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.

Table 1 Summary of studies assessing seasonal variation in vaccine responses.

Immune challenge	Setting	Study size	Age at challenge	Season with strongest immune response	Antigen circulating in environment?	Age and sex controlled for or distributed equally?	Challenge-test interval	Equal challenge-test interval in all subjects?
Rabies vaccine[15]	Gambia	472	6 to 9 years	Dry season	No	Yes	14 days	Yes
Rabies vaccine[16]	Pakistan	257	25 to 35 years	Summer	No	Yes	7 days	Yes
HBV vaccine[17]	Netherlands	522	17 to 20 years	None	Minimal	ND	Various	No
HBV vaccine[16]	Gambia	138	0 to 16 weeks[a]	Unclear	Yes	Yes	36 weeks	Yes
HBV vaccine[18]	Austria	1874	6 to 80 years	Unclear	Minimal	ND	4 weeks to 5 years	No
Rubella vaccine[19]	Israel	203	12 months[a]	Winter	Minimal	ND	3 to 4 years	No
Rubella vaccine[17]	Netherlands	718	14 months[a]	None	Minimal	ND	1 to 6 years	No
PPV[15,16]	Gambia	472	6 to 9 years	Unclear	Yes	Yes	4 weeks	Yes
PCV[21]	Gambia	212	6 to 18 weeks[a]	Rainy season	Yes	ND	4 weeks	Yes
Diphtheria/tetanus vaccine[16]	Gambia	138	8 and 12 weeks[a]	None	Yes	Yes	4 weeks	Yes
Typhoid vaccine[16]	Pakistan	257	25 to 35 years	None	Yes	Yes	14 days	Yes
Influenza vaccine[25]	Russia	584	16 to 18 years	Winter	Yes	Yes	20 to 25 days	No
Influenza vaccine[26]	Russia	588	16 to 18 years	Winter	Yes	ND	21 days	Yes
OPV[27]	Israel	121	2 to 6 months[a]	Winter	Yes	ND	2 months	Yes
OPV[28]	India	50	3 to 9 months	Winter	Yes	ND	2 weeks	Yes
OPV[29]	Gambia	679	1 to 5 months[a]	Dry season	Yes	ND	≥4 weeks	No
OPV[29]	Brazil	730	0 to 3 months[a]	None	Yes	ND	4 weeks	Yes

HBV: hepatitis B virus/PPV: pneumococcal polysaccharide vaccine/PCV: pneumococcal conjugate vaccine/OPV: oral polio vaccine/ND: not documented.
[a] Potential for birth cohort effect

Rabies vaccine

Responses to rabies vaccine are a potentially useful biomarker for seasonal analysis because rabies antigen does not circulate widely in the environment. A study in 472 Gambian children aged between 6 and 9 years found a statistically significant seasonal variation in antibody levels following first rabies vaccination, with the strongest antibody responses to rabies vaccine if given in May (late dry season).[15] A study in 257 adults in Pakistan found that antibody levels following rabies vaccination (two doses given seven days apart) showed a statistically significant monthly variation, with highest responses in August, during the peak of summer.[16] However because the study only included the months from April to September, it cannot fully address the question of seasonality.

Hepatitis B virus (HBV) vaccine

A study in 522 young adults in the Netherlands found little variation in antibody levels according to the season of first HBV vaccination (given at 0, 1 and 6 months).[17] A study in 138 infants in The Gambia found the highest responses to HBV vaccine (given at 0, 8 and 16 weeks of age) in infants vaccinated in October and November, however this was not statistically significant.[16] A study in 1874 older children and adults in Austria found significantly higher antibody levels following a course of HBV vaccine (given at 0, 1 and 6—12 months) if the third vaccination was performed in winter compared to summer.[18] Interpretation of this latter finding is difficult due to the multiple doses of vaccine given across different seasons, as well as the variable period between first and third vaccination. In addition, antibody responses were measured between 4 weeks and 5 years after finishing the HBV vaccine course.

Rubella and measles vaccines

A study in 203 children in Israel found that children receiving a single dose of measles, mumps and rubella (MMR) vaccine in the summer had significantly lower rubella antibody levels than children vaccinated in the winter.[19] Children received MMR at age 12 months ($\pm$10 days), and antibody levels were measured when the children were 4—5 years old. Due to high vaccine coverage rates, rubella incidence has been very low in Israel since the late 1990s, suggesting that environmental exposure to rubella antigens is unlikely to have been driving the seasonal variation.[20] A study in 718 children in the Netherlands found no differences in antibody levels against measles or rubella according to season of receiving MMR vaccination.[17] These children received MMR at age 14 months, and antibody levels were measured at 2—7 years of age.

Pneumococcal vaccines

Antibody levels following a single dose of pneumococcal polysaccharide vaccine in 472 children aged 6—9 years in The Gambia showed complex variation according to the month of vaccination, with different seasonal patterns for different serotypes[15,16] As part of a Gambian vaccine trial, antibody responses following three doses of pneumococcal conjugate vaccine (given at 6, 10 and 14 weeks of age) were assessed according to the season of vaccination in 212 children. Children who received all three doses of vaccine in the rainy season had higher antibody levels than those who received doses across both the dry and rainy seasons.[21] Pneumococcal antigens circulate cyclically in the environment,[22] and exposure to pneumococcal antigens is known to interfere with the immunogenicity of pneumococcal vaccines.[23,24] Thus examining the immunogenicity of pneumococcal vaccines according to the season of vaccination is particularly vulnerable to confounding from environmental antigens, which may explain the inconsistent results from these studies.

Diphtheria and tetanus vaccines

A study in 138 infants in The Gambia found little variation in antibody responses to diphtheria or tetanus according to the month of vaccination.[16] Infants were vaccinated with combined diphtheria, tetanus and pertussis vaccine at 8, 12 and 16 weeks of age, and antibody levels were measured at 16 weeks of age.

Typhoid vaccine

A study in 257 adults in Pakistan showed little variation in antibody response according to month of vaccination with typhoid vaccine (As noted above however, this study only included the months from April to September).[16]

Live influenza vaccines

Two studies in the former USSR found the highest antibody responses to live intranasal influenza vaccines occurred in individuals vaccinated in the winter. In the first study 584 males aged 16—18 years were vaccinated either in June or January. Seroconversion (defined as a fourfold or greater increase in antibody levels compared to before vaccination) was assessed 20—25 days after vaccination, and occurred in 38% of those vaccinated in June and 51% of those vaccinated in January.[25] The second study included 588 subjects aged 16—18 years. Those vaccinated in the summer had a lower seroconversion rate (defined as above) 21 days after vaccination compared to those vaccinated in winter (16% in summer, compared to 23% in winter).[26]

Oral polio vaccine (OPV)

A study in 121 infants in Israel found higher seroconversion rates in infants vaccinated with OPV in winter compared to summer.[27] A study in 50 infants in India also found higher seroconversion rates in those infants vaccinated in the winter months.[28] In The Gambia, a study in 679 infants found those infants receiving more OPV vaccinations in the rainy season had a lower seroconversion rate.[29] In contrast to these three studies, a study in 730 infants in Brazil did not find any significant variation in OPV immunogenicity according to the season of vaccination.[29] A major driver of the observed seasonal variations in OPV antibody responses appears to be the seasonal variation in the prevalence of non-polio enteroviruses: infants vaccinated when non-polio enterovirus circulation was at its peak had poorer antibody responses to OPV.[27,28,29,30] This strong environmental determinant of OPV immunogenicity reduces the usefulness of OPV for assessing seasonal immune modulation.

Studies examining DTH responses

DTH testing involves the intradermal injection of one or more antigens. If the antigen has been encountered

previously by the individual, this will elicit a cell mediated immune response: antigen presenting cells are activated by the intradermal antigens, and then present these antigens to memory T-cells, which in turn release cytokines resulting in an infiltration of various inflammatory cells. Thus DTH testing provides an *in vivo* measure of an integrated, clinically relevant immune response. The width of the skin induration due to the inflammatory response is measured 48 h after injection of the antigen. Induration less than a specific cut off (usually 2 mm) is indicative of anergy to that antigen. We found 5 studies examining DTH responses according to the season of testing. These studies are summarised in Table 2, and discussed below.

Several studies have examined DTH responses to the seven skin test antigens included in the multitest kit (proteus, trichophyton, candida, tetanus, diphtheria, streptococcus, and tuberculin). In The Gambia, 472 children aged between 6 and 9 years underwent DTH skin testing with these seven antigens, with a single administration of the multitest at different times of the year in different children. Consistent with the results from the rabies vaccination study in this same population, the average number of positive responses to the seven antigens was highest in April/May (late dry season).[15] A study in southern Bangladesh followed a cohort of 705 children aged between zero and five years over the course of a year, administering the seven multitest antigens at three month intervals. A potential weakness of this study was the use of repeated DTH testing in the same children, because repeated DTH testing may lead to boosting of the later responses. This may not have biased the results substantially however, as a larger proportion of children were anergic to all seven antigens upon testing during the rainy season (August, the second DTH test) compared to during the hot dry season (May, the first DTH test) despite any boosting that may have resulted from the first DTH test: Anergy to all seven antigens occurred in 20.6% of children tested in the rainy season compared to 11.8% tested in the hot, dry season (RR 1.74 [95%CI 1.07 to 2.90]).[31] In a study in northwest Kenya, 57 children aged between 6 months and 10 years were tested with five of the seven multitest antigens (the tetanus and diphtheria antigens were removed). The children were tested first during the rainy season, and again during the dry season, and showed little seasonal variation in DTH responses to the five antigens: 58% of children showed anergy to all five antigens during the rainy season, compared to 53% in the dry season.[32] It is possible that boosting due to the repeat testing in this study may have obscured any difference between seasons. A study in Guinea-Bissau administered the seven multitest antigens to 884 children at seven to nine months of age. Children were tested once between October 1996 and September 1997. The study only reported results for 3 antigens, finding that during the rainy season, anergy to tuberculin on DTH skin testing was more common (OR 1.76 [95%CI 1.33 to 2.33]) as was anergy to diptheria and tetanus antigens (OR 1.31 [95%CI 0.99 to 1.72]).[33] In another study from Guinea-Bissau, anergy to all seven multitest antigens upon DTH testing in children aged 3—13 years was more common if the children were tested in the rainy season compared to the dry season (OR 4.8 [95%CI 2.2 to 10.3]) however the study only examined 5 months of the year, and only one of these months (May) was during the dry season.[34]

Table 2 Summary of studies assessing seasonal variation in DTH responses.

Immune challenge	Setting	Study size	Age at challenge	Season with strongest immune response	Antigen circulating in environment?	Age and sex controlled for or distributed equally?	Potential for birth cohort effect?	Equal challenge-test interval in all subjects?
Multitest DTH[15]	Gambia	472	6 to 9 years	Dry season	Yes[a]	Yes	No	Yes
Multitest DTH[31]	Bangladesh	705	0 to 5 years	Dry season	Yes[a]	No	No	Yes
Multitest DTH[32]	Kenya	57	0 to 10 years	None	Yes[a]	No	No	Yes
Multitest DTH[33]	Guinea-Bissau	884	7 to 9 months	Dry season	Yes[a]	Yes	Yes	Yes
Multitest DTH[34]	Guinea-Bissau	391	3 to 13 years	Dry season	Yes[a]	Yes	No	Yes

a However multiple antigens were tested.

Experimental infection: clinical outcomes following the administration of live vaccines

Experimental infection provides the most clinically relevant assessment of immune defences against infection. Innate, cellular, and humoral immune responses will all be elicited to varying degrees to reduce the intensity of infection. Measured outcomes may be symptomatology of infection, or microbiological outcomes such as ongoing pathogen isolation. We found two studies examining clinical responses according to the season of experimental infection. These studies are summarised in Table 3, and discussed below.

As discussed above, two studies in the former USSR examined human challenge with live influenza vaccine in non-immune volunteers. The first of these reported a higher risk of fever in 360 individuals vaccinated during the winter compared to 197 vaccinated in summer.[25] Although influenza and other viruses causing febrile illness are more common in the winter in the study setting, it appears the increased risk of fever in those individuals vaccinated in the winter was a direct result of the influenza vaccination, as the placebo group did not show any signs of fever during the winter vaccine challenge. The other study from the former USSR reported similar results, with a significantly higher risk of fever following influenza vaccination in the winter compared to in the summer, and a significantly higher amount of nasal secretion of vaccine virus two and three days following vaccination in winter compared to summer.[26] Taken together these studies suggest that in winter, vaccinated individuals are more likely to become infected with the vaccine viruses, with subsequent viral replication and fever.

Discussion

Sources of bias in the retrieved studies

During our critical appraisal of the studies retrieved by our literature search, we identified a number of sources of bias specific to studies comparing immune status at different time of the year. These sources of bias are discussed below, and in Tables 1—3 we also indicate which studies are at risk of these biases.

Circulating antigens
If a test antigen circulates seasonally in the environment (as is the case for many antigens including pneumococcal, enteroviral and tuberculin antigens) any seasonal variation observed in immune responses following challenge with these antigens may be due to variations in the level of circulating antigen rather than variations in immune competence.[23,35] For this reason, when assessing seasonal immune modulation using vaccines it is advisable to use responses to vaccine antigens that are not circulating in the environment. Because DTH testing examines the immune response to previously encountered antigens, environmental antigens are required as the test antigens. Thus to minimise confounding when using DTH testing it is advisable to use a combination of antigens with different seasonal patterns of circulation, such as when assessing the proportion of children with anergy to all seven of the antigens in the DTH multitest. Anergy to all seven multitest antigens is a more reliable measure of reduced immune competence than a negative result to a single antigen.[15]

Age and sex
Immune responses vary with age, and age specific responses to immune challenge (whether the challenge is vaccine, DTH test, or infection) are well documented in many studies.[15,16,36] For DTH testing there is an additional complication: as previous exposure to the test antigen is required for a positive DTH reaction, this means negative DTH reactions are more common in younger children, who have had less chance for previous exposure.[31] These factors clearly implicate age as a potential confounder in any study assessing seasonal immune modulation. A second factor that needs to be considered is the potential for confounding by birth cohort effects. If all children are the same age at antigen challenge (particularly if they are infants) then disentangling the effect of the season of birth from the effect of the season of antigen challenge will be difficult. For example if all children are six months old at antigen challenge, and those children challenged in March have reduced responses, is would be difficult to assess whether this was due to an environmental insult in March, or sometime during their gestation (January to September the previous year). Examples of birth cohort effects would include seasonal variations in maternal antibody levels,[29,37,38] which can affect responses to antigen challenge in infants,[39,40] as well as maternal exposures during gestation, which could potentially result in altered responses to a wide variety of antigens in children according to season of birth.[41] In order to properly control for both age and birth cohort effects in multivariate analysis, the antigen challenge should be administered to children of different ages (to avoid birth cohort effects) and the analysis of seasonal variation in immune response should be adjusted for any age difference between the comparison groups. Responses to immune challenge also often vary according to sex, and this should also be controlled for in multivariate analysis.

Table 3 Summary of studies assessing seasonal variation in clinical responses to experimental infection.

Immune challenge	Setting	Study size	Age at challenge	Season with least clinical infections	Antigen circulating in environment?	Age and sex controlled for or distributed equally?	Potential for birth cohort effect?	Equal challenge-test interval in all subjects?
Influenza infection[25]	Russia	557	16 to 18 years	Summer	Yes[a]	Yes	No	Yes
Influenza infection[26]	Russia	471	16 to 18 years	Summer	Yes	ND	No	Yes

[a] However study was placebo controlled.

Follow-up time following challenge

The strength of an immune response also varies with time following challenge. For DTH testing, skin tests are routinely read 48 h after challenge. For vaccinations the follow-up time is less consistent. Follow-up times must be equal following challenges in different seasons to avoid confounding, and it would be prudent to test antibody responses within one to two months following vaccination (some of the reviewed studies measured antibody levels several years following vaccination, allowing the potential for other environmental factors to influence the immune response in the interim). Follow-up times should also be equal for studies using experimental infection, as symptoms will vary with time following infection, according to the incubation period.

Repeated immune challenges

Repeat immune challenges with the same antigen may lead to boosting of later responses. For DTH testing the available evidence suggests such boosting is probably maximal if DTH tests are repeated within two months, however some boosting may occur if DTH tests are repeated up to a year later.[42–45] The boosting effect of repeated vaccination is well known. The simplest way to avoid bias due to boosting is to assess immune responses to antigen challenge in different subjects at different times of the year.

Antigen storage

The immunogenicity of antigens depends on adequate storage, in particular the maintenance of the cold chain during transport and storage. In many settings maintaining the cold chain may be more difficult at different times of the year. High temperatures in summer, and difficulties in transport during the rainy season, are two seasonal factors that may be detrimental to proper vaccine storage. Most of the reviewed papers have documented the efforts taken to maintain the cold chain during the studies. No papers reported any observed problems with cold chain maintenance.

Possible drivers of seasonal immune modulation

Table 4 lists the studies least likely to be affected by the sources of bias discussed above, and include studies using rabies vaccine (1 study), multitest DTH responses (3 studies), and experimental infection (2 studies). Possible drivers of the observed seasonal variation in immunity in these six studies are discussed below.

In The Gambia, immune responses in children following both rabies vaccine and DTH multitest were strongest late in the dry season (April/May). Similarly, in nearby Guinea-Bissau, anergy to the DTH multitest in children was less common in May than during the rainy season. In this part of West Africa the rainy season is often a time of poor nutrition known as the hungry season,[46,47] and this malnutrition is exacerbated by an increased incidence of diarrhoeal illness during the rainy season.[4,48] A number of studies have demonstrated a direct link between poor nutritional status, reduced cell mediated immune responses, and an increased risk of infection in children.[31,49–51] In contrast, vaccine responses appear less affected by malnutrition.[52] Malaria infection is also at its peak during the rainy season, driven by increased mosquito numbers. Malaria infection appears to affect host immunity: malaria parasitaemia reduces the antibody response to some vaccines and malaria parasitaemia also appears to affect DTH responses to some antigens.[53–55] In The Gambian study, children with malaria parasitaemia had reduced responses to the rabies vaccine, but parasitaemia did not affect DTH testing. Whatever the cause of the apparent

Table 4 Summary of studies included in final discussion.

Setting	Challenge	Study size	Age at challenge	Comparison	Results
Gambia[15]	Rabies vaccine	472	6 to 9 years	Months from April to February	The strongest antibody response was in children vaccinated in May (end of dry season)
Gambia[15]	Multitest DTH	472	6 to 9 years	Months from April to February	The number of positive responses (out of seven antigens) was highest in April and May (end of dry season)
Bangladesh[31]	Multitest DTH	705	0 to 5 years	May v August	Anergy to all seven antigens was more common in August (mid rainy season) than May (end of dry season)
Guinea-Bissau[34]	Multitest DTH	391	3 to 13 years	Months from May to September	Anergy to all seven antigens was least common in May (end of dry season)
Russia[25]	Influenza infection	557	16 to 18 years	June v January	Higher risk of fever in those infected during January (winter) compared to those infected in June (summer)
Russia[26]	Influenza infection	471	16 to 18 years	June v February	Higher risk of fever, and increased nasal secretion of virus, in those infected during February (winter) compared to those infected in June (summer)

reduction in both cell mediated and humoral immunity during the rainy season in this setting, it appears plausible that this seasonal reduction in immunity may drive further infections. Respiratory infections in children are generally at their peak late in the rainy season in The Gambia.[56] The timing of this peak is consistent with respiratory infection seasonality being at least partly driven by the observed seasonal reduction in cellular and/or humoral immunity.

In Bangladesh, anergy to all seven DTH multitest antigens was more common upon testing in the rainy season compared to the hot dry season. As with the West African examples, in Bangladesh the rainy season is often a time of poor nutrition, with reduced household food security and decreased maternal and child growth.[57,58] Malaria is not endemic in the district the DTH study was performed in. It is plausible that the observed seasonal reduction in cellular immunity may play a role in driving the seasonality of respiratory infections in this setting. Respiratory infections in children generally occur at two times of the year in Bangladesh: during the winter, and late in the rainy season.[59,60] The timing of the second peak is consistent with respiratory infection incidence being at least partly driven by the observed seasonal reduction in cell mediated immunity.

In young adults in the temperate climate of the former USSR, fever and viral secretion were less frequent following nasal inoculation with live influenza vaccine in the summer. Possible underlying causes for seasonal immune modulation in temperate winters are reduced nutrition and reduced vitamin D levels. It is possible that micronutrient intake may fluctuate with season due to the availability of seasonal produce: this appears to be the case in Russia, where micronutrient deficiencies are generally more severe in winter and spring.[61] Vitamin D levels are consistently lower during the winter and spring months in temperate settings, and vitamin D deficiency appears to increase the risk of respiratory infection in children.[62–64] The most specific effect of vitamin D deficiency on immunity is a reduction in the antimicrobial peptide cathelicidin, part of the innate immune system, and expressed in leukocytes and bronchial epithelial cells.[65,66] In this temperate setting, respiratory infections are most common in late winter/early spring.[67,68] While improved viral survival due to the low winter temperatures in temperate settings is one plausible driver of this seasonal variation in respiratory infections, reduced immune competence during the winter may also play a role in driving the observed seasonality of respiratory infections.

Conclusions

The studies reviewed here suggest seasonal immune modulation occurs in humans, and that seasonal immune modulation in humans is a plausible driver of the observed seasonal patterns of respiratory infections in the reviewed settings. Other driving factors undoubtedly are also influencing transmission and seasonality of infectious diseases: variations in climate are likely to affect pathogen survival in the environment, while host mixing behaviour is also likely to vary throughout the year. Further research is required to assess the relative importance of these different driving mechanisms. The dominant factors driving infectious disease seasonality are likely to vary according to the infection, and according to the setting.

It remains to be seen whether or not the observed seasonal patterns of immune modulation may be amenable to intervention. For example, immune modulation resulting from seasonal variation in day length may prove difficult to address, while immune modulation due to malnutrition or vitamin D deficiency is more amenable to intervention. Improved understanding of the mechanisms underlying the seasonality of immune modulation may enable more effective use of interventions. The fact that seasonal immune modulation is apparent at the population level suggests that interventions for population groups at risk of reduced immune competence may have "herd" level benefits as well as individual level benefits.

Our review has also demonstrated the lack of studies examining seasonal changes in clinical measures of human immunity. We have focused our review on studies examining three clinical measures of immune status (vaccine immunogenicity, DTH responses, and infectious challenge) because of the high relevance of these measures to clinical outcomes. This strategy has reduced the number of studies available for our review, and our critical appraisal of the retrieved articles has further reduced the number of articles available for interpretation. More research is required to better understand the dynamics of host immune modulation. To this end we have made several recommendations for reducing bias in future studies using the clinical measures reviewed in this article (Box 1).

Box 1. Recommendations for reducing bias when assessing seasonal immune modulation

- To assess consistency from year to year, ideally studies should continue for several years.
- To better assess causality, regular measurements of immune status (ideally monthly) are preferable.
- For vaccines, use antigens that do not circulate in the environment.
- For DTH testing, assess anergy to a number of test antigens administered at the same time.
- To avoid confounding, maintain similar age and sex distributions of children in the comparison groups (or control for any differences in analysis).
- Administer the antigen challenge to children over a range of ages in order to control for birth cohort effects.
- For vaccines, testing the antibody response after a single dose will give clearer results.
- Avoid repeated challenges in the same subjects as this can cause boosting of responses.
- The delay between the immune challenge and measurement of the immune response should be the same in the comparison groups (and it would be prudent to test antibody levels within two months of vaccination).
- Ensure cold chain maintenance is the same during different seasons.

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