

## Factors Influencing the Seasonal Patterns of Infectious Diseases

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### ABSTRACT

The recognition of seasonal patterns in infectious disease occurrence dates back at least as far as the hippocratic era, but the mechanisms underlying these fluctuations remain poorly understood. Many classes of mechanistic hypotheses have been proposed to explain seasonality of various directly transmitted diseases, including at least the following; human activity, seasonal variability in human immune system function, seasonal variations in vitamin D levels, seasonality of melatonin, and pathogen infectivity. In this short paper will briefly discuss the role of these factors in the seasonal patterns of infectious diseases.

**Keywords:** Diseases, human activity, infection, season

### INTRODUCTION

Many infectious diseases flourishes when the weather is cold and when the people living in closed houses and decrease in warmer weather and the people get out of doors and ventilate their homes. The mechanism underlying these fluctuations remain poorly understood. Is it the cold? Dry air? Crowding together of people indoor in winter? The identification of the reasons for seasonality of infectious diseases 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.<sup>[1]</sup>

In this short paper will briefly discuss the most factors influencing the seasonal patterns of infectious diseases, providing an overview of seasonal infectious disease epidemiology. It is divided into five sections and a conclusion. The first section outlines summary information on the seasonal changes in human physical activity and their association with different modes of human infectious disease transmission. The second section provides an overview of seasonal environmental changes and maintenance of pathogens infectivity. The third section deals with the seasonal variation of immune system function. In the four and five sections, discuss the possible links between seasonal variation of vitamin D levels and melatonin in the seasonal patterns of infectious diseases.

#### Human activity

Pathogens like crowded environments. With the onset of cooler weather, the people spent most of their time indoor. Inadequate and poorly designed ventilation in crowded public places and urban

transit systems may boost exposure to air-borne pathogens. Besides, higher relative humidity may also affect the stability of air-borne droplets in which pathogens transmitted from person to person. For example, the transmission of the Influenza virus by droplets is enhanced in cooler, more humid seasons. In many countries the onset of cooler, more humid weather coincides with the increased aggregation of people and the seasonal effect can be exacerbated. Cholera being more frequent in warm season, seems to be related to the ability of *vibrios* to grow rapidly in warm environmental temperatures etc., However, diseases do not look at calendars. Their incidence rises and declines because of changes in factors associated with the diseases. In all cultures, most of social proceedings are synchronized by calendars; and usually all calendars reflect the cyclic rhythm of nature. Social celebrations or gathering people observed by communities according to calendars, for example. Increased contacts between children during schools time, or in summer camps, reflecting schools calendars, and also reflect the time of some infectious diseases associated with it.<sup>[2]</sup>

Human physical activity is high in summer and spring compared to winter. In a study, it is observed that the majority of Australians and Germans have decreased the level of physical activity in winter, especially as it relates to outdoor activity or work activity.<sup>[3]</sup> From this we can conclude that weather has a modest effect on the physical activity of population. Moreover, the magnitude of weathers impact socioeconomic conditions. Weather acts as a barrier to physical activity, and social communication. One study conducted in Japan, shows that the physical activity increased as temperature became warmer, up to 17°C, and then declined as the temperature decreased.<sup>[4]</sup>

Seasonal clothing styles due to weather conditions, is a step of adaptation with environment. Wearing heavy clothing in winter and less clothing in summer and spring also has a significant influence on seasonal variations in human behavior. Several studies show that clothing styles that cover whole the body have adverse effects on vitamin D concentration and can lead to vitamin D deficiency due to limited exposure of skin surface to sunlight. In order to meet the requirement of converted vitamin D from sunlight, it is important that the most vulnerable region of the body like the arms, legs and face be exposed to the sunlight at least two or three times a week.<sup>[5]</sup>

### Pathogens infectivity

“The maintenance of infectivity by any pathogen outside the host is dependent on a number of factors including temperature, moisture, dehydration, and UV light. Temperature has the greatest effect, since the rate of most chemical and physical processes are dependent upon it”.<sup>[6]</sup>

It can be postulated that the occurrence of infectious diseases is driven by seasonal environmental changes directly on pathogen abundance, survival, or virulence,<sup>[7]</sup> due to the annual changes in seasonal cycle are associated with changes in the physical environment like temperature, oxygen concentration and humidity. For example, some micro-organisms like *E. coli* strains were most stable at low-humidity conditions and markedly unstable at high-humidity conditions. Viruses (e.g., polioviruses) without structural lipids are more stable at high-humidity conditions, whereas viruses (influenza and vaccinia) with structural lipids are least stable. Pox viruses have been shown to survive for several months under natural indoor conditions.

In case of *Mycobacterium tuberculosis* the observational studies showed that they are inducing changes in the cell wall as a response to the temperature variation in the surrounding environment.<sup>[8]</sup> The studies suggest that the complex composition of mycobacterium cell wall which contains waxes, glycoproteins and glycolipids are responsible for the virulence of the mycobacteria and gives it the ability to survive in hard environmental conditions such as dehydration or increase in the environment temperature. However, very little is known about the mechanisms by which mycobacteria modulate the expression of cell-wall components in response to changes in the environment, such as oxidative stress, growth, anaerobiosis, nutrient deprivation and temperature shifts.<sup>[8]</sup>

### Immune system function

Changing seasonal and environmental factors, such as temperature, sunlight, rain, wind and humidity has a direct link with the increasing number of infectious diseases. Example can be seen in increase in meningococcal epidemic in sub-Saharan Africa during the season of dry winds and ending with the onset of the rains. Correspondingly, respiratory syncytial virus epidemics occur in the colder months of winter and spring in the United

States. While respiratory syncytial virus epidemics are significantly correlated with the hotter months in Singapore.<sup>[2]</sup> It has been proposed that dryness of mucosal surfaces increases the probability of bacteremic spread. Rain moistens the mucosa, therefore decreasing the spread of the organism by dust.<sup>[9]</sup> Dry air and temperature changes may alter mucociliary function. A recent explanation of seasonal variation in the incidence of respiratory infection suggests that this variation is due to the effects of atmospheric pollutants on host mucociliary action.<sup>[10]</sup> Nonetheless, the change of environmental factors influence the host susceptibility to infection, either as a result of seasonal changes on host immune function (humoral and cellular immunity) or as a result of direct environmental effects.<sup>[9]</sup> The mechanisms of seasonal influence on the host immune system vary, evident from data of the experiments that have been performed on animals and human. Recent experimental studies on rodents, birds and humans suggest that the immune system is weakened during the winter.<sup>[11]</sup> A different study on Siberian hamsters showed an increase in the natural killer-cell activity and lymphocyte blastogenesis but decrease of phagocytosis and oxidative burst activity by granulocytes in summer days.<sup>[9]</sup> As observed in rodents, seasonal variations caused substantial variations in lymphocyte mitogenic responses and in the quantity of circulating lymphocytes, neutrophils, CD4 and CD8 cells and IL-6.<sup>[9]</sup> Some values, such as for lymphocyte aryl hydrocarbon hydroxylase activity, peak in summer,<sup>[12]</sup> while others, such as a number of circulating CD4<sup>+</sup>T, CD25<sup>+</sup>T, CD20<sup>+</sup>B cells, and CD4<sup>+</sup>/CD8<sup>+</sup> ratio peaked in winter and lowest in summer. Additionally, a down-regulation of TLR-4-mediated IL-1 $\beta$ , IL-6, TNF- $\alpha$ , interferon (IFN)- $\gamma$  and IL-10 production in summer was observed compared to winter.<sup>[13]</sup> Furthermore, few studies observed seasonal variations in other immunological values during the annual seasons. For example, significant variation in total number of white blood cells, with peaks occurring in winter (maximum around December-March) and troughs in summer (May-August) and seasonal variation in number of circulating T and B Lymphocytes were observed. Such as number of T cells peaked in late fall, whereas B cells peaked in winter.<sup>[14]</sup> In a study of healthy West African children, the lymphocyte percentage, the absolute lymphocyte count, the absolute CD4<sup>+</sup> T-lymphocyte count, and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio were significantly

lower during the rainy season (June-October) compared with the dry season (November-May), whereas the CD8<sup>+</sup> percentage was higher during the rainy season than the dry season.<sup>[15]</sup> In another study, four healthy individuals were followed for 7 years, the absolute numbers of CD4<sup>+</sup> T lymphocyte were lowest in summer when the CD8<sup>+</sup> T- lymphocytes were highest. There were no significant seasonal changes in the total number of white cells or in total lymphocyte counts.<sup>[16]</sup> Similarly, the total leukocyte and lymphocyte counts in a different study of six healthy subjects did not show seasonal variation over the course of one year, whereas the percentage of B cells in the coldest month was at almost twice the level observed in summer.<sup>[16]</sup> Suggested by a more recent study, the lower level in the mean number of CD4<sup>+</sup> T cells and mean CD4<sup>+</sup>/CD8<sup>+</sup> ratio were found in HIV-infected men during summer and spring.<sup>[17]</sup> The mechanism underlying the circannual change in immune function has been linked with adrenocortical hormones activity. Adrenocortical hormones vary on a circannual basis with increased levels of secretion in winter and decrease in summer. One consequence of this variation is a circannual pattern in immune function. Adrenal corticosteroids, especially glucocorticoids, depress cellular immune function and show to be more effective against T-suppressor cells. Thus, when adrenocortical activity is elevated, T-cell activity is depressed and B-cell activity is elevated. In contrast the circadian fluctuations in immune parameters appear to be independent of glucocorticoid secretion.<sup>[18]</sup>

To determine whether the seasonal variation in immune activity is temperature dependent or not, one study of eight healthy men shows elevation in NK cell activity after exposed to acute cold air.<sup>[19]</sup> Another study found a significant increase in the proportion of monocytes, lymphocytes and the percentage of CD14<sup>+</sup> and CD25<sup>+</sup> cells after acute cold-water (14°C) immersion, three time a week for a duration of 6 weeks.<sup>[20]</sup> Conversely, low temperature did not show effects on the proportion of B cell.<sup>[21]</sup> Thus, the degree of influence of coldness on the immune function remains controversial.

### Seasonality of vitamin D

The link between vitamin D deficiency and susceptibility to infection has been suggested for longer than a century. More recently, epidemiologic studies have demonstrated strong associations between seasonal variations in vitamin D levels and the

incidence of various infectious diseases.<sup>[22]</sup> 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.<sup>[1]</sup> One study conducted in Boston (42°N) found the conversion rate of pro-vitamin D3 to pre-vitamin D3 in June and July at maximum, and then gradually decreasing in August and October. There was little production of pre-vitamin D3 detected through November until March. A similar study conducted in Edmonton, Canada (52°N), the conversion of pre-vitamin D3 ceased after mid October and did not return until mid April.<sup>[23]</sup> In a study of healthy subjects living in Baltimore aged from 20 to 94 years, there was increase in the level of 25-OH D from a nadir in April-May of 72.9 nmol/l to a zenith in October of 95.8 nmol/l.<sup>[24]</sup> Studies from many parts of the world have confirmed a significant seasonal variation in vitamin D.<sup>[25]</sup> Epidemiological evidence suggests that seasonal variability is due to the effect that mainly people in winter are more frequently indoors and wear more clothing, thereby expose less skin surface area to sunlight. Furthermore, the amount of UV light that reaches to any subjects on the earth's surface varies with season and latitude, particularly in winter.

### Seasonality of melatonin

Melatonin is a powerful natural hormone that is well known for its association with circadian and seasonal rhythms, and its synthesis is regulated by the environmental light/dark cycle. Melatonin participates in various functions of the body, among which its immunomodulatory role has assumed considerable significance in recent years. Melatonin has been reported as effective in combating various bacterial and viral infections. Melatonin has been shown to be involved in the regulation of both cellular and humoral immunity. Melatonin not only stimulates the production of natural killer cells, monocytes and leukocytes, but also alters the balance of T helper (Th)-1 and Th-2 cells mainly towards Th-1 responses and increases the production of relevant cytokines such as interleukin (IL)-2, IL-6, IL-12 and interferon- $\gamma$ .<sup>[26]</sup> The seasonal changes in immune function observed in animals and humans are likely to be mediated by the changes in the duration of melatonin secretion. This fact may in part account for the cyclic pattern of symptom expression shown

by certain infectious diseases, which become more pronounced at particular times of the year.

## CONCLUSION

Seasonal variability in infectious disease incidence is likely to be influenced by population susceptibility and behaviours; however, environmental influences are also important considerations. Such environmental factors can impact the abundance of pathogens. 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 about the importance of proper housing ventilation and the potential benefits of increased outdoor activity in natural UV light. Furthermore, adequate vitamin D status may be required particularly in winter to decrease infection rates; future population-based studies to evaluate broad effects of vitamin D supplementation on infection rates may be warranted.

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