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Seasonality of tuberculosis in India: is it real and what does it tell us?

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India has a third of the world's tuberculosis cases. Large-scale expansion of a national programme in 1998 has allowed for population-based analyses of data from tuberculosis registries. We assessed seasonal trends using quarterly reports from districts with stable tuberculosis control programmes (population 115 million). In northern India, tuberculosis diagnoses peaked between April and June, and reached a nadir between October and December, whereas no seasonality was reported in the south. Overall, rates of new smear-positive tuberculosis cases were 57 per 100 000 population in peak seasons versus 46 per 100 000 in trough seasons. General health-seeking behaviour artifact was ruled out. Seasonality was highest in paediatric cases, suggesting variation in recent transmission.

Since late 1998, effective tuberculosis control programmes have been rapidly expanding across India allowing for population-based analyses with standardised register data. Although tuberculosis is not widely recognised as having seasonal trends, regional periodic variation in case detection across India prompted this descriptive study. Europe—and South Africa for childhood tuberculous meningitis—have reported seasonal variation in tuberculosis incidence.[1–3] Older texts refer to historical seasonal fluctuations in tuberculosis mortality in the Americas.[4] However, no previous studies have described tuberculosis seasonality in Asia, to our knowledge.

We reviewed surveillance data from India's Revised National Tuberculosis Control Programme (RNTCP), which includes systematic aggregate reporting of tuberculosis cases diagnosed in the public sector. Case detection was determined for each calendar quarter by dividing tuberculosis diagnosis counts by year 2001 census data. To ascertain long-term seasonal trends we examined quarterly data over 5 years (April 1, 1996, to June 31, 2001) in three pilot districts, where early RNTCP operations began. A second, larger analysis examined all districts in India with at least 80% RNTCP coverage by early 1999. This analysis included a non-random selection of 54 districts across India (areas to the northwest and Kashmir were under-represented), covering a population of about 115 000 000 people. For these districts, we assessed data from Jan 1, 2000, to June 31, 2001. We measured average amplitude across seasons (peak to trough distance) with region-specific Poisson regression models, using a sinusoidal covariate. β coefficients were exponentiated and average amplitude was calculated with $e^{Bi} - e^{-Bi}$.

The three pilot districts included Gulabi Bagh and Hamirpur in the north of India, and Pathanamthitta in the south. During the 5-year period, 11 101 cases of tuberculosis were diagnosed and treated in the public sector. Average annual case detection was highest in Hamirpur (207 per 100 000 population), compared with that in Gulabi Bagh (97 per 100 000) and in Pathanamthitta (57 per 100 000). Review of quarterly tuberculosis rates showed consistent peaks between April and June (Q2) and lows between October and December (Q4) for both Gulabi Bagh and Hamirpur (figure 1). Quarterly tuberculosis rates in Pathanamthitta did not systematically vary over time. The average seasonal amplitude between the second and fourth calendar quarters was 28·5% (95% CI 20·6–37·5) for Hamirpur, 32·6% (20·1–45·2) for Ghulabi Bagh, and 3·5% (–12·6 to 19·6) for Pathanamthitta. We then calculated seasonal variation for two types of tuberculosis disease: new smear-positive pulmonary and extrapulmonary tuberculosis. In Gulabi Bagh and Hamirpur, the two northern districts, seasonal variation was highest in extrapulmonary cases, with amplitudes of 55% (95% CI 29–83) and 40% (19–63), respectively. The amplitude of smear-positive tuberculosis was slightly lower (37% [16–59] and 38% [24–52], respectively). There was no distinct trend in Pathanamthitta.

In the larger sample of 54 districts, rates also peaked between April and June and dropped during October to December. Areas to the north had the highest seasonal variation, and low or no seasonality was noted in central and southern regions, respectively (figure 2). The magnitude of seasonal variation correlated positively with tuberculosis case rates (Pearson's correlation coefficient, r=0·61, p=0·019). Seasonality of new smear-positive cases was strongest in children younger than

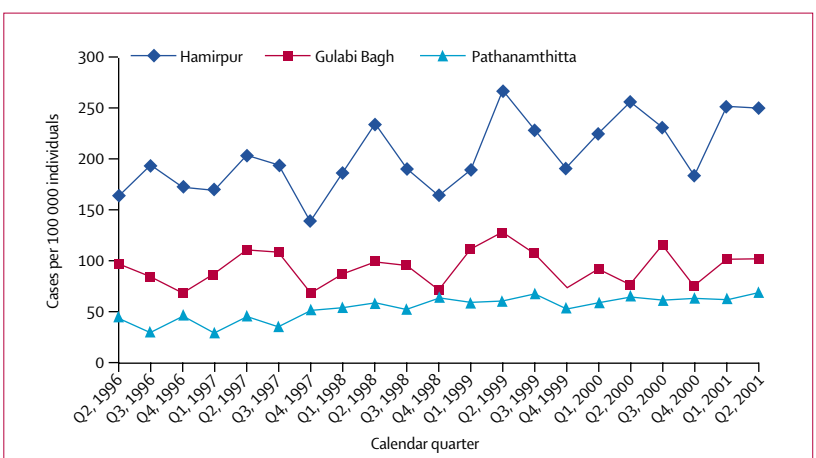

Figure 1: **Annualised rate of total tuberculosis diagnoses by quarter, in three Indian districts, 1996–2001**

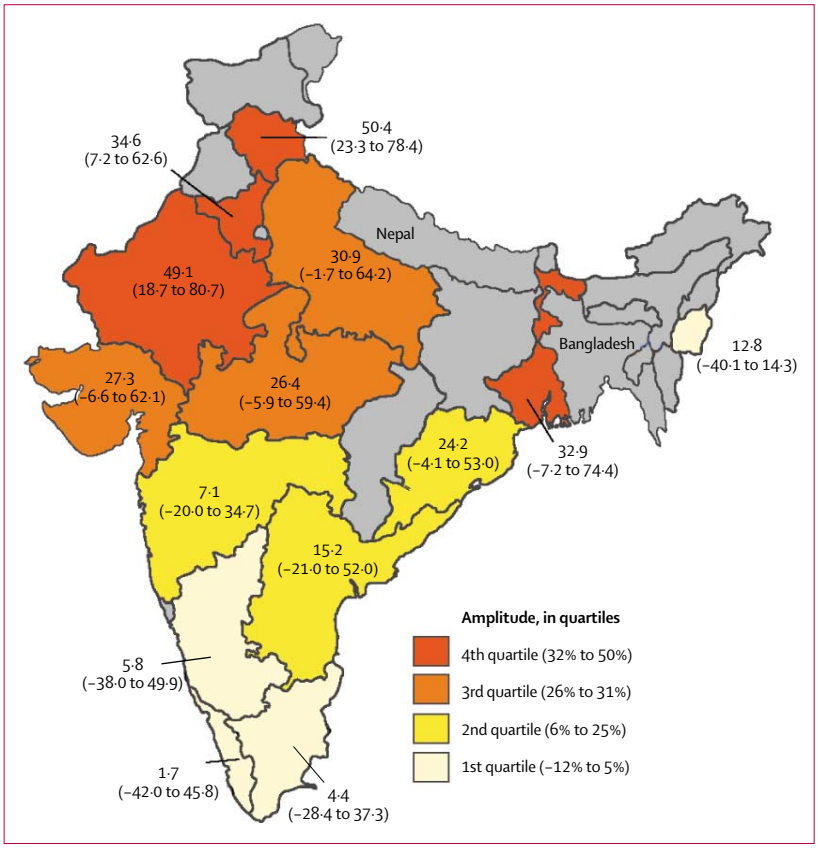

Figure 2: **Amplitude of seasonal variation (95% CI) of new smear-positive tuberculosis by State, in India, 2000–2001**

14 years (47%), and declined significantly with increasing age (24% in 15–44 year olds, 21% in 45–64 year olds, and 8% in those 65 years and older). We noted no differences in tuberculosis seasonality by sex.

In the 54 districts, the overall annualised mean rate of new smear-positive tuberculosis diagnoses was 57·0 per 100 000 population (95% CI 56·6–57·5) between April and June, compared with 46·2 cases per 100 000 population (45·8–46·6) between October and December. If these rates were representative of the country, about 27 000 additional cases of infectious tuberculosis would occur in peak season compared with the fourth quarter.

To discount general health-seeking behaviour bias we examined trends in total patient visits to primary health clinics, as reported to the RNTCP. No seasonal variation occurred in the average quarterly rate of patient visits; in fact, visiting rates were slightly higher between October and December than between April and June (26 858 *vs* 24 812 patient visits per 100 000 population). Similarly, the proportion of clinic patients assessed for tuberculosis remained stable (2·2% *vs* 2·1%).

Exactly why tuberculosis rates might vary by season is unknown. We noted heightened variation in cold mountainous areas of India. Researchers who reported similar trends in children with tuberculous meningitis in South Africa have suggested that winter indoor crowding in poorly ventilated settings could lead to increased transmission of *Mycobacterium tuberculosis*, which then manifests itself 3–6 months later.[3] Other researchers have postulated a link between a rise in tuberculosis and vitamin D deficiency from reduced sunlight exposure, suggesting that deficiencies in vitamin D lead to reactivation of latent infection.[5] Data from India suggest that tuberculosis seasonality could be due to variations in recent transmission of *M tuberculosis*, since seasonality was reported to be strongest in paediatric tuberculosis cases.

Limitations of this analysis include the fact that standardised tuberculosis reporting is new in India, restricting the timeframe and geographic scope in which the study could be undertaken. We were, however, able to confirm 5-year trends in a larger sample that represented more than 13% of the nation's population. Grouped quarterly data also precluded a more sensitive month-by-month assessment.

As a result of our analysis, state-specific correction factors have been incorporated into India's drug supply management system to improve logistic accuracy and ensure that anti-tuberculosis drugs are not depleted at the local level. The regular, uninterrupted supply of free drugs is a basic component of WHO's directly observed treatment therapy short-course tuberculosis control strategy and is critical in efforts to minimise drug resistance.

Contributors

T Frieden and L Thorpe designed the study. L Thorpe did the analysis and wrote the first draft of the paper. C Wells and K Laserson contributed to the analysis and critically reviewed the paper. G R Khatri and T Frieden developed the national tuberculosis programme's data collection process and critically reviewed the paper. No outside or special funds were used to conduct this analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

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