monthly data was available.

There is conflicting evidence about whether TB seasonality is greater at latitudes farther from the Equator. Four studies reported results from multiple locations within the country. Studies in Australia⁵⁵ and India^{28,58} discovered stronger seasonal variation in areas further from the equator compared with those closer to it. However, a nationwide study of the United States displayed no difference in magnitude of seasonality over latitude.¹⁴ Additional reports from locations near the Equator were few, but conflicting. While Singapore at ~1°N showed little seasonal variability,⁴¹ studies in Cameroon at ~4°N⁵⁹ and northern Lima, Peru at ~12°S⁴ reported some seasonality (exact amplitudes unavailable).

Environmental factors have been sporadically correlated with seasonal variation in TB incidence. In China, temperate areas showed stronger seasonality than subtropical and tropical regions.² Recent findings from China also report an association between PM2.5 (atmospheric particulate matter that have a diameter less than 2.5 µm) concentration and tuberculosis incidence with a time lag, listing possible mechanisms as impairment of the immune system by PM2.5 and increased indoor crowding due to high PM2.5 levels,⁴⁵ though there is also seasonal variation that may confound this relationship.⁶⁰ In Cameroon, a direct correlation between TB case notification and rainfall was observed, and the peaks and troughs of TB were shown to lag 1 to 3 months after those of temperature.⁵⁹ Expanding on this finding, a study in Japan found that both hot and cold extreme temperature events were followed by a spike in tuberculosis notifications about 12 weeks later.⁶¹ Three papers comparing the dry and rainy season found increased TB incidence in the rainy season.^{24,59,62}

Four studies reported tuberculosis seasonality with reference to vitamin D levels and/or seasonal sunlight exposure, a common proxy. Peak tuberculosis incidence followed the nadir of sunshine hours in South Africa (specifically tuberculous meningitis)⁶³ and the UK,¹¹ with a 3- to 6-month lag. One study in Cape Town reported lowest vitamin D levels occurring from July through September and highest tuberculosis notifications in the three months thereafter (October through December).⁹ In Peru, vitamin D deficiency and hours without direct sunlight peaked in winter, and TB diagnoses lagged by approximately six months.⁴

Five studies from diverse settings (New York City, China, India) reported stronger seasonality among children compared with adults or the entire population.^{2,14,22,58,52} Children were defined as under 5 years old in one study, under 14 years old in three studies, and under 18 years old in the final study. The sole contradictory finding was a Portuguese study that reported the greatest difference in peak and trough incidence in adults 25–54 years

old; calculation of standardized seasonal amplitude was not possible for this study due to data reporting method.⁶⁴ Additionally, in some studies, younger patients also displayed an earlier⁶⁵ or later² peak than the general population.

Only two studies reported differences in tuberculosis seasonality by sex: one from Portugal found greater seasonal differences among men,⁶⁴ while one from Germany reported greater differences among women.¹⁵ Some studies also reported stronger seasonality among students^{2,21} and migrants.²¹ The study from Portugal also noted that seasonality appeared stronger in areas of higher TB incidence.⁶⁴

Five studies reported stronger seasonality in extrapulmonary TB presentations, diagnoses, or notifications compared to the general population or pulmonary TB alone.^{2,10,16,58,66} Two studies in the Netherlands did not observe any substantial seasonal variation in pulmonary TB notifications among natives, despite distinct peaks in extrapulmonary TB notifications.^{10,16} One study in the UK observed stronger seasonality in adults with extrapulmonary TB compared to adults with pulmonary TB.¹¹ Among pulmonary TB cases, notifications of cavitary TB displayed stronger seasonality than non-cavitary notifications in the US.¹⁴

Seasonality in genetically clustered cases, representing recent transmission, also displayed conflicting results. While studies in the Netherlands³⁵ and across the entire United States¹⁴ reported greater seasonal amplitude in clustered compared to unique cases, a second study in the Netherlands did not find a meaningful difference in magnitude of seasonality between clustered and unique extrapulmonary TB cases¹⁶ and weaker seasonality was observed among clustered cases in New York City.²²

Meta-analysis and meta-regression

We obtained the seasonal amplitude from 34 studies, with an unweighted mean of 22.0% (range: 2.7–85.5%); after weighting by sample size, the mean across the 34 studies was 17.1%.

We conducted statistical analyses to test for association between seasonal amplitude and two factors of interest for which sufficient data was available. In alignment with conflicting qualitative results, no trend was found in a linear or quadratic regression of normalized seasonal amplitude against latitude (eFigure A). Similarly, we did not find any noteworthy relationship between seasonal amplitude and TB incidence (Figure 3).

Model results

Using literature estimates for tuberculosis natural history and diagnosis, we found that a simple model with sinusoidal variation in disease progression or transmission recapitulated observed seasonality of tuberculosis incidence (Figure 4).

Notably, seasonality in diagnoses has smaller seasonal amplitude than seasonality in incidence, due to the addition of the distribution of time from disease to diagnosis. At the weighted average seasonal amplitude (17%), the peak of incidence (notifications) occurred in March under most assumptions, 3 months after the peak in progression or transmission. Lower levels of seasonal forcing shifted the peak of notifications to April. The variation in

primary progression, transmission, and reactivation rates required to generate the average seasonal amplitude of 17% was around 30% above baseline at peak ($\alpha = 1.3$) for all rates, around 40% above baseline at peak ($\alpha = 1.4$) if both reactivation and primary progressive rate varied, or around 260% above baseline at peak ($\alpha = 3.6$) if only transmission rate varied. To generate the extremes in seasonality observed in some studies (>85%) would require seasonal forcing of greater than six-fold for all three parameters. Figure 5 depicts the seasonal amplitudes in notification rates across a range of transmission, primary progression and reactivation rate seasonal multipliers. In the figure, seasonal amplitude is calculated as half the difference in TB incidence during the month with the greatest notifications (peak) and the month with the lowest notifications (trough) as a proportion of the mean monthly notifications, which is equivalent to the standard definition of seasonal amplitude that was used to compare the empirical findings. A seasonal amplitude of zero indicates that monthly notifications are constant, while a higher seasonal amplitude implies a wider difference in notification volume between peak and trough months.

DISCUSSION

This review demonstrates that seasonality of tuberculosis is widespread and conserved across countries, subpopulations, and levels of TB burden. Fifty-seven papers reported seasonal data for TB incidence, with three reporting no notable trend. Among these studies, 49 reported the highest level of TB incidence in spring or summer, with a nadir in fall or winter. There was no evident pattern among the few studies that reported either no seasonal trend or multiple peaks of incidence. Across 34 studies with sufficient data, the weighted mean of normalized seasonal amplitudes was 17.1% (range 2.7–85.5%). Seasonal trends were broadly consistent across different measures of TB incidence, including timing, presentation, diagnosis, notification, and Directly Observed Therapy (DOT) registration. No associations were found between seasonal amplitude and latitude or seasonal amplitude and local TB incidence rate. Additionally, we found that a simple mathematical model with moderate seasonal forcing was able to recapitulate the timing of seasonality and the observed mean seasonal variation (17%), but that substantial seasonal forcing in progression and/or transmission rates was required to reproduce some of the larger observed seasonal variation values (>85%).

A fundamental question has been whether seasonal variation in progression (primary or reactivation) risk or transmission is the predominant driver of TB seasonality. Direct evidence on this subject is limited, but there is some indirect evidence in the form of specific populations that are at high risk. In particular, the finding of greater seasonality among children, in whom primary tuberculosis is more common, is suggestive of a variation in transmission risks.⁶⁷ Two of four studies reporting seasonality by clustering reported higher rates among clustered cases, additionally supporting an association between seasonality and transmission. Several studies did not stratify data by age, but noted stronger seasonality among extrapulmonary TB cases, which are more frequent in children and HIV co-infected individuals, and therefore also support recent transmission as a seasonal driver.⁶⁷ An alternative hypothesis is that seasonality is easier to detect among children, HIV-positive patients, and extrapulmonary TB cases due to lower inter-person variability in progression rates among these groups. Extrapulmonary tuberculosis has also been associated with

vitamin D deficiency, which may explain the stronger seasonal trends.⁶⁸ Our findings are also consistent with data suggesting that indoor contact intensity, a marker of TB transmission risk, is greater in winter months.⁶⁹ Our mathematical model, however, indicates that greater variability in transmission, compared with progression rate, is needed to achieve the same seasonal variation. The reason is that transmission acts earlier in the cascade of disease, and its seasonal impact is dampened by individual variability in both progression and diagnosis rates, while the impact of seasonal progression variation is only dampened by variability in diagnosis times; therefore, a comparable change in progression has a greater impact on the magnitude of seasonal variation. Overall, we believe that both differences in progression and transmission likely contribute to TB seasonality, though their relative contributions may differ between locations.

One important consideration is whether there are seasonal differences in case detection that could contribute to the observed TB seasonality. While some variation in case detection likely occurs, for example, around holidays, we did not find evidence for substantial and consistent case detection variation in the literature that could explain the marked seasonal trends. Additionally, in settings where all individuals of a group were screened (e.g. migrants into Kuwait),⁵¹ the same seasonal trends appear. Peaks also appear around the same time when measures of mortality or hospitalization are used.^{17,18,20,40,63} One might expect that these more extreme occurrences would be less prone to case detection variation. Taken together, there appears to be little support for variation in case detection as a major explanatory mechanism for TB seasonality.

Our systematic review revealed a number of hypotheses concerning the mechanisms of seasonal variation in progression or transmission. Seasonal vitamin D deficiency was the most frequently cited mechanism to explain increased progression/reactivation and/or transmission of tuberculosis in the winter, followed by manifestation of symptoms in the spring. Recent studies have found associations between vitamin D deficiency and tuberculosis incidence,⁷⁰ but evidence linking vitamin D deficiency and seasonal patterns in incidence are sparse,⁷¹ and difficult to disentangle from other seasonal drivers that may confound the relationship. Some studies have attempted to parse out this relationship by separately reporting seasonality in darker-skinned groups and have attributed stronger seasonal amplitudes in these groups to less effective absorption of vitamin D, especially during winter months;^{10,12,15} however, darker-skinned groups is a somewhat vague categorization that can merge effects of race, migration from high-incidence areas, and/or effects of diet. As discussed earlier, several papers have also explored the association in seasonal trends between sunshine hours and incident TB cases,^{4,11,63} but the association between vitamin D levels and sunshine hours is weak and poorly understood.⁷¹

Other frequently proposed and explored mechanisms include some form of seasonal crowding (often due to unpleasant winter conditions or travel for a national holiday) and environmental factors. The hypothesized effect of “crowding” is difficult to study; countries such as Iran²³ and China^{21,47} with distinct festival periods do report spikes in TB incidence following that period, but it is unclear whether the rise in cases is due to increased incidence from crowding, delayed healthcare-seeking behavior during the festival period, or other factors. A Dutch study reporting similar seasonal peaks between genetically clustered and

unique extrapulmonary TB cases used this finding as evidence against winter crowding as a driving seasonal factor, but in general exactly how to measure the effects of “crowding” is unclear.¹⁶ Various papers explored the association between patterns of TB incidence and climatic factors of rain and temperature,^{27–29,59,61} but no consistent trends emerged. Three papers reported increases in TB cases or mortality in relation to influenza epidemics,^{17,18,25} and animal models have demonstrated potential mechanisms for these associations;⁷² however, distinguishing the effects of influenza or other seasonal respiratory viruses from other seasonal drivers identified above remains challenging.

Greater understanding of the relative contributions of seasonal drivers and underlying mechanisms at the local level could inform prevention and case detection interventions. If reactivation is thought to be the driving factor in certain regions, campaigns for treatment of high-risk groups with latent TB may precede the peak season. If transmission is thought to be more important, improved ventilation or other measures to mitigate “crowding” (e.g. of public transportation) may be effective. In either case, mass screening interventions may be most efficient, in terms of number needed to test, if conducted in the spring.

Our mathematical model confirmed that the observed patterns and timing of TB seasonality are plausible given widely accepted parameters of TB transmission, progression and diagnosis. Both the magnitude and timing of seasonal incidence were recreated in the model, with the highest observed values of seasonal amplitude (>85%) at high levels of seasonal forcing in both the reactivation and transmission parameters. This may indicate that high values of seasonal amplitude may only occur with extreme seasonal dynamics or with interactions between transmission, reactivation, and other parameters (e.g. diagnosis rate). This framework, modified with relevant parameters, may be useful to explore magnitude and timing of seasonality at the local level.

Our review was limited by existing peer-reviewed literature reporting TB seasonality. As described earlier, results were geographically skewed towards the Northern Hemisphere and results from the Southern Hemisphere focused almost exclusively on South Africa. Data indicating weak seasonality may be underreported in the published literature, biasing the magnitude of seasonality of our estimates upward; as such, the results of this analysis should be taken as an estimate among settings reporting seasonality rather than a global estimate. In addition, multiple studies included data aggregated at a country level, which may have masked local seasonal trends or patterns among key subgroups, such as HIV-coinfected patients. Data quality is also highly variable between different national or local registers; for example, the World Health Organization reported Portugal as having one of the highest TB detection rates at 87% of smear-positive cases in 2008, while other national registries, such as China's, had capture rates of 72% and many even lower.⁷³ Some papers reporting on overlapping datasets with other papers from the same location; in instances where data from one paper was not completely subsumed in another paper, we included both.

The mathematical model also faced several limitations. Our implementation of seasonal forcing utilized a sinusoidal curve to create a gradual seasonal pattern with a non-zero trough. Other implementations incorporated more abrupt seasonal variation; for example, one study modeled 80% of transmission occurring over three winter months and the

remaining 20% split evenly across the rest of the year.³⁵ There is limited evidence to support either implementation, but our method may produce comparatively conservative estimates of amplitude. Additionally, transmission and reactivation were modeled with identical early disease development pathways. Variable development pathways (e.g., longer early disease period for recently transmitted cases) may lead to greater differences in seasonal amplitude and peak timing between reactivation and transmission forcing; again, limited evidence was available on this topic. We used data on intervals between infection, disease, and diagnosis from published literature, which likely vary between populations; we examined the impact of this variation in sensitivity analyses (eFigure C). Finally, the parameter for proportion of new infections developing primary progressive TB (p) was set to 0.05 at baseline; though this value is generally accepted for populations with low prevalence of TB and HIV co-infection, it may not be suitable for all populations. This assumption is likely sufficient for this basic model assessing seasonality.

In conclusion, seasonality of tuberculosis is a globally observed phenomenon that may be an important consideration in tuberculosis policy, planning, and resource allocation. While this review was unable to resolve the fundamental question of whether transmission or progression variation is the primary driver of tuberculosis seasonality, our findings indicate that moderate variation in either or both are required to generate the levels of seasonality observed in many settings. In order to develop a more holistic picture of seasonal patterns, data is needed from underrepresented regions and high-risk groups, including Southern Hemisphere countries and HIV co-infected patients, including stratification by age and localization site. Finally, causal studies investigating the relationship between vitamin D deficiency, crowding, respiratory viral infections and other potential factors on TB incidence will be necessary to understand the mechanisms of TB seasonality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
PRISMA flowchart depicting selection of studies for review.

Figure 2. Model framework with Susceptible, Latent, Early disease, Infectious, Treated, and Recovered compartments. Recovered individuals are automatically considered to be Latent. Early disease is split into 10 compartments with progression rate of $10i$ between compartments to simulate a normal distribution of TB progression times. Model assumes a constant population.

Figure 3.

Relationship between local annual TB incidence (per 100,000 individuals) and normalized seasonal amplitude (%). Normalized seasonal amplitude is half of the peak observed value (for a given time period) minus trough observed value as a percent of the mean observed value. Unweighted linear regression is shown with 95% confidence interval. If incidence for the specific study location was unavailable, country incidence (WHO 2014) was used. Resulting estimate of association was 0.00266 (95% CI: -0.019, 0.025; p-value: 0.82).

Figure 4.

Seasonal variation in annualized incidence, notification rate (equivalent to treatment in this model) and seasonal multiplier at steady state. Maximum seasonal multipliers for reactivation, transmission and primary progressive rate are set at 1.3 in this simulation in order to recreate the weighted observed seasonal amplitude average of 17%. Rates x for month t are determined by the equation $x_t = x_0 \alpha^{\cos(2\pi(t/12))}$ where x_0 is the baseline parameter and the remainder of the formula is the seasonal multiplier depicted in the figure. The model is simulated over 3000 time-steps representing months. Plotted in gray are the empirical monthly deviations from the mean for the Northern Hemisphere ($n=22$) as reported in Table 2.

Figure 5.

Normalized seasonal amplitude of notifications with respect to strength of simultaneous seasonal forcing (α) in transmission rate, reactivation rate and primary progressive rate. Dotted line indicates combinations of seasonal forcing that recreate the weighted observed seasonal amplitude average of 17% ($\pm 0.5\%$). The colors correspond to the seasonal amplitude at the parameter combination. The notification peak occurs in April at lower levels of seasonal forcing but shifts to March with stronger seasonality. Seasonal forcing is implemented with the formula $x_t = x_0 \alpha^{\cos(2\pi(t/12))}$ where x_t is the rate at month t , x_0 is the baseline parameter and α is the seasonal forcing multiplier depicted on the x- and y-axes, for the respective parameter(s).

Table 1

List of model parameters corresponding to Figure 2 with definitions and baseline values. Parameters are compiled from Blower 1995,³³ Ziv 2001,³⁴ Soetens 2013,³⁵ Andrews 2012,³⁶ and Colijn, Cohen, and Murray 2006.³⁷ Model calibrated to baseline global average annual incidence of 150 cases per 100,000 individuals by adjusting transmission coefficient β .

Parameter	Definition	Baseline Value
β	Transmission coefficient (effective contact rate)	35/person/year
p	Proportion of new infections that develop primary progressive TB	0.05
v	Reactivation rate of latent TB	0.003072/person/year (~5% progression in 20 years)
a	Relative risk of primary progressive TB for reinfection compared to new infection	0.21
i	Disease progression rate (development of bacterial load)	8.12/person/year (mean progression time of 6 wks)
t	Treatment rate	4/person/year
c_N	Natural cure rate	0.22/person/year
c	Cure rate	2/person/year
μ	Mortality rate	0.02/person/year
μ_{TB}	Mortality rate due to TB	0.139/person/year

TB indicates tuberculosis.

Table 2

and percent deviation from the mean monthly incidence of given events by month, for all studies that reported monthly data. Monthly data was from tables or estimated from graphs with PlotDigitizer software. Studies are ordered from northernmost to southernmost by latitude; the mean is used for cases in which a range of latitudes is indicated. Each color represents a range of 10 percentage points (0–10%, 10–20%, etc.) with darker blue indicating higher positive values and darker red indicating strongly negative values.

	Latitude	Total cases	Seasonal event	TB localization	TB confirmation	J	F	M	A	M	J	J	A	S	O	N	D
Wales, & Scotland, ⁴⁸	50–59 N	42,165	Notification	All	Not specified	-18.6%	3.2%	-0.7%	0.1%	2.1%	4.0%	13.8%	10.3%	1.9%	-3.0%	-3.1%	-4.9%
Wales, UK ³	50–6 N	57,713	Notification	All	Not specified	-12.3%	-4.4%	-3.3%	-1.2%	8.0%	1.0%	12.3%	10.7%	-1.5%	2.3%	3.2%	-2.1%
Wales, ³⁵	51–53 N	4,746	Notification	All	Culture+	-4.3%	5.2%	14.7%	8.6%	8.2%	17.7%	0.5%	0.7%	-5.1%	-8.1%	-4.5%	-33.7%
Wales, ¹⁶	51–53 N	9,979	Notification	All	Culture+	-6.2%	22.4%	10.6%	6.1%	30.7%	9.5%	-0.8%	-7.3%	-16.3%	-18.3%	-17.1%	-13.1%
Wales, ²	41–52 N	14,905	Notification	PTB	SS+	-16.6%	-5.3%	15.0%	51.0%	39.4%	33.0%	7.8%	-8.7%	-25.0%	-30.5%	-24.5%	-35.7%
Wales, ⁴⁵	48 N	31,071	Notification	All	Lab or clinical	-11.2%	-2.3%	5.0%	9.1%	7.7%	6.6%	3.3%	-0.7%	-5.1%	-8.3%	-4.4%	0.3%
Wales, ⁴⁶	48 N	~19,300	Notification	All	Lab or clinical	-23.7%	-25.5%	23.7%	25.5%	18.2%	-0.5%	13.9%	15.1%	10.8%	-10.8%	-41.1%	-5.6%
Wales, ⁴⁶	24–29 N	~136,400	Notification	Not specified	Not specified	-2.4%	1.4%	18.7%	15.4%	17.8%	14.2%	7.5%	8.8%	-4.0%	-6.1%	-22.8%	-48.5%
Wales, ⁴⁶	18–24 N	10,233,022	Notification	Not specified	Lab or clinical	-18.2%	-19.5%	18.7%	19.2%	11.1%	10.4%	4.8%	2.4%	-3.2%	-11.4%	-8.3%	-6.0%
Province, Iran ⁴⁸	35 N	3,313	Diagnosis	Not specified	Not specified	-14.5%	-16.7%	4.3%	-8.4%	25.0%	7.2%	19.5%	8.3%	-8.7%	-0.8%	-7.6%	-7.6%
Province, China ⁴⁹	32–39 N	273,305	Notification	PTB	Not specified	20.0%	5.6%	29.2%	18.7%	11.7%	3.9%	-1.3%	-6.9%	-9.5%	-16.0%	-20.7%	-34.9%
Province, China ²⁶	31–39 N	27,665	Notification	PTB	Lab or clinical	17.7%	6.8%	23.5%	18.0%	20.1%	4.1%	4.6%	-5.9%	-20.7%	-14.1%	-27.4%	-26.7%
Province, China ¹⁹	24–30 N	34,012	Notification	PTB	SS+	-6.8%	2.2%	7.1%	-4.9%	21.6%	8.9%	0.8%	3.6%	-8.2%	-8.4%	-8.3%	-7.6%
Province, China ¹⁹	24–30 N	10,587	Notification	All	All	-6.9%	2.1%	11.4%	-8.2%	17.5%	10.7%	6.5%	-5.4%	-4.3%	-6.5%	-9.1%	-8.0%
Province, China ⁴³	26–34 N	35,875	Notification	PTB	All	5.4%	-11.7%	20.5%	14.3%	14.9%	6.4%	1.4%	-1.5%	2.1%	-5.0%	-17.4%	-29.2%
Province, China ⁴³	26–34 N	445,557	Notification	PTB	Lab or clinical	42.7%	-3.2%	14.4%	13.2%	7.6%	5.0%	1.6%	1.3%	-8.4%	-9.7%	-21.2%	-43.1%
Province, China ⁴³	28–30 N	4,608	Diagnosis	PTB	SS+ or culture+	-4.2%	-12.2%	17.4%	2.1%	8.9%	9.9%	13.8%	5.7%	-7.3%	-19.8%	-5.7%	-8.6%
Province, China ⁴³	29 N	28,161	Diagnosis	All	All	-22.6%	-8.0%	11.1%	19.9%	14.5%	18.5%	16.1%	5.0%	5.9%	-15.2%	-23.2%	-22.0%
Province, China ⁴³	29 N	417	DOTS	PTB	SS+	-38.1%	-5.7%	127.0%	35.6%	9.1%	0.2%	-41.0%	-44.0%	-8.6%	0.2%	-11.5%	-23.3%
Province, China ⁴³	22–25 N	~74,903	Notification	Not specified	Not specified	-7.9%	-18.3%	6.3%	3.4%	15.8%	3.4%	1.9%	4.4%	-0.6%	1.8%	-4.0%	-6.4%
China ⁵⁴	22 N	82,104	Notification	All	All	-10.8%	-21.7%	-3.3%	-2.2%	11.6%	3.2%	10.0%	8.2%	0.0%	5.5%	3.0%	-3.4%
China ⁴⁵	22 N	~18,900	Notification	All	Lab or clinical	-9.0%	-18.9%	-0.9%	2.6%	5.8%	7.9%	12.6%	3.9%	0.3%	-3.1%	4.5%	-5.6%

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	Latitude	Total cases	Seasonal event	TB localization	TB confirmation	J	F	M	A	M	J	J	A	S	O	N	D
	10–44 S	11,576	Notification	Not specified	Not specified	–4.6%	–12.8%	–5.5%	–9.3%	–9.1%	–16.8%	–3.7%	–0.1%	11.5%	18.5%	16.4%	15.4%
ce, South	30–34 S	~430,500	Notification	PTB	SS+	7.3%	0.6%	5.5%	–7.0%	–8.0%	–18.1%	–15.3%	–3.5%	1.0%	10.3%	12.6%	14.5%
ce, South	30–35 S	1,204	Presentation	All	Culture+	21.2%	–12.4%	–2.2%	–16.3%	–8.9%	–13.7%	–16.9%	1.7%	15.0%	44.3%	0.7%	–12.6%
part of South	33 S	5,783	Registration	PTB	SS+	22.1%	–2.8%	–7.9%	–8.4%	10.0%	–5.1%	–4.8%	17.0%	8.9%	15.1%	–13.9%	–30.3%

sis; PTB, pulmonary tuberculosis; DOTS, directly observed therapy, short-course; SS+, sputum-smear positive

Table 3

Summary of key findings from systematic review.

Key finding	Supporting studies	Conflicting studies	Possible hypotheses
Stronger seasonality in younger populations compared to general/older population	Thorpe <i>et al.</i> , 2004 ⁵⁸ Behera and Sharma, 2011 ⁵² Parrinello <i>et al.</i> , 2012 ²² Willis <i>et al.</i> , 2012 ¹⁴ Li <i>et al.</i> , 2013 ²	Bras <i>et al.</i> , 2014 ⁶⁴	Seasonality is driven by recent transmission, as the majority of TB in younger patients is due to primary progressive disease.
Stronger seasonality among genetically clustered cases compared to unique cases	Willis <i>et al.</i> , 2012 ¹⁴ Soetens <i>et al.</i> , 2013 ³⁵	Parrinello <i>et al.</i> , 2012 ²² Top <i>et al.</i> , 2013 ¹⁶	Seasonality is driven by recently transmitted (genetically similar) cases.
Stronger seasonality in EPTB cases compared to PTB cases	Thorpe <i>et al.</i> , 2004 ⁵⁸ Korthals Altes <i>et al.</i> , 2012 ¹⁰ Li <i>et al.</i> , 2013 ² Top <i>et al.</i> , 2013 ¹⁶ Margalit <i>et al.</i> , 2016 ⁶⁶		The factors affecting seasonal variation may have a stronger impact on extrapulmonary disease; for example, a larger proportion of EPTB may be recently transmitted compared to PTB. EPTB is strongly correlated with younger patients - further analysis is required to account for the confounding factor of age.
Stronger seasonality at latitudes farther from the Equator within the same country	Thorpe <i>et al.</i> , 2004 ⁵⁸ MacLachlan <i>et al.</i> , 2012 ⁵⁵ Narula <i>et al.</i> , 2015 ²⁸	Willis <i>et al.</i> , 2012 ¹⁴	Seasonal fluctuation of UVB exposure is decreased at latitudes closer to the Equator, therefore decreasing seasonal variability in vitamin D levels and susceptibility to TB disease.

TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; UVB, ultraviolet B