# Seasonality of Tuberculosis

**Auda Fares**

*Department of Internal Medicine, St. Johannes-Hospital, Troisdorf, Germany*

## ABSTRACT

**Objectives:** This study was designed to review previous studies and analyse the current knowledge and controversies related to seasonal variability of tuberculosis (TB) to examine whether TB has an annual seasonal pattern. **Study Design and Methods:** Systematic review of peer reviewed studies identified through literature searches using online databases belonging to PubMed and the Cochrane library with key words "Tuberculosis, Seasonal influence" and " Tuberculosis, Seasonal variation". The search was restricted to articles published in English. The references of the identified papers for further relevant publications were also reviewed. **Results:** Twelve studies conducted between the period 1971 and 2006 from 11 countries/regions around the world (South Western Cameroon, South Africa, India, Hong Kong, Japan, Kuwait, Spain, UK, Ireland, Russia, and Mongolia) were reviewed. A seasonal pattern of tuberculosis with a mostly predominant peak is seen during the spring and summer seasons in all of the countries (except South Western Cameroon and Russia). **Conclusions:** The observation of seasonality leads to assume that the risk of transmission of *M. tuberculosis* does appear to be the greatest during winter months. Vitamin D level variability, indoor activities, seasonal change in immune function, and delays in the diagnosis and treatment of tuberculosis are potential stimuli of seasonal tuberculosis disease. Additionally, seasonal variation in food availability and food intake, age, and sex are important factors which can play a role in the tuberculosis notification variability. Prospective studies regarding this topic and other related subjects are highly recommended.

**Key words:** Seasonal influence, Seasonal variation, Tuberculosis

## INTRODUCTION

It is well known that the incidence of many respiratory infections shows seasonal variation, and it is much less well documented for tuberculosis (TB).[8] In the pre-antibiotic era, the TB mortality rate was higher in late winter and early spring than that any other time of the year.[1] Although the exact mechanism underlying the fluctuation of tuberculosis in a particular time of the year is still not clear, several researchers have suggested that the environmental and social factors such as temperature, humidity, sunlight, as well as crowding and person-to-person contacts, are a source of TB seasonality, particularly, in winter time.[1,3] This explanation applies to primary or re-infection TB, but not to reactivation TB. To explain the seasonal trend of both reactivation and primary TB, it is usual to consider that the main cause of TB seasonality is intrinsic.[5] A possible link between vitamin D deficiency and impaired host defence to *Mycobacterium tuberculosis* infection leading to primary TB has been postulated.[4] Moreover, significant seasonal vitamin D variations were observed in several communities, and reveal that variation of values for (25-OH D) decreases in spring and winter. Immune system competencies vary through the year with significant periodicity in cell function, proliferation, and percentage or number of peripheral blood leukocytes subsets.[5] For example, the level of B lymphocytes in the peripheral blood has been shown to vary throughout the year, being lower in winter than in summer.[5] The absolute number of CD4+ T lymphocytes is the lowest in summer when the level of CD8+ T lymphocytes is the highest.[1] The seasonal variability of TB notification may reflect the seasonality of vitamin D and human immunity or may be caused by the influence of seasons on human activity. However, these questions related to seasonality of tuberculosis remain controversial.

This article reviewed previous studies to analyse the current situation and controversies related to seasonal variability of tuberculosis by describing intensively the data available on seasonal notification rate/TB incidence in various parts

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**Address for correspondence:**
Dr. Auda Fares, E-mail: audafares@yahoo.com

of the world and by reviewing comprehensively scientific literature that investigates the seasonal fluctuations of tuberculosis and to explore all the relevant information of basic biology, immunology and epidemiology that is related with tuberculosis and seasonal influences, and by summarizing the critical sequences that need to be expressed for clinical presentations of tuberculosis at different periods of the year. The identification of the reasons for seasonality may offer the possibilities for preventive measures, and can even help in the development of effective policies and allowing for use resources more efficiently and effectively.

## METHODS

### Literature search terms

This review was restricted to published research articles and abstracts that compared the aggregated TB notification data during the course of the year to determine seasonal patterns of tuberculosis. These studies were identified in the following three ways:

1. Medline was searched through Pubmed by using search terms: "Tuberculosis, Seasonal influence", and "Tuberculosis, Seasonal variation".
2. Cochrane Library database was also used for literature searches using the same search terms mentioned above.
3. The bibliographies of all identified paper were checked for further relevant publications.

### Inclusion criteria

The following inclusion criteria were applied to select the studies:

1. Papers in English language and published in peer-reviewed journal were considered. Review articles, clinical trial, cross-section study, meta-analyses, letter, editorial, textbook chapters, case reports, practice guidelines, and biomechanical studies were gathered to augment overall knowledge and to identify research articles or data not obtained using the search engines.
2. Studies dealing with *M. tuberculosis*, and examining the seasonal variability on tuberculosis incidence in human subjects were considered.
3. Studies had to be used data on patients notified with tuberculosis in primary or secondary care setting stratified by months or weeks, sex, site of disease, symptom onset, and mode of detection.

### Patients' diagnosis procedures

All studies included patients with a confirmed TB diagnosis, based on positive *Mycobacterium* culture, positive AFB, positive radiological or histological findings, inpatients and outpatients, new case or re-treatment. Patients with PTB and pulmonary TB are included. All age and sex are considered, only one study subjected children only.[6]

### Statistical analysis

Due to lack of consistency among the statistical methods used in most of the studies, and limitation of data provide particularly related to age, sex, and site of disease. Therefore, it was not possible to do statistical analysis to integrate the results for all countries.

### Studies area

Twelve descriptive data analysis studies conducted in different countries/regions around the world including Hong Kong, Japan, South Africa, South Western of Cameroon, Spain, UK and Ireland, Russia, and Mongolia. Migrant workers living in Kuwait came from India (31%), Bangladesh (14%), Sri Lanka (14%), Egypt (12%), Indonesia (9%), Philippines (5%), Pakistan (5%), and 10% from African counties such as Tanzania, Mali, Gambia, and Sudan.

### Countries climate profile

Data on countries climate status and season periods were obtained from two main Internet databases; Map of world (www.mapsofworld.com) and Photos (www.photius.com). Another Internet website was used when the information was not available using above websites. In general, four seasons are recognized: Spring, summer, autumn, and winter. Considering the geographical variation of seasons, the earth is split into the Northern and Southern hemispheres. In this review, two studies were conducted in the Southern hemisphere (South Western Cameroon and South Africa), other studies in the Northern hemisphere (UK, Ireland, Spain, Japan, Hong Kong, Russia, Mongolia, India, and Kuwait). For the countries listed in the Northern hemisphere, the spring season begins in March, summer in June, autumn in September, and winter in December. Conversely, for the countries listed in the Southern hemisphere: spring begins in September; summer in December, autumn in March, and winter in June.[51] In some tropical and subtropical regions, it is more common to speak of the rainy, wet or monsoon season vs. the dry season. The rainy season (winter) lasts from April to November and the dry season (summer) from November to March.[11]

## RESULTS

### Term search result

A total of 186 studies were identified from the initial Pubmed search. Of these articles, 12 studies were met the inclusion criteria involving 296,841 participants. One of these studies was conducted in UK from 1983 through 1992 and another one carried out in UK and Ireland for the period from 1993 to 1994, both were included. Another two studies in Spain from 1971 to 1996 and 1996 to 2004 were also included. No additional references were identified from other databases. For one study from Japan, the total number of participants was not available. The total number of TB notification from 1971 to 1996 in Spain was not available. The number we have included for this study was obtained from the table present in the notification number of 1997. All the studies that we have selected investigated the seasonal pattern of tuberculosis except the one from Russia, it investigated the "seasonal variation and hospital utilization for tuberculosis" but the monthly tuberculosis notification during the period of study was provided. The whole time of selected studies were conducted from 1971 through 2006.

### Result of selected studies

Comprehensive results from 12 studies for the period from 1971 to 2006 from 11 countries around the world (South Western Cameroon, South Africa, India, Hong Kong, Japan, Kuwait, Spain, UK, Russia, and Mongolia) show that the manifestation of TB (acquired from number of admissions, notifications, etc.) have a variable seasonality peak with the most predominant peak in most of the countries during the spring and summer seasons [Table 1]. There was no marked seasonal difference between pulmonary and extrapulmonary cases in notification. The number of notification cases among males were slightly more frequent than the cases among females in Mongolia and South Western Cameroon, there were no significant gender difference reported in Hong Kong and India. Few studies used different age's group, the notification number of TB cases was high among young children in India and Hong Kong and declined with increasing age. In South Western Cameroon, the highest number of cases was reported in the age group 21–30, there were no marked seasonal difference was found among all age groups in Japan.

## DISCUSSION

This review discloses the facts that the seasonal pattern of TB in most the subject countries are predominant during the spring and summer seasons. There was no marked seasonal difference between pulmonary and extrapulmonary cases. The seasonality of notified cases in Mongolia and South Western Cameroon was slightly more marked among males than among females. No significant gender differences were reported in Hong Kong and India. Seasonality of TB smear positive cases was highest among young children in India and Hong Kong and declined with increasing age. In South Western Cameroon, seasonality of tuberculosis was reported to be highest in the age group 21–30. In contrary, there were no marked seasonal differences found among all age groups in Japan. Seasonal pattern of TB was reported to be different between Northern and Southern regions of India.

The spring and summer peaks of tuberculosis cases are clearly demonstrated in most of the studies reviewed in this article. The exact reason why TB case notification rates vary by season is unknown, although several factors have been suggested to give a plausible explanation, e.g., exposition to sunlight, indoor activity, seasonal change in

**Table 1: A summary of studies deals with TB seasonality**

| References | Study period | Patients no. | Country | Months peak | Months decline |
|---|---|---|---|---|---|
| Akhtar and Mohammad[2] | January I, 1997 to December 31, 2006 | 4608 | Kuwait | March –August (Sping-summer) | August–December (autumn–winter) |
| Leung *et al.*[7] | 1999–2002 | 82,104 | Hong Kong | July–August (summer) | January–February (winter) |
| Nagayama and Ohmori[1] | 1998 and 2000–2003 | NA | Japan | March–August (spring – summer) | November–February (autumn–winter) |
| Thorpe *et al.*[8] | April 1,1996 to June 31, 2001 | 11 11,101 | India | April –June (spring) | October and December (autumn) |
| Ríos *et al.*[9] | 1971–1996 | 9187 | Spain | February–June (spring) | July–January (summer–winter) |
| Luquero *et al.*[10] | 1996–2004 | 71,553 | Spain | First peak in June and second peak in March and October | October–February (autumn–winter) |
| Ane-Anyangwe *et al.*[11] | April, 2002–July 2004 | 2809 | South Western Cameroon | April–November (winter) | November–March (summer) |
| Schaaf *et al.*[6] | 1 November 1983 to 31 October 1993 | 1204 | South Africa | September–November (spring) | March–August (autumn–winter) |
| Atun *et al.*[12] | January 1999–December 2002 | 420,00 | Russia | No seasons peak | |
| Douglas *et al.*[13] | 1983–1992 | 57,313 | UK | April–September (summer) | October–March (winter) |
| Kelsey *et al.*[14] | 1993–1994 | 55 | UK and Ireland | April–September (summer) | October–March (winter) |
| Naranbat *et al.*[15] | 1998–2006 | 149,07 | Mongolia | April –June (spring) | September–December (autumn– winter) |

immune function, and health care seeking behaviors. The data available on tuberculosis consist mostly on the time of admission and notification and not on the date of diagnosis or onset of disease. As the preclinical period, from infection to development of active TB, may last from few weeks to several months, it is probable that the peak of noted tuberculosis cases during the spring and summer seasons is the consequence of *M. tuberculosis* transmission during the winter months, particularly in the overcrowded and poorly ventilated settings. Winter weather has been linked with increased rates of morbidity and mortality of respiratory diseases (including tuberculosis).[16] In the case of latent tuberculosis reactivation, the time was too long between the transmission of the microorganism and the onset of disease. Hence, seasonal variation cannot be explained only by factors related to *M. tuberculosis* transmission.[10] For that reason, other possible reasons should be discussed. Below we hypothesize several factors that may explain seasonal variation in the number of notified TB cases and possible factors that play a role in the seasonal appearance of acute TB disease and reactivation cases. A brief summary of related studies quoted in text are given in [Table 2].

## Indoor activity

Generally man spends more time indoors in cold (winter) than in warm season (summer), which coincides with the scientific fact that overcrowding, increased humidity, and low airflow provide a suitable environment for *M. tuberculosis* to survive. Additionally, transmission is more likely during winter months due to diminished amounts of natural ultraviolet light. In summer season, the absorption of natural ultraviolet light is higher and can kill *M. tuberculosis* within a short time, while it can survive in darker conditions for a longer period. These properties of *M. tuberculosis* support the suggestion that most disease transmissions occur indoor. The fact that there are higher transmissions rates in winter followed by the development of disease several months later would be supported of the findings of this study.

## Vitamin D status variability

The potential factor that has been suggested in most articles is the link between vitamin D level and impaired host immunological defence with the reactivation of latent *M. tuberculosis* infection.[4] Several studies from various regions, ethnic groups, and cultures show positive association between the serum level of vitamin D and susceptibility to TB infection or reactivation.[17] Serum vitamin D concentrations are significantly lower in TB patients compared with those in control groups. Several mechanisms have been proposed to explain this relation, most of them concerned with the possibility of the role of active metabolite vitamin D (25-(OH) D) in the hosts defence against human tuberculosis, thus suggesting that metabolite (25-(OH) D) can act to suppress the growth of *M. tuberculosis* through the induction of nitric oxide (NO) production by macrophages.[18]

Significant seasonal vitamin D level variations were observed in several communities, which reveal a variation of values for 25-(OH) D, increased during summer and spring, while gradually decreasing in autumn and winter.[19,20] Various authors are in favor of the idea that highest TB rates in spring and summer are associated with the seasonal variation of vitamin D level.[1,2,8] The significant observations of the seasonal peak of tuberculosis in Indian immigrants in Kuwait in late April was consistent with the findings of tuberculosis peaking from April to June in northern India. Also, it may well be that the immigrants from India have a very high proportion of TB and arrives Kuwait mainly in winter month while migrants from Sri Lanka and other low burden countries have a low proportion of TB and arrive mainly in summer.[2]

Several studies on vitamin D level variations suggest that heavy clothing in winter is considered as a barrier that can reduce ultraviolet radiation reaching the body and thus, the conversion of vitamin D. In addition, some cultural factors such as style of clothing (veiled clothing) were shown as potential factors which influence serum vitamin D concentrations, particularly in women. Women in some conservative cultures also tend to spend longer periods of time indoors.[21,22] According to these findings, one could hypothesize that women in some communities are more susceptible to TB than men as a consequence of vitamin D deficiency and/or duration of time spent indoors. Other studies conducted in various countries show that the vitamin D deficiency is more predominant among women regardless of age, lifestyle, and clothing (veiled).[23-26] This finding is contradicted by studies which show no significant difference between genders in seasonal notification of tuberculosis.

## Regional variation

Seasonal pattern of tuberculosis was reported to be varying between northern and southern regions of India. These regions were also varying in TB incidence rates. India is a large country with varying climate zones. In the southern region, the weather in winter is mild, whereas the northern region is much colder. The northern part is well connected by roads, thus giving the patients better access to health centers and consequently noting the case faster.[27] Similarly,

**Table 2: A brief summary of related studies quoted in text**

| Authur | Year published | Sample size | Study design | Conclusions |
|---|---|---|---|---|
| Maes *et al*.[5] | 1994 | 26 | Experimental study: seasonal variation in peripheral blood leukocyte subsets and in serum interleukin-6, and soluble interleukin-2 and -6 receptor concentrations in normal volunteers | It was found that most of the immune variables change rhythmically during the seasons as a group phenomenon |
| Nakaji *et al*.[16] | 2004 | NA | Retrospective study: seasonal changes in mortality rates from main causes of death in Japan (1970–1999) | Winter weather has been linked with increased rates of morbidity and mortality of respiratory diseases (including TB) |
| Nnoaham and Clarke[17] | 2008 | 531 | Meta-analyses: low serum vitamin D levels and tuberculosis | Low serum vitamin D levels are associated with higher risk of active tuberculosis. |
| Rockett *et al*.[18] | 1998 | NA | Experimental study: 1,25-Dihydroxyvitamin D3 induces nitric oxide synthase and suppresses growth of *Mycobacterium tuberculosis* in a human macrophage-like cell line | 1,25-$D_3$ acts to inhibit the growth or viability of *M. tuberculosis* in human myeloblastic cell line (HL-60) through an NO-dependent mechanism |
| Webb *et al*[19] | 1988 | 38 | Cluster interventional trial: influence of season and latitude on the cutaneous synthesis of vitamin D: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D synthesis inhuman skin. | The circulating concentrations of 25(OH)D were found to change with a change in the season |
| Sherman *et al*.[20] | 1990 | 281 | Cross-section study: vitamin D status and related parameters in a healthy population: the effects of age, sex, and season | A significant seasonal variation in 25OHD and 1,25-$(OH)_2D$ were observed in both sexes ($P < 0.005$) |
| Kim and Moon[21] | 2000 | 179 | Cross-section study: time spent outdoors and seasonal variation in serum concentrations of 25-hydroxyvitamin D in Korean women | Significant seasonal variation of serum 25-OHD were noted in 26 of the subjects and the serum 25-OHD level also correlated with sunlight exposure especially at 12.00 p.m. to 2.00 p.m. as assessed by the time spent outdoors |
| Guzel *et al*.[22] | 2001 | 60 | Case–control study: vitamin D status and bone mineral density of veiled and unveiled Turkish women | 25-OHD levels were positively correlated with exposure to sunlight and negatively correlated with the duration of being veiled |
| Islam *et al*.[23] | 2006 | 121 | Cross-section study: hypovitaminosis D is common in both veiled and nonveiled Bangladeshi women | Women in Bangladesh, regardless of different age-groups, lifestyle and clothing were at risk of developing hypovitaminosis D |
| Mishal [24] | 2001 | 146 | Cross-section study: effects of different dress styles on vitamin D levels in healthy young Jordanian women | Vitamin D levels were significantly lower in women than in men |
| Nakamura *et al*.[25] | 2001 | 77 | Cross-section study: low serum concentrations of 25-hydroxyvitamin D in young adult Japanese women | Serum 25(OH)D concentrations in young adult Japanese women (<30 year old) are lower than those of older adult women (30–66 years). |
| Grootjans-Geerts and Wielders JP[26] | 2002 | 55 | A pilot study of hypovitaminosis D in apparently healthy, veiled, Turkish women: severe vitamin D deficiency in 82%. | Hypovitaminosis D are common among veiled Turkish women living in the Netherlands |
| Agbotwalla *et al*. [29] | 2003 | 200 | Cross-sectional, descriptive study gender perspectives on knowledge and practices regarding tuberculosis in urban and rural areas in Pakistan | Knowledge regarding TB has been found to be extremely deficient in both sexes, but especially in rural females. |
| Paynter *et al*.[30] | 2004 | 71 | Retrospective cohort study: patient and health service delays in initiating treatment for patients with pulmonary tuberculosis | The median case finding delays were between 78 and 99 days. Median patient-related delay was between 34.5 and 54 days. Median health care-related delay was 29.5 days |
| Strachan *et al*.[32] | 1995 | 156 | Case –control study: vegetarian diet as a risk factor for tuberculosis in immigrant south London Asians | Vitamin D deficiency, common among vegetarian Asians in south London |
| Yellon *et al*.[33] | 1999 | NA | Experimental study: influence of photoperiod on immune cell functions in the male Siberian hamster | In hamsters in short days, natural killer cell cytolytic capacity, as well as spontaneous blastogenesis, were enhanced compared with that in hamsters in long days. |
| Sharma et *al*.[34] | 2007 | 19,378 | Surveillance of communicable diseases in tertiary health care system in Chandigarh, UT | Morbidity of tuberculosis were observed maximum during summer compared to winter |
| Lisse *et al*.[35] | 1997 | 803 | T-lymphocyte subsets in West African children: impact of age, sex, and season | Compared with dry-season results, the lymphocyte percentage, the absolute lymphocyte count, the absolute CD4+ T-lymphocyte count, and the CD4+/CD8+ ratio were significantly lower during the rainy season, whereas the CD8+ percentage was increased during the rainy season. |
| DeCastro JM[38] | 1991 | 315 | Cross-section study: Seasonal rhythms of human nutrient intake and meal pattern. | A marked seasonal rhythm of nutrient intake was observed with increased total caloric intake, especially of carbohydrate, in the fall, associated with an increase in meal size and a greater rate of eating. |
| Prentice *et al*.[39] | 1981 | 143 | Cross-section study: long-term energy balance in child-bearing Gambian women | Wet season energy intakes were clearly inadequate among Gambian women compared to dry season. |
| Ustainowski *et al*.[40] | 2005 | 210 | Case-note analysis: prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London | 25$(OH)D_3$ deficiency commonly associates with TB among immigrants living in London due to lack of sunlight exposure or vegetarian diet |
| Kumar *et al*.[41] | 1997 | 2706 | Tuberculosis in England and Wales in 1993: results of a national survey | TB proportion cases were observed maximum among immigrants living in UK, particularly those recently arrived in this country |
| Borgdorff *et al*.[44] | 2001 | 3479 | Retrospective study: transmission of *M. tuberculosis* depending on the age and sex of source cases | Transmission of tuberculosis is associated with the age and sex of source cases as well as the age of secondary cases. |
| Graham *et al*.[45] | 2008 | 89 | Cross-sectional study: vitamin D status of year 3 children and supplementation through schools with fortified milk | Vitamin D3 levels are low in low-decile year 3 children in midwinter |

in South Africa, the TB rates of the nine provinces show significant differences, the highest rate being found in the Western Cape Province (approximately 1,500/100,000 notification).[28] The Western Cape receives most of the rain in winter, some areas with high mountains get snow at this time. Therefore, the possibility of contracting TB infection due to overcrowded or poorly ventilated houses in winter is highly proposed, particularly, in the areas where the TB incidence is high. This concept could clarify the seasonal variability between the north and south regions of India.

Differences in TB incidences between rural and urban areas may also play a role in the seasonal variability of notified case number. In most countries, rural areas have higher TB incidences than urban areas, because of low health awareness and poor knowledge among rural people about TB.[29] The traditional style of rural housing, with high numbers of family members sharing one room, can facilitate transmission of *M. tuberculosis*. Additionally, the health services in rural areas are less likely to have adequate health facilities for being able to diagnose and treat tuberculosis. Travel to urban areas or the city center is not easy, especially during winter climate. Surprisingly, there was no difference in seasonal patterns of tuberculosis reports between rural and urban areas in Mongolia. This could reflect an equal health service accessibility distribution between rural and urban areas.

## Delay in diagnosis or in health care seeking

The cell-mediated immunity (CMI) develops tow to 6 weeks after primary infection with *M. tuberculosis*. Active tuberculosis develops if the immune system fails to control multiplication of the bacteria. In UK, the average time from the onset of symptoms to diagnosis and starting treatment was estimated to be between 11 and 18 weeks.[30,31] Therefore, theoretically people who are infected in autumn or winter (as suggested above) and develop active tuberculosis shortly after infections are on average diagnosed 3–4 months after the first onset of symptom, resulting in a higher number of notifications in spring and summer. This, if one assumes the infection occurs in winter when the people spend more time indoors particularly in their homes, can easily accelerate transmission of *M. tuberculosis* within family members.[15]

Delay in seeking health care in winter season may be the cause and can give plausible explanation to the predominance of tuberculosis notification cases in spring and summer. In contrast, winter climate has not shown to influence health care seeking behavior in Russia, where hospital admissions for tuberculosis are more frequent in colder months than warmer months. However, these excess in winter of admission numbers in Russia is probably not associated with seasonal changes in tuberculosis notification rates because most of the patients were unemployed and prisoners. Thus, the patients most likely use the hospital services in cold months to meet their social and environmental needs such as shelter, heating, and food supply.[12]

Authors in Hong Kong presented the Chinese New Year festival (a major winter festival for the Chinese) as a factor that may prevent patients from seeking medical attention. The number of chest clinic consultations during this period is low. This delay in TB diagnosis may increase the risk of disease transmission (due to overcrowding) and may contribute to the increase of TB notifications during spring and summer in Hong Kong.[7]

## Seasonal immunity competence

The exact mechanism of *M. tuberculosis* reactivation in a particular time of the year is still not well understood in most cases.[32] Recent evidence suggests that the immune system competencies vary through the year with significant periodicity in immune cell function and in the number of some peripheral blood leukocytes subsets.[5] In this regard, it is not surprising to see seasonal variability in tuberculosis manifestation with a peak of notification rates in spring and summer. Experimental studies findings support these observations. For example, the natural killer cells and CD4 T-cells have been reported to be increased in winter associated with an increased level of Interleukin-6.[5,33] This could be a reason for a better immune response against *Mycobacteria* in winter compared to summer, obviously not preventing infection, but allowing to control it in winter, whereas the infection later progresses to disease. Moreover, these findings consist with a study conducted in India, showing that the morbidity of tuberculosis is high in summer compared to winter.[34] In contrast, in Western Africa, CD4 cells count were low in children in the rainy season (winter).[35] That may give an explanation for a peak of tuberculosis notification in Cameroon during the winter season.

In addition, there is some evidence that the fluctuation in weather temperature during winter seasons may act on the respiratory epithelium by slowing mucociliary clearance and inhibiting phagocytosis, which then lead to increase the susceptibility to infection.[36] This may give us an explanation about the findings of this review regarding the peak of seasonal notification of tuberculosis cases and the possibility of infection during winter season.

### Seasonal variations in transmission risk and sickness response

For acute infectious diseases with shorter incubation periods such as influenza, measles, cholera, and malaria, variations in transmission dynamics are likely to exert a direct effect on the seasonal pattern.[37] However, the situation with a disease such as tuberculosis, where the time period between infection and disease can be prolonged and variable (weeks in primary tuberculosis up to decades in the case of reactivation), reasons for the observed seasonality seem to be very complex. The outcome of infection with *M. tuberculosis* varies from person to person, some people develop active disease in either short periods (primary tuberculosis) or long periods (reactivation), and some are able to control infection and settle into a latent state. A reason for the seasonality of tuberculosis could be that the infection takes place preferably in winter, but is controlled by the immune system, and progresses later to active tuberculosis. In the case of a weak immune system function such as with HIV or in malnourished patients, this could accelerate progression of disease earlier.[32]

The observations of the seasonal trend in Hong Kong are only evident among the new TB cases, but not for re-treated cases. These findings might support the hypothesis of increased risk of transmission in winter. Additionally, there were no marked seasonal differences between pulmonary and extrapulmonary tuberculosis reported in most of the studies reviewed. As pulmonary and extrapulmonary TB develop at different times after infection, similarity of seasonal fluctuation in both forms would not be expected, but this finding "strongly suggests the presence of a disease modulating factor, rather than increased risk of transmission alone".[7]

### Food habits and seasonal rhythm of nutrient intake

It is well known that malnutrition increases risk of contracting tuberculosis and profoundly affects immune system functions.[1] This influence may vary according to the seasonal cycle, because the availability of food or in the amount of food intake during the seasons. One study conducted in the USA shows seasonal variations in the nutrient intakes and the meal patterns of humans. A marked seasonal rhythm with increased total caloric intake was observed, especially of carbohydrate, in the fall, associated with an increase of meal size and a greater rate of eating, but not found changes in winter and spring.[38] Another study conducted in Gambia found energy intake among women in the wet season was clearly inadequate, while in the dry season intake almost met energy requirements.[39] This finding may be linked with seasonal variability of tuberculosis particularly in wet season in Cameroon with high number of tuberculosis case notifications.

Additionally, vegetarianism and tuberculosis have been linked with increased incidence of tuberculosis among immigrants from the Indian subcontinent who live in the UK.[32] Vegetarian diets have been reported to be associated with deficiencies of certain minerals and vitamin in particular vitamin D. This kind of food (vegetarian) is common among Hindus due to religious restrictions.[41] That could be a contributing factor and may help to explain the seasonal peaking notification of tuberculosis among Indian origin patients in the UK. Recently, immigrated persons had a higher risk of developing tuberculosis disease than those who had been in the UK more than 5 years or who were born in the UK.[9,41] Thus, people may have latent tuberculosis which is reactivated when their vitamin D level is diminished due to the largely dark climate of the UK in addition to the absence of vitamin D diet resource as a consequence of vegetarianism.[4,21]

### Share of the seasonality with other infectious diseases

Winter is known to be a season of respiratory infectious diseases, both viral and bacterial.[6] In addition, some infectious diseases exhibit frequent and shared patterns in the same season such as increased incidences of pneumococcal and meningitis during influenza season and the occurrence of streptococcal disease, varicella zoster virus infection, and bacterial super-infection in children with seasonal measles virus.[43] This frequency may contribute to explain a result of predisposition to infection with other pathogens in winter, which could be also a reason to the high rate of tuberculosis notification in Spain in late winter (February) and spring associated with flu viral infections as the authors suggest. That could also relate to increased admission of patients with respiratory tract infections in the UK and Russia during the winter season thereby, leading to the diagnosis of tuberculosis particularly in children. This diagnosis can be made by vigorously investigating children with existing respiratory complaints for possible tuberculosis.[6] The Influenza virus or other pathogens cannot cause tuberculosis, but may accelerate disease manifestation in patients with latent tuberculosis or increase susceptibility of individuals to infection and therefore, develop the disease faster than those without these diseases. The process is probably aggravated by an increasing frequency of coughing consequential from other winter viral and bacterial respiratory infections.[6] However, the general finding of this review coincides with this hypothesis due to the higher number of tuberculosis notifications in spring and summer especially among children.

## The influence of age on the seasonal pattern of tuberculosis

Several studies show the clinical development of tuberculosis as being age-dependent. It is observed to decline as age increases,[44] therefore making it obvious that the notification rate of tuberculosis cases to be high among young children in India, Hong Kong, and Western Cape Province of South Africa. Those age groups, in particular, have been reported to possess low vitamin D levels, especially in the mid-winter.[45] This could reflect the increased susceptibility of growing children to infection during winter, and may help to determine seasonality of tuberculosis resulting from recent infection. In particular, the children are infected by sputum smear positive family member or another close contact. They often present with cervical tuberculous adenitis or intestinal tuberculosis, but can also develop pulmonary tuberculosis (PTB) or disseminated disease.[46] Children can present with tuberculosis at any age, but the most common age is between one and four and is most likely due to an undeveloped immune system. This would be consistent with the findings of age distribution of children and seasonal presentation of tuberculosis in Western Cape Province of South Africa. The highest notification rate of tuberculosis among children in Western Cape Province of South Africa has been reported between ages 0 and 2 years. Additionally, many sick children are not brought to health centers due to the costs of consultation and treatment as well as the cost of travel if a health center is not nearby. Another factor which may act as a deterrent is the limited diagnostic capacity of health centers found mostly in developing countries. Furthermore, since active tuberculosis in children often affects more than one organ system, signs and symptoms are vague, making diagnosis difficult. One study shows that more than 95% of children with active tuberculosis would have a negative sputum smear. Studies in hospital settings have found that extrapulmonary tuberculosis is more common in children than pulmonary tuberculosis and misdiagnosis is a regular occurrence.[47] Regardless of the number of missed cases and difficulties faced in the diagnosis of pediatric tuberculosis, the result is possibly supportive of seasonality of tuberculosis among children.

In contrast, the seasonal notification rates of tuberculosis in India and Hong Kong are in decline in ages over 14 years, but again show increases in ages over 60. This coincides with another study from Japan which shows the prevalence of tuberculosis increasing with age, reaching 80% in ages >80 years.[48] All together, these findings suggest that the infection in young children is mostly recent. In other age groups, the result is mixed among recent infection, reactivation, and re-infection. Moreover, one study conducted in India shows the children in North India are at a higher risk than in the rest of the country, as researchers found only 45% of children were vaccinated with BCG, while 64% had received vaccination in the Southern region of India.[49] Potentially, this may support the presence of seasonality in northern India, especially with higher notification rates in young children.

## TB seasonal pattern and gender difference

The seasonal pattern of tuberculosis has been reported to be different by gender in the studies conducted in Cameroon and Mongolia, the number of notified cases was higher for male than that of female. This has been attributed to their often more extroverted activities which include high social interaction (often in overcrowded environments), drinking and smoking; all activities which enhance the spread of tuberculosis. It also may be due to a lack of health facilities for women and a preference for women to visit traditional healers which could relate to lower seasonal notification rates among women in Cameroon and Mongolia. These findings are consistent with global findings of higher tuberculosis case notification rates in males than in females. In contrast, there were no gender differences in the number of notified cases which have been reported in other studies throughout assessing seasonal pattern of tuberculosis. Women generally exhibit higher immune response to infection than men, while males have been revealed to be more susceptible than females to various infections and certain types of cancer such as lymphoma and leukemia[50] Epidemiological studies suggest this variation is closely related to the rate of exposure to pathogens, social behaviors, habitat, and diet. The laboratory studies demonstrate that even in controlled settings, males show more susceptibility to infections than females; this difference has been linked with the influence of steroid hormones on immune function.[51,52,53] These variations could be reflecting the basic seasonal difference in tuberculosis notification between males and females. As mentioned above, the predominance of hypovitaminosis D among females has been reported. This also leaves room for the suggestion that, due to gender difference in immune response, there may be a higher rate of latent tuberculosis among females, but lower progression rate to disease. In this regard, further studies would be helpful to understand the season variability between both genders.

## Confounders and limitation of the study

There are some possible confounders in this study. Primarily, the number of notification cases could be underestimated because the quality of tuberculosis notification systems and the reliability of the reported data are questionable in some regions. This means it is hard to obtain an accurate number of diagnosed and treated cases, especially in the private sector. The cases notified are more likely to have a positive microbiology than the cases not notified. The unnotified cases are more likely to have only a positive histopathology or had a surgery done such as patients with nonpulmonary tuberculosis.

Moreover, there are a number of people who are the most vulnerable in communities and might have a lower rate of notification in some places. This includes people of lower socioeconomic standing, such as the homeless, refugees, ethnic minorities, and illegal immigrants. There is evidence that the cases not notified to the public health system have a higher risk of morbidity and mortality.[54] In addition, the people who have had contact with the unnotified cases are also at risk if they are not screened and treated appropriately for active or latent disease.[54]

Secondly, the data available on tuberculosis consists mostly on the time of admissions and notifications and not on the date of diagnosis or onset of tuberculosis. The number of unnotified cases is not known. These factors are potential confounders in the study of tuberculosis seasonality variation.

The data of tuberculosis in the studies reviewed did not always provide details on concomitant diseases or risk factors that are commonly associated with tuberculosis (e.g. HIV, DM, smoking habit, etc.). It is not possible comprehensively to examine the variation in tuberculosis seasonality or differences in seasonal patterns of tuberculosis without consideration of the influence of factors that can play a role in a person's susceptibility to infection by *M. tuberculosis*. Additionally, many studies do not provide detailed information about gender and age difference or give the monthly number of tuberculosis case notification in detail. These statistics could provide useful information and eventually lead to better conclusions about the seasonality of tuberculosis.

There are other important local environmental and climate parameters (rainfall, temperature, regional differences, etc.) that require further consideration in future studies.

Despite the potential confounders and limitations, the dataset in these studies are adequate to expose important evidence on the seasonal pattern of tuberculosis around the world.

## CONCLUSION AND RECOMMENDATIONS

The seasonal variability of tuberculosis is quit clearly demonstrated by the epidemiological data; showing mostly a peak in notification numbers in early spring and summer months. This finding may have important implications, it seems that the risk of *M. tuberculosis* transmission appears to be the greatest during the winter months, particularly in overcrowded and poorly ventilated settings. There are several possible reasons of the seasonality of tuberculosis: serum vitamin D level variability, indoor activities, seasonal changes in immune function and patient or health care system delays in the diagnosis and treatment of tuberculosis. Additionally, seasonal variation in food pattern, age and sex are important factors which can play a role in tuberculosis notification variability. Further prospective studies are required to better understand the fundamental pathophysiologic mechanisms underlying seasonal immune system competence and tuberculosis.

The knowledge of the role of environmental factors (infection, cold, etc.) or other triggers (indoor activity, vitamin D intake) could be used to improve prevention measures and educational strategies, especially in people with a risk of infection. People should be informed of the increased risk of disease transmission during the cold seasons, and educated about the importance of seeking health care if they develop tuberculosis symptoms. People should be informed about the importance of proper housing ventilation and the potential benefits of increased outdoor activity in natural UV light. Furthermore, people should be motivated to maintain health dietary habits including a nutrient rich in vitamin D. There is also a need to improve health accessibility of health care services, especially in rural areas in some countries. Clinical practitioners have to be educated on the importance of continuous and good surveillance and timely reporting of tuberculosis patients.

There are many gaps in the current knowledge, but it can be assumed that research on behavioral and physiological mechanisms and their effect on the seasonality of immune function are likely to provide important insight into the role of the environment in influencing health and well-being.

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