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REVIEW

Seasonal immune modulation in humans: Observed patterns and potential environmental drivers

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Summary *Introduction:* Cyclical fluctuations in host immunity have been proposed as a driver of respiratory infection seasonality, however few studies have attempted to directly assess whether or not seasonal immune modulation occurs in humans.
Materials and methods: We reviewed studies assessing immune status at different times of the year, restricting our review to studies assessing any of the following three biomarkers: antibody responses following vaccination, delayed-type hypersensitivity responses following skin testing, and clinical responses following experimental infection.
Results: After systematic review and critical appraisal of the literature, six separate studies were available for final discussion. These results indicate that human immunity does vary by season. In the tropical setting of West Africa, both cell mediated and humoral immune responses appear to be reduced in children during the rainy season. In the tropical setting of Bangladesh, cell mediated immune responses also appear to be reduced in children during the rainy season. In the temperate setting of Russia, resistance to influenza infection appears to be reduced in young adults during winter.
Conclusions: Seasonal variation in immunity appears to occur in humans, and it is plausible that this variation may contribute to the seasonality of respiratory infections. Further research

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to assess the extent of seasonal immune modulation is required. We outline a number of recommendations to minimise bias in future studies.

Introduction

The seasonal patterns of infectious diseases have been observed for millennia. Seasonality is observed in almost all infectious diseases, from respiratory infections such as influenza and respiratory syncytial virus,[1,2] to diarrhoeal diseases such as cholera,[3] and vector borne diseases such as malaria.[4] Despite numerous epidemiological studies investigating infectious disease seasonality, the underlying drivers of this seasonality remain unclear for many infections, and for respiratory infections in particular. Proposed environmental drivers of respiratory infection seasonality include seasonal variations in host contact rates, and seasonal variations in the environmental survival of pathogens.[5] Another proposed driver is seasonal variation in host immunity. Seasonal variations in host resistance to infection have been documented in a number of non-human vertebrates,[6] and there are a number of biologically plausible mechanisms that could result in similar seasonal immune modulation in humans. Seasonal variation in sunshine levels may play a role: it has been proposed that seasonal variations in vitamin D levels could drive respiratory infection incidence,[7] and seasonal variations in photoperiod have also been proposed as a driver of seasonal immune modulation.[8] Exposure to environmental immunotoxins may also vary by season: for example aflatoxin levels are often increased in grain and groundnuts stored in non-harvest seasons.[9] Seasonal variations in nutrition also occur in many settings, and the link between malnutrition and reduced host resistance to infection is well established in children.[10] Infectious diseases and host immunity are linked in a cyclic manner: while depressed immunity increases the risk of clinical infection in those exposed to pathogens, infection itself can debilitate the host, resulting in reduced immune defences. Thus some infectious diseases, driven by external seasonal forces such as climate, may seasonally debilitate human hosts and in turn predispose to secondary infection, resulting in seasonality in this secondary infection. A particularly well documented example is that of diarrhoeal illness in children predisposing them to subsequent pneumonia.[11,12] Whether reduced host immunity is caused directly by environmental factors such as reduced sunshine, immunotoxin exposure or malnutrition, or is secondary to other infectious diseases, studies to directly assess whether seasonal immune modulation actually occurs in humans are a clear starting point to assess all of these hypotheses.

A number of studies have assessed immune status in humans during different seasons of the year. The methods used in these studies differ, and can be classified in two ways: studies can be either *in vivo* or *ex vivo* studies, and can be either challenge studies (where the immune response to an antigen challenge is assessed) or basal studies (where the background levels of immune markers are assessed). In this paper we have restricted our review to studies using the following *in vivo* biomarkers of immune function, which all assess responses to an immune challenge: antibody responses to vaccination, delayed type hypersensitivity (DTH) responses to skin test antigens, and clinical responses following experimental infection. These immune biomarkers are considered to have the best combination of clinical relevance, biological sensitivity and practicality.[13,14] We have critically reviewed these studies to assess whether seasonal immune modulation occurs in human populations. We also discuss whether the observed variations in immunity can be plausibly linked to respiratory infection seasonality in the study settings. We conclude by recommending a systematic strategy for future studies.

Materials and methods

We searched Medline (search date 18 April 2014) for studies measuring the above biomarkers during different seasons. A keyword search was performed using the following terms:

AB ("immune response*" OR "vaccine response*" OR immunogen* OR "antibody response*" OR "delayed type hypersensitivity" OR anergy) AND AB (summer OR winter OR spring OR autumn OR "wet season" OR "rainy season" OR "dry season")

A MESH term search was performed using the following terms:

((MH "Immunity, Cellular") OR (MH "Immunity, Humoral") OR (MH "Adaptive Immunity")) AND (MH "Seasons")

Search results were restricted to those published in English. We performed citation searches of the retrieved articles, and also searched articles citing the retrieved articles using Google Scholar.

Results

Studies examining vaccine antibody responses

Vaccination elicits antibody production via humoral immunity. For most vaccines, antigen presenting cells are activated by vaccine antigens, and then present these antigens to 1) B-lymphocytes, which then differentiate into antibody producing plasma cells, and 2) T-lymphocytes, which facilitate this process (unconjugated polysaccharide vaccines elicit a T-lymphocyte independent response, where the polysaccharide antigen directly binds to B-lymphoctes, stimulating their differentiation into antibody producing plasma cells). Thus measuring antibody levels following vaccination provides an *in vivo* measure of an integrated, clinically relevant immune response. We found 17 studies examining antibody responses according to the season of vaccination. These studies are summarised in Table 1, and discussed below.