Common Cold
ed. by R. Eccles and O. Weber

Etiology of the common cold: Modulating factors

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Abstract

The development of a "cold-like illness" (CLI) usually requires infection with an upper respiratory virus such as rhinovirus, influenza virus, respiratory syncytial virus, parainfluenza virus, coronavirus or adenovirus, among others, and the development of sufficient signs, symptoms and pathophysiologies to qualify as being ill based on personal and cultural definitions. A viral upper respiratory tract infection (vURTI) in the absence of overt illness (subclinical vURTI) will not be made manifest to the individual or to observers and, therefore, will not be diagnosed as a CLI. The degree of illness occurring during a vURTI is directly related to the extent of provoked inflammation, which in turn depends on the engagement of antiviral defense systems. Thus, risk factors for CLI can modulate either the vURTI risk by affecting virus exposure and/or susceptibility to infection, or the CLI risk given a vURTI by affecting immunocompetence, the provoked inflammation and/or the interpretation of illness as a CLI. In this chapter, we review published studies for evidence of CLI risk-modulating factors and report that climate, crowding and perhaps female gender can affect the probability of exposure to vURTI viruses, that extant immunological factors and age can affect the probability of virus infection given exposure, that stress levels (moderated by social environment), health practices (exercise, tobacco and alcohol consumption, sleep efficiency) and genetics contribute to CLI risk most probably by modulating the immune-inflammatory response to infection, and that other factors such as pollution, home environment and certain personality traits affect CLI risk by biasing illness interpretation for a given set of symptoms and signs.

Introduction

This chapter reviews those factors that are suspected or proven to influence an individual's susceptibility to the 'common cold'. Because the common cold is an illness attributable to a viral upper respiratory infection (vURTI), we need to consider factors that moderate an individual's risk for infection with a common cold virus as well as those that moderate illness expression in infected individuals. Before reviewing the results of specific studies that address these issues, it is necessary to present a general background for

purposes of establishing definitions and introducing certain concepts that lay the foundation for that discussion.

Definition of the 'common cold'

The first reported use of 'a cold' as an illness descriptor was in 1537 and reflected the noted similarities between the symptoms and signs of the 'disease condition' and the physiological responses to cold temperature exposure [1]. Indeed, a belief that cold air exposure caused the common cold was widespread during the time of Benjamin Franklin (1706–1790), who countered that developing the illness depended on contact with ill persons [2]. Much later it was shown that most illnesses recognized as a common cold were caused by viruses that infect the upper respiratory tract [3]. Recent definitions for the common cold note its infectious etiology, but still focus on a listing of the signs and symptoms characteristic of the illness. For example, the Merriam-Webster Medical dictionary defines the common cold as: "an acute contagious disease of the upper respiratory tract that is marked by inflammation of the mucous membranes of the nose, throat, eyes and Eustachian tubes with a watery then purulent discharge and is caused by any of several viruses" [4]. Thus, in discussing the common cold, we are referring to a culturally accepted constellation of upper respiratory symptoms (if perceptible only by the affected person) and signs (if perceptible by both affected persons and observers) [5] that signals the presence of a vURTI caused by rhinovirus (RV), respiratory syncytial virus (RSV), adenovirus, influenza virus, parainfluenza virus, coronavirus and metapneumovirus, among others [6–10]. While usually self-limiting and of short duration, vURTIs can be associated with a variety of complications [8, 11, 12] that include otitis media [10, 13, 14], sinusitis [15], bronchiolitis [11], asthma exacerbations [16, 17] and pneumonia [18]. Because the use of 'common cold' as an illness descriptor often carries the implicit connotation of RV infection, here we use the more inclusive term, cold-like illness (CLI) in referring to upper respiratory illness during a vURTI.

Definition of the viral symptom/sign complex

The viral symptom/sign complex (vSSC) is a summary measure of illness during a suspected vURTI and can be defined by the magnitudes and durations for a set of commonly expressed symptom and/or sign elements [19]. Most simply, the vSSC is measured as the area under the curve (AUC) relating the sum of vSSC element magnitudes to time for a specified period. In research, a commonly used vSSC element set is that originally defined by Jackson to include sneezing, runny nose, nasal congestion, sore-throat, cough, malaise, chills and headache [20, 21]. In other vSSC constructions,

these elements are supplemented with additional symptoms/signs of an uncomplicated vURTI (e.g., confusion, insomnia, anorexia, fever, muscle ache and joint pain, among others) and/or the symptoms/signs associated with vURTI complications such as earache (otitis media), sinus pain/fullness (sinusitis), wheezing (bronchiolitis, asthma exacerbation) and chest congestion/difficulty breathing (pneumonia) [22]. While the viruses that cause vURTIs are diverse, the vSSC for all viruses is similar with few consistently expressed elements that would allow for assignment of an illness episode to a particular virus or group of viruses in the absence of additional information such as seasonality [5, 23–25].

CLI, vSSC and vURTI relationships

The vSSC is not equivalent to a CLI, but rather the vSSC is used by an assessor to define the presence of a CLI based on past experiences and cultural context. The symptom vSSC is used by affected individuals in making judgments as to whether or not they have a CLI, while the sign vSSC is used by others to mark an individual as 'ill' for possible contact avoidance [26]. Thus, persons assign themselves (and others) as to whether or not they 'have' a CLI based on selected aspects of vSSC and not on the presence/absence of vURTI. Importantly, a vSSC and the derived CLI assignment are not prerequisite expressions of a vURTI [27–31]. For example, experimental exposure of susceptible adults to usual vURTI viruses (influenza A virus, RV, RSV) causes a CLI in only about 60% of those with documented infection [32–34] and nasal/nasopharyngeal detection of vURTI viruses in children is associated with a parent-identified CLI for the child in only about 60–85% of the detections [35]. Moreover, the frequencies of vURTI complications are only partially conditioned by the vSSC or presence of a CLI [10, 14, 36]. These relationships are illustrated in the Venn diagram presented as Figure 1 where the CLI set is a subset of the vSSC set, which, in turn, is a subset of the vURTI set, but the intersection of the complication set with that for either the vSSC or CLI is not unity.

CLI assignments

Figure 2a shows an idealized vSSC (sum of element magnitudes *versus* time) for a vURTI. There, the onset of increased vSSC magnitude occurs at a variable time after virus infection and the vSSC magnitude shows a curvilinear increase to a plateau and then a decrease to baseline [19]. This type of curve embeds a number of signals that can be abstracted by an individual for purposes of assigning the presence of a CLI. These include, the AUC, the rate of change in vSSC magnitude between days or over a period of days after illness onset (slope of the vSSC rise), the maximum vSSC magnitude and the time

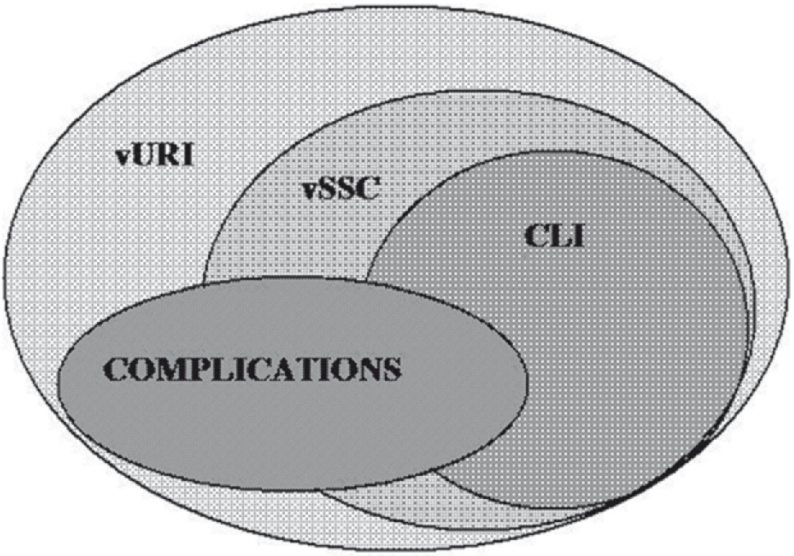

Figure 1. Modified Venn diagram depicting the nested relationships among a vURTI, the vSSC, a CLI and complications.

during which the vSSC magnitude exceeds a certain value (width of the time-window bounding the vSSC at a specified vSSC magnitude). Studies of CLI assignments made by adult subjects with experimental vURTIs and by parents for their children with natural vURTIs show that different persons may use different signals to make their CLI assignments [19, 22] and document a relative weighting of the vSSC elements (e.g., greater weight for rhinorrhea and nasal congestion when compared to other elements) used in vSSC construction that is not uniform across the population. For these reasons, there is not a 1:1 correspondence between an objectively measured vSSC and an individual's subjectively constructed vSSC or between either type of vSSC and an individual's CLI assignment. This is made explicit in the Jackson definition of a clinical 'cold', which requires either an individual's assignment of a CLI and the concurrent presence of specific symptom vSSC elements or a symptom vSSC that conforms to certain criteria [20, 21]. Recognizing that perceived symptoms need not scale linearly with objectively measured signs [37–39], some investigators differentiate subjective and objective CLIs (clinical colds). For example, Cohen and colleagues defined a subjective CLI using the Jackson criteria as modified by Gwaltney and colleagues [40] and an objective CLI using measurable vSSC sign elements [41].

Figure 2b shows a more realistic vSSC that includes a discrepancy between the subjective (dashed curve) and objective vSSCs (solid curve), a pre-exposure, basal SSC (bSSC) and two (T1 and T2) subjective vSSC magnitude thresholds for assigning a CLI. From this vSSC representation, it

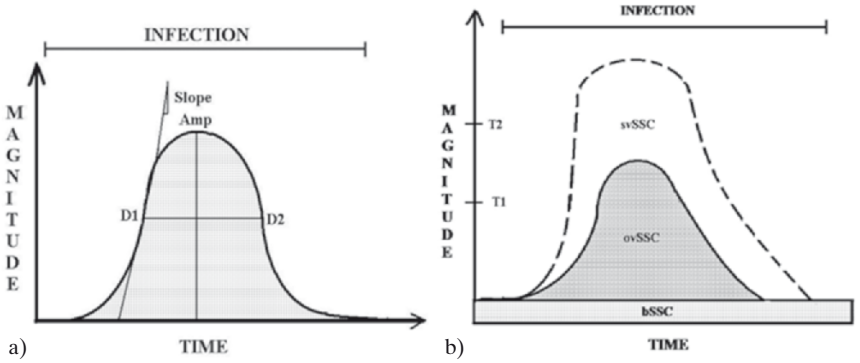

Figure 2. (a) Simple depiction of a vSSC represented by the function relating the sum of symptom or sign element magnitudes to time. Signals for extracting the presence or absence of a CLI include the slope of the vSSC rise (Slope), the maximum vSSC magnitude (Amp), the width of the time-window bounding the vSSC at a specified vSSC magnitude (D2-D1) and the AUC (shaded area). (b) A more realistic vSSC that includes a discrepancy between the subjective (svSSC, dashed curve) and objective vSSCs (ovSSC, solid curve), a pre-exposure, basal SSC (bSSC) and two (T1 and T2) subjective vSSC magnitude thresholds for assigning a CLI.

is clear that CLI assignment can be affected by the chosen threshold criterion (either T1 or T2), by the subjective vSSC bias (difference between the subjective and objective vSSC) and by the magnitude of the bSSC. Also, the objective vSSC can be modified by changes in the inflammatory reactivity of the upper respiratory tract as measured by the magnitude of provoked inflammation for a given stimulus intensity. For example, reactivity can be dramatically increased by pre-exposure to certain inflammatory stimuli (e.g., allergy, pollutants, cold air), a phenomenon termed 'priming' [42]. Priming by a non-vURTI stimulus would be manifest as an increased objective vSSC and a higher probability of CLI assignment during a vURTI. Alternatively, a vURTI can 'prime' the upper respiratory tract to other inflammatory stimuli such as cold air [43], which would increase the objective vSSC and possibly transform a subclinical vURTI into a CLI. These effects may partly explain modulation of CLI risk by certain personality traits (e.g., positive subjective vSSC bias attributable to neuroticism [38]), adverse environments (e.g., increased bSSC attributable to air pollution [44]), allergy (e.g., priming of the vSSC by household mold [45]), cold weather (e.g., priming of the inflammatory response to cold air by a vURTI [43]) and by other factors described in the Results section.

Interpretive model

Numerous studies document that the immune-inflammatory responses of the upper respiratory tract to a noxious stimulus are orchestrated and con-

trolled by the synthesis of potent signaling chemicals, including the cytokines, and by the synthesis and/or release of effector chemicals, including the more traditional inflammatory mediators such as histamine, bradykinin and arachidonic acid metabolites [46]. The interactions of these signaling chemicals are complex, self-amplifying and feedback modulated, and allow for detecting the nature of the threat (e.g., pollutant, allergen, virus exposure), adaptively tailoring the evolution of a threat-appropriate immune-inflammatory host response to eliminate the source of the threat, and down-regulating those responses once the threat has been eliminated.

Figure 3 presents a simple interpretive model for understanding signal processing from initial virus exposure through the development of symptoms, signs and complications during the course of a vURTI and for defining the various nodes at which modulating factors can act. Briefly, virus exposure is processed by a set of biological filters that may or may not prevent infection and/or limit viral replication and viral spread to adjacent cells. These filters are tuned by environmental factors (e.g., air pollution, cigarette smoke exposure), genetic factors (e.g., HLA haplotypes), the functionality of existing physical barriers to infection (e.g., mucociliary clearance system) and the immune status of the host (e.g., extant presence of non-specific antiviral chemicals, homotypic sIgA antiviral antibody titers). If infection is established, viral sensors detect the event and trigger the activation and/or up-regulation of the innate immune system and of both the humoral and cellular components of the adaptive immune systems. In turn, these systems up-regulate the activities of the biological filters with the teleological goals of progressively decreasing viral load, limiting viral spread to adjacent anatomical compartments, eliminating infected cells, preventing secondary bacterial infections, establishing immune memory to prevent re-infection with the same virus and healing the damaged mucosa [26]. Failure to achieve threat-appropriate responses or to adequately coordinate the up- and down-regulation of these responses can lead to the development of an exaggerated inflammatory response as well as to vURTI complications.

Activation of these signaling pathways generates an inflammatory response that is expressed as the symptom and sign elements of the vSSC [5]. Because that inflammatory response provides feedback modulation to the biological filters, many of the vSSC elements can be considered to be protective. For example, nasal congestion can prevent further inhalation of aerosolized virus, rhinorrhea can provide a vehicle for the delivery of specific and nonspecific antiviral chemicals and effector cells to the infected mucosa, sneezing and cough can forcibly expel virus laden secretions from the upper and lower respiratory tracts, respectively, fever can create an inhospitable environment for viral replication and anorexia may modulate T-helper (Th1/Th2) balance [26, 47–49]. However, pharmacological interventions that moderate selected aspects of the inflammatory response are not associated with either delayed viral clearance or delayed CLI resolution

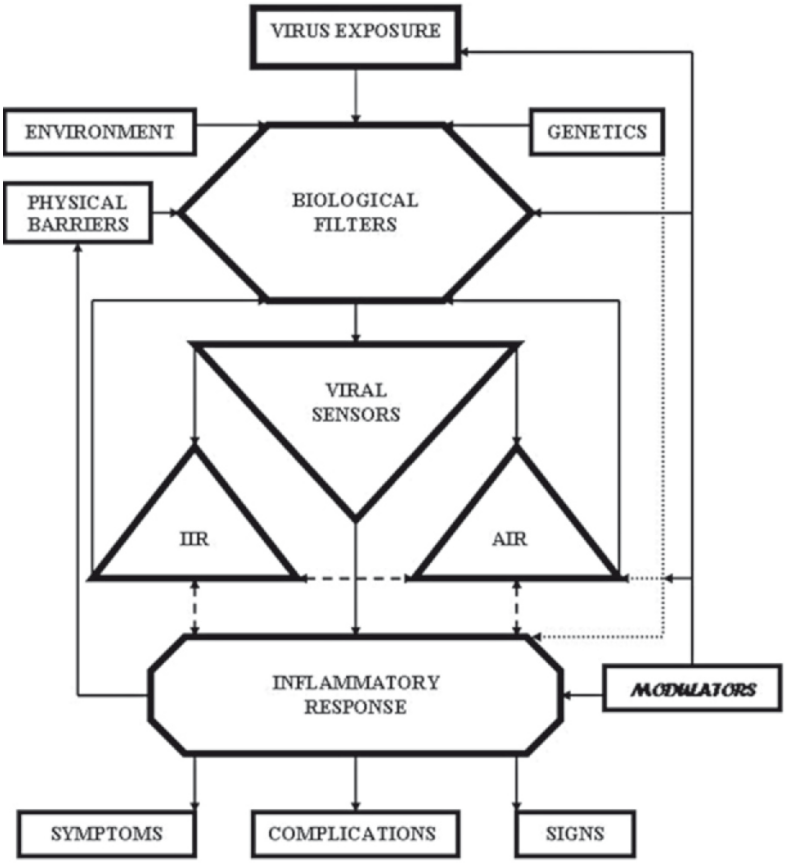

Figure 3. A simple interpretive model illustrating the pathways for signal processing from initial virus exposure through the development of symptoms, signs and complications during the course of a vURTI and for defining the various nodes at which modulating factors act (AIR, adaptive immune response; IIR, innate immune response).

[50–52] and vURTI resolution is not delayed in persons who fail to develop a vSSC or a CLI [32, 53]. Thus, much of the inflammatory response represented as the vSSC may be peripheral to host defense and modifiable by CLI risk factors independent of an effect on immunocompetence.

Modulators that affect CLI risk can act on a variety of nodes in these pathways, e.g., by reducing/enhancing the risk of virus exposure, modifying the initial state of the biological filters, modifying the innate and/or adaptive immune responses and controlling the inflammatory response as reflected in the objective vSSC. Also, as discussed above, these modulators could affect the interpretation of the objective vSSC as a subjective vSSC and as a CLI.

Caveats to results interpretation

The studies reviewed here for evidence of CLI risk-modulating factors used a variety of formats including retrospective cohort studies, prospective natural history studies and experimental virus exposures in otherwise healthy adults. None of these designs is optimal for identifying risk-modulating factors and the presented results need to be interpreted in perspective. This is especially true when considering whether an identified modulating factor exerts its influence on CLI risk by affecting the underlying vURTI risk or by affecting the vSSC (i.e., CLI risk) given a vURTI. In most studies, the enumerated event was a subjective CLI as ascertained from pre-existing data by recall for a past time interval or by identification during a prospective period of follow-up. Obviously, accuracy of the CLI risk estimate is less for recall data when compared to concurrent assessments in a prospective design, but in both cases, CLI risk may or may not reflect the underlying vURTI risk since the frequency of CLIs given a vURTI may be modified by the modulating factor. In some studies, the enumerated event was a vURTI (by culture, seroconversion, antigen detection or PCR) given the co-existence of a signaling event such as a predefined vSSC, a CLI or a complication. The accuracy of vURTI risk estimates for these studies varies within and across viruses as a function of assay sensitivity. Moreover, because the frequency of vURTIs in the absence of the signaling event is not known, this format cannot distinguish between an effect of a modulating factor on the risk of a signaling event and an effect on the vURTI risk. In a few studies, the enumerated event was a vURTI as assessed by repeated assays at specified time intervals. As noted, the accuracy of vURTI risk estimates depends on the assay method used and documenting an event by seroconversion alone is troublesome since modulating factors may affect the rate of seroconversion given a vURTI. Nonetheless, this study format provides reasonable estimates of vURTI risk for evaluating the effects of potential modulating factors. A number of the reviewed studies used experimental virus challenge (exposure) in adult humans to evaluate the effect of modulating factors on CLI and vURTI risk. That format provides good control over subject susceptibility to the challenge virus, virus exposure dose and potential confounding factors, accurate pre-exposure assessments of the risk factor(s) under study, and the capability for accurate assessments of the provoked subjective and objective vSSC, CLIs and vURTIs. However, in many of the reviewed studies, a relatively high frequency of virus infection in the challenged population was documented. Thus, for this format, it is often difficult to evaluate the effect of modulating factors on vURTI risk and most, but not all, studies report the effect of those factors on CLI risk given a vURTI. In the presented review, an attempt is made to distinguish between the effects of a modulating factor on CLI and vURTI risks by using CLI risk to indicate the relative incidence of CLIs without attempted confirmation of viral infection, CLIv risk to indicate the relative incidence of CLIs with

confirmed viral infection, and vURTI risk to indicate the relative incidence of confirmed viral infections with/without CLIs and/or complications.

Results

In this section, evidence supporting the effects of different modulators on the vSSC and on the CLI and vURTI risks in humans is reviewed. The section is organized under general headings of Environmental and Host factors and, within each, nested listings of factors with evidence supporting CLI risk modulation. This organization follows a simple logical outline but is somewhat arbitrary in that the position of a given modulator could be reasonably reassigned to a different category. Also, the presented list of modulators should be considered to be representative and not necessarily exhaustive.

Environmental modulators

Climate

Early research documented a pronounced CLI seasonality for temperate climates with the incidence of illness in a community being relatively low in the warmer, summer months and high in the colder months [54]. After the introduction of assays for specific viruses, this effect was shown to mirror seasonal patterns in vURTIs caused by RV, influenza virus, RSV and parainfluenza virus, among other viruses [27, 55–59]. For example, while rvURTIs were detected year round, but with a major peak in the fall and a minor peak in the spring, vURTIs caused by each of the other viruses showed a more discrete fall-winter, winter, or winter-spring peak and more restricted temporal activity [60, 61]. Slight shifts in the months of peak rvURTI incidence were noted for different geographical areas and the seasonality of all vURTI viruses worldwide was shown to be different for temperate, cold or rainy climates [61–64].

Recent developments including PCR for virus detection and determination of phylogenetic relationships among virus strains [65], advanced computer modeling of viral spread [66, 67] and the establishment of multisite consortiums covering a wide range of climates [68] have led to a better, although still incomplete, understanding of the role played by climate in determining vURTI and CLI risks. Current models of climate effects on CLI and vURTI incidence involve a complex, virus-specific interplay among meteorological variables [68–71], physiochemical properties of the virus [72–74], virus reservoir [75–77], mechanism of virus transmission [67], spatial density of the population [78], distribution of 'susceptibility' to infection in the population [66, 67] and human behavior [65]. Nonetheless, for a given virus such as RSV [68] or influenza [69], meteorological variables including temperature, relative humidity, barometric pressure and ultraviolet radiation can explain as much as 40% of the variance in vURTI risk and

this appears to be closely related to the physical conditions favoring virus survival [72–74].

Crowding

Crowding, a measure of population density at the community (e.g., persons per square mile), housing (e.g., people per room) and congregational (e.g., preschool, school) levels, can increase CLI incidence by increasing virus-exposure rates. Cross-sectional studies of populations living in crowded communities support this effect. For example, Bang and colleagues [79] compared CLI incidence among three low income communities in West Bengal and reported the highest incidence for a 'crowded' urban community, an intermediate incidence for a suburban village and the least incidence in an isolated village. While other CLI risk factors were reported to be similar for the three settings, in general, these types of studies are characterized by problems with CLI documentation and with control over confounding factors [e.g., socioeconomic status (SES), air pollution, malnutrition]. However, crowding was also demonstrated to increase vURTI risk in family studies where vURTI incidence within the family was directly proportional to the number of children sharing a bedroom [80] and CLI spread from child to mother was common [81]. Day care or preschool, school, shared work areas, community homes and hospitals can be considered to be environments characterized by crowding. Day care is consistently identified as a CLI risk factor [11, 82–85], opening of the school year is coincident with the peak in rvURTI incidence [61], sharing an office with one or more colleagues was reported to significantly increase CLI risk [86] and nosocomial vURTIs are common in the hospital and nursing home environments [87–89].

Pollution

Air pollution is associated with generalized upper and lower respiratory symptoms and signs [44, 90, 91], and has been identified as a possible CLI risk factor in a number of studies. For example, a study conducted in northern Finland compared the CLI incidence rates measured in children over a 1-year period among three cities and within two regions of one city with different levels of air pollution. CLI incidence was higher in the more polluted city when compared to the less polluted cities and in the more polluted region of a city when compared to the less polluted region [92]. A cross-sectional survey of upper respiratory illness in children from Swiss communities that had a documented decrease in particulate air pollution over a 9-year period reported a corresponding decrease in CLI incidence over that period, and this difference was retained after controlling for SES and other potential CLI risk factors [93]. Similar results were reported for a second cross-sectional community study where CLI incidence decreased as air quality improved [94].

An effect of indoor air pollution on CLI incidence was reported in a prospective study done in an industrial area of Delhi, India. There, mean indoor particulates was greater than outdoor particulates and was significantly higher in homes of children with a positive history of frequent respiratory illness (including CLIs) when compared to homes of children with a negative history [95]. Other studies reported a direct relationship between CLI incidence and the presence of moisture and mold in the home environment [45, 96].

Stress

Stress is a generalized set of diverse host responses to external or internal stimuli (stressors) that are or are perceived to be harmful [97]. Stress causes changes in immune function [98, 99] and higher levels of stress were reported to be associated with an increased risk for infectious and noninfectious diseases [100]. Stress (both physical and psychological) may be the integrating factor for such diverse influences on CLI risk as low SES [101, 102], crowding [79], intense exercise [103, 104] and job-related factors [105–108], among others.

A large body of work has focused on the CLI risk of psychological stress [109] defined as occurring when life events and demands exceed coping ability [110]. A number of studies documented a positive correlation between psychological stress levels and the vSSC. For example, in a prospective family study of life events and CLIs in 58 children, Boyce and colleagues [111] reported a significant association between negative life events and the vSSC. In an early study of experimental RV exposure in 52 adults, Totman and colleagues [112] reported a significant positive correlation between a measure of stress, the Totman Change Index, and the magnitude of virus shedding, and between a second measure of stress, the Totman Loss Index, and the provoked vSSC. A later study of 55 subjects experimentally infected with influenza A virus reported that the level of perceived stress was directly related to the provoked objective and subjective vSSC and to the post-exposure nasal IL-6 concentration [113].

Other prospective cohort studies documented a direct relationship between CLI risk and negative life events and/or perceived stress [114–121]. Using experimental virus challenge as a vURTI model, Cohen and colleagues [53] exposed 394 adult subjects to 1 of 5 upper respiratory viruses (RV types 2, 9 and 14, RSV and coronavirus) and then assessed infection and illness. Prior to exposure, they assessed the frequency of major negative life events in the past year, perceived stress and negative affect, which were combined to form a stress index for each subject. After adjusting for control variables, the rates of both provoked vURTIs and CLIvs increased with increasing values of the stress index. In a subsequent analysis of those data, they reported that that negative life events were the only significant predictor of CLIv risk, whereas perceived stress and negative affect were

significant predictors of vURTI risk [122]. This pattern was reproduced in a smaller study of 17 subjects experimentally infected with RV that reported a significant positive correlation between major negative life events, but not perceived stress or negative affect, and CLIv risk [123]. In a later study, the frequency and severity of acute and chronic negative life events in the previous year was measured in 276 adult subjects who were subsequently exposed to RV and followed for the development of a CLIv [33]. The results documented that severe chronic negative life events (primarily underemployment or unemployment and enduring interpersonal difficulties with family and/or friends), but not severe acute negative life events, were associated with an increased CLIv risk.

Cohen and colleagues [41] reported that one marker of stress, urinary epinephrine, but not two others (urinary norepinephrine and cortisol), measured before RV challenge predicted CLIv risk. However, controlling for epinephrine level did not decrease the effect of the chronic negative life events on CLIv risk, suggesting independent contributions. In a prospective study of 115 adult subjects, negative life events were measured, and the physiological responses to an acute stressor assessed. The subjects were then monitored over a 12-week period for the development of a natural CLI [124]. The results documented an interaction between the cortisol response to acute stress and negative life events in predicting CLI risk, such that those who produced high levels of cortisol to the acute stressor (reactors) and had high levels of negative life events were at greater risk for a CLI than were high reactors with low levels of negative life events and low reactors irrespective of their life events. Also reported was the observation that baseline immunological measures of reactivity [$CD8^+$ number, natural killer (NK) cell number, and NK cell cytotoxicity] interacted with weekly perceived stress levels in predicting concurrent self-reported CLI episodes. For these outcomes, it was low immune reactors who were more likely to experience a CLI during high stress than low stress weeks, while high immune reactors did not exhibit differences in weekly CLIs as a function of weekly stress level. Three earlier studies in children reported that measures of the physiological response (increase in heart rate, increase in CD19 white blood cells and decreased serum antibody response to vaccination) to acute stress modulated the CLI risk associated with background stress levels [125, 126]. However, while suggestive that certain measures of the physiological response to acute stressors can discriminate between groups at high and low risk for CLIs under stressful conditions, the results of these studies were not consistent regarding the measure of the acute stress response that interacts with background stress levels to predict CLI susceptibility, and further work in this area is needed.

Social environment

There has been considerable interest in the role played by social network structure, quality and quantity of social interactions and social support in

maintaining health. Past literature reviews document abundant evidence that higher levels of social support and more positive social relationships improve immunoregulation and are associated with less chronic illnesses and less all-cause mortality [127–129]. One hypothesized mechanism to explain this relationship is that quality social interactions and social supports dissipate stress, thereby attenuating the harmful effects of stress on immunity and other physiological functions [127], but this mechanism does not explain all of the beneficial health effects of social support, suggesting the existence of other linkage pathways [130]. For example, one recent study reported that adults with smaller social networks had a poorer immunological response to influenza vaccination [131].

Evidence that social support moderates CLI risk during stress was provided by the results of two longitudinal cohort studies. Evans and colleagues [118] enrolled 100 subjects in a daily diary study of desirable and undesirable events and CLIs. Desirable events were significantly decreased in frequency in the 4 days before CLI onset and individual item analyses showed that perceived intimacy, social support and self-esteem moderated the effect. Smith and colleagues [116] followed 92 asthmatic adults over 1 year for asthmatic exacerbations during a CLI. Eighty percent of the population developed at least one event, and, of those, persons reporting more negative life events and lesser levels of social support had a greater frequency of episodes. However, two studies of stress, social support and CLI risk in adults and children reported that, while higher life event stress was associated with increased CLI risk, social support buffered that risk only in those with low background stress [120, 121].

Cohen and colleagues [41] used an experimental model of virus infection to explore the role of social ties in moderating CLIv susceptibility. Two hundred and seventy-six otherwise healthy adults provided information on their participation in 12 types of social ties and were assessed for typical health practices, negative mood states and urinary cortisol and catecholamine concentrations. Then, all subjects were experimentally exposed to RV and followed for the development of CLIvs. Results showed that those participating in a greater number of social ties had significantly less virus shedding, lesser vSSCs and fewer CLIvs. The magnitude of the effect on CLIv risk was not modified after controlling for pre-challenge viral specific antibody, standard demographic variables, magnitude of viral shedding, serum levels of cortisol and catecholamines or absolute number of contacts.

Host modulators

Demographic factors

Sex, age and race

Analyses of the data from a large community study conducted between 1965 and 1981 reported that CLIvs were more frequent in males prior to

the age of 3 years and in females after that age [81, 132]. Also, CLIvs were less frequent in women who worked outside of the home when compared to those who did not, an effect most likely mediated by the more frequent contact with ill children in the latter group [81]. However, sex was not identified as a predictor of CLIv risk in experimental studies of virus exposure in men and women aged 18–54 years [41, 53, 133, 134].

In the community study and in an earlier family study of CLI transmission, the CLIv incidence decreased with advancing age from a high of two to ten episodes/year in the youngest children to a low of two to four episodes per year in the oldest adults [54, 132]. More recently, Ball and colleagues [84] reported a significant interaction between day care attendance and age on CLI incidence in children. There, compared to young children raised "at home" with their mothers, children in day care experienced more CLIs/year at younger ages (<6 years) but fewer CLIs/year at older ages (>6 years). An age-dependent pattern for CLI incidence was found in a 1996 survey of illness in the United States that reported CLI (including influenza) incidences of 1.73, 0.92, 0.65, 0.64 and 0.37 CLIs/year/person for individuals aged <5 years, 5–17 years, 18–24 years, 25–44 years and >45 years, respectively [135]. However, an analysis of the data for studies of experimental viral exposure in adults aged 18–54 years did not find associations between age and CLIs [41, 53, 133, 134].

There are few comparative data for natural vURTIs and/or CLIs to determine if race influences CLIv or vURTI risk. However, analyses of the data from several large cohorts experimentally exposed to upper respiratory viruses did not evidence an association between self-assigned race (primarily White vs Black) and CLIv risk [41, 53, 133, 134].

Socioeconomic status

SES is a composite measure of economic, social and occupational status as reflected by income, education and occupation [136]. When assessed over its full scale from poverty to affluence, SES is an inverse predictor of mortality and of the risks for both acute and chronic diseases [136–138]. The effect of SES on health is believed to be mediated in part by the relationships between SES and nutrition, population demographics, health practices, daily environment, stress levels, social interactions and personality structure [136]. For example, one recent study of 196 adults reported that lower SES was associated with higher levels of two markers of ongoing stress, salivary cortisol and urinary epinephrine, with less diverse social networks and with poorer health behaviors such as higher rates of smoking, associations that were independent of race [101].

Few studies have evaluated the effect of SES on CLI risk. In an early community study, Monto and Ulman reported a higher annual CLIv incidence in persons with low family incomes when compared to those with middle or high family incomes [132]. In contrast, Alper and colleagues [139] prospectively followed 60 children from two communities aged 1–4 years by

daily parental diary for CLIs over the 8 months of the typical CLI season (October through April) and recorded a total of 267 CLIs. Multivariate analysis documented a significant effect on CLI risk of age (younger > older), gender (male > female) and the CLI burden in the child's sibling (higher > lower) but no effect of SES as measured by parental education and occupation, despite significant variability in those measures for the population.

Cohen and colleagues conducted two studies of the effect of SES on the response of adult subjects to experimental virus exposure [102, 134], but neither documented an effect of concurrent SES as measured by income, education or home ownership on vURTI or CLIv risk. However, in the second study that enrolled 193 adults aged 21–55 who were exposed to influenza or RV, perceived SES as measured by where a subject believes that they rank in terms of income, education and occupation with respect to the United States population was a significant inverse predictor of CLIv risk.

There is a growing literature indicating that early childhood SES influences susceptibility to disease in adults [140]. In a study that experimentally exposed 334 adults to RV, a significant negative correlation between childhood SES as measured by years of parental home ownership and adult vURTI and CLIv risks was observed. The effect of childhood SES on CLIv susceptibility was fixed by the time of adolescence since subjects whose parents did not own their home early in life but did during adolescence were at the same increased CLIv risk as those whose parents never owned their home.

Health behaviors

Diet

A study of 1600 children in India reported a direct association between malnutrition and the incidence of CLIs with and without complications [141]. Analyses of the data from two studies of poverty in the United States (the Community Childhood Hunger Identification Project and the third National Health and Nutrition Examination Survey) documented an increased risk for CLIs in poor, food-insufficient (hungry) children when compared to poor, food-sufficient children [142].

Relatively few studies have evaluated diet as a risk factor for vURTIs and CLIs in food-sufficient persons. Cohen and colleagues [41] collected dietary data by standard questionnaire on 276 healthy volunteers who were subsequently exposed to RV. Of the dietary items (e.g., zinc, selenium, vitamins), only intake of ≤85 mg vitamin C was an independent predictor of CLIv risk. However, in a cohort study of 4273 faculty and staff at Spanish universities, daily dietary intake of vitamin C and zinc assessed by questionnaire did not predict CLI risk during the 1-year period of follow-up [143]. Also, analyses of the data for a cohort of 21 796 male smokers drawn from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study did not

document an effect of dietary vitamin C and E and beta-carotene on CLI risk [144].

There is a wide variety of conventional and alternative dietary supplements that are promoted as being effective in reducing CLI risk [145, 146]. Nonetheless, there is little convincing evidence that dietary supplementation with vitamin C [144, 147], beta-carotene [144], vitamin E [144], zinc [143, 148] or *Echinacea* [149] affects CLI or vURTI risk in the general population of otherwise healthy adults. However, there is limited evidence for reduced CLI risk attributable to some of these supplements in certain subpopulations such as the elderly (vitamin E) [144, 150] and those engaged in strenuous activities (vitamin C) [151, 152]. Other studies reported prophylactic efficacy with respect to CLIs of such diverse dietary supplements as probiotic bacteria plus vitamins and minerals [153], *Camellia sinensis* (green tea) capsules [154], micronutrient-fortified beverages [155] and hydrolyzed rice bran [156], but these studies need to be replicated before the findings can be accepted.

Alcohol and tobacco use

Tobacco smoke is a major health risk and both tobacco smoke and nicotine have immunosuppressive effects [157, 158]. While debated, alcohol is considered to be immunoenhancing in low doses and immunosuppressive in high doses [159, 160] and low doses of alcohol may have anti-inflammatory effects [161]. These observations suggest that exposure to tobacco smoke will be associated with a greater risk for both vURTIs and CLIs, while moderate alcohol consumption will be associated with a lesser vSSC magnitude and a lesser frequency of CLIs when compared to populations of teetotalers or alcohol abusers.

Population-based studies focused on both passive and active tobacco smoke exposure as risk factors for CLIs and vURTIs have reported mixed results. For example, an analysis of Australian health survey data did not establish a relationship between mother, father and combined tobacco smoking and CLI risk in their children [162], but an analysis of the Women's Health Study data reported a slightly increased CLI risk in women passively exposed to cigarette smoke [163]. Interestingly, the latter study did not document an increased risk for CLIs among heavy smokers when compared to non-smokers. In contrast, a cohort study focusing on job demands and CLI risk identified cigarette smoking as a significant, independent predictor of CLI risk [105]. The results of epidemiological studies on tobacco smoking and vURTI risk are inconsistent with influenza vURTIs linked to tobacco smoking, but not vURTIs caused by other viruses [55, 164–166].

Three cohort studies reported that compared to teetotalers, persons who consumed alcoholic beverages were at decreased risk for CLIs. The first followed 92 asthmatic adults for CLIs complicated by asthma exacerbations and reported that the subgroup with no qualifying events consumed more alcohol when compared to the subgroup with qualifying events [116]. The

second followed 4272 faculty and staff at five Spanish universities for CLIs after assessing each individual's 'usual' alcohol consumption by means of a questionnaire. The results showed that consumption of wine (but not total alcohol, beer or spirits intake) was associated with a lower risk for CLIs [167]. The third followed 107 adults over a 15-week period for investigator verified CLIs and reported that subjects who consumed alcohol were at significantly less risk of developing a verified CLI when compared to non-drinkers and that, for those who consumed alcohol, CLI risk was indirectly related to the amount of alcohol consumed [120].

In a study of experimental virus exposure in adults, Cohen and colleagues [168] collected data for 'typical' smoking and alcohol consumption on 322 subjects who were subsequently exposed to one of five viruses and followed for the development of a vURTI and a CLIv. Effects analyses controlled for demographics, virus type, personality, stress, antibody titer, allergy and other study variables and showed that smoking was associated with greater vURTI and CLIv risks, that alcohol consumption decreased the CLIv risk in a dose-response manner, but that 'smokers' were not protected from CLIvs by drinking alcohol. These effects of 'typical' alcohol consumption and tobacco smoking on CLIv risk were reproduced in a second study of 276 healthy adults experimentally exposed to RV [41].

Exercise

Exercise (and physical activity) affects immune function with moderate intensity, regular exercise being immunoenhancing and long-duration strenuous exercise being immunosuppressive [169–171]. These immunological effects were hypothesized to translate into an effect of exercise on vURTI and CLI risks characterized by a 'J' curve [104, 172]. There, CLI risk would be greatest in the strenuous exercisers, intermediate in sedentary persons and least in moderate exercisers. While some studies reported an increased risk for CLIs with strenuous exercise, most of these were limited to assessments of the difference between CLI incidence during training and after competition in 'elite athletes' [104]. However, inherent biases in the natural pre-selection of persons for membership in that group make generalization of any relationships to other populations tenuous [173]. Hemila and colleagues [151] reviewed those studies and noted that many were underpowered and that the results were inconsistent. Using cohort data collected on 14 401 male smokers enrolled in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial, they analyzed CLI risk for effects of exercise during leisure times and of physical activity at work but found no significant associations. In contrast, evidence supporting the J risk curve was provided by a recent study that prospectively assessed CLI and vURTI incidence over a 5-month period in 32 elite and 31 recreationally competitive triathletes and cyclists, and in 20 sedentary controls. As predicted by the J model, respective CLI incidences were 4.5, 0.7 and 1.9 CLIs per person for the three groups, but an infectious etiology could be documented in less

than 30% of the CLIs despite the use of both culture and PCR methodologies [174].

With respect to the hypothesized effect of regular, moderate intensity exercise in lowering CLI and vURTI risks, Osterback and colleagues [175] followed school children who did and did not participate in organized sports for CLIs as assessed by maternal interview every 2 months and physical examinations every 3 months but found no between-group differences in the CLI incidence. Weidner and colleagues [176] randomly assigned 34 healthy adults to an exercise group and 16 healthy adults to a non-exercise control group and challenged all subjects with RV. Those assigned to the exercise group completed 40 minutes of supervised exercise every other day for a 10-day period and the vSSC was assessed on all subjects at 12-hour intervals. There were no significant differences in the vSSC between groups or within the exercise group before and after exercise, suggesting that moderate exercise during a vURTI does not affect the vSSC.

In contrast, regular exercise as assessed by history reduced the CLIv risk in a study of 276 healthy adults experimentally exposed to RV [41]. A later study of 61 healthy active volunteers aged 66–84 years estimated daily energy expenditure and leisure time sports activity by questionnaire at baseline and then assessed the vSSC daily by diary for 1 year. The results showed that the CLI burden (days/year with illness) and incidence were negatively correlated with both estimates of energy expenditure [177]. More recently, Chubak and colleagues [178] randomly assigned 115 overweight and obese, sedentary, postmenopausal women to either 45 minutes of moderate-intensity exercise 5 days per week or 45-minute stretching sessions once per week for 12 months and assessed CLI incidence by quarterly questionnaires. A significantly decreased CLI incidence for the exercise group relative to the control group was reported.

Sleep efficiency

Sleep deprivation is associated with altered immune function reflected as reduced NK cell activity and IL-2 production [179], increased levels of circulating pro-inflammatory cytokines [180] and poorer antibody responses to hepatitis A [181] and influenza [182] vaccinations. A cohort study comparing CLI risk assessed by retrospective questionnaire for the previous 4 months between day and shift workers reported that shift workers had poorer sleep quality, a greater number of days with fatigue and more CLI episodes [106]. Two studies of experimental RV exposure in 276 and 334 adults reported that poor sleep efficiency measured before challenge predicted increased CLIv risk [41, 133]. In a later study of 153 healthy adults aged 21–55 years, sleep duration and efficiency were measured for 14 consecutive days and then the subjects were challenged with RV and monitored for the development of vURTIs and CLIvs. The analysis documented that average sleep duration and efficiency, but not the percent of days feeling rested, were inversely related to CLIv risk. Those results were unaffected

after controlling for pre-challenge virus-specific antibody, age, sex, season of the year, body mass, education, income, perceived socioeconomic rank, race and physical activity [183].

Pre-exposure virus-specific immune status

During a vURTI caused by a novel virus, the adaptive immune system participates in eliminating free virus and destroying virus-infected cells as well as in establishing an immune memory that ideally reduces the probability of reinfection with the same virus. A salient feature of the humoral component of immune memory is the development of specific antiviral antibodies resident in secretions (sIgA) and serum (IgG). In humans, the best correlate of protection from a vURTI caused by a specific virus is the pre-existing anti-virus-specific IgG antibody titer [184–186]. In animal models, virus-specific sIgA antibody protects from infection [187] but this is difficult to demonstrate in humans where the local sIgA titers are highly correlated with the respective serum IgG antibody titers [188–190]. Also, for established vURTIs, pre-existing serum IgG antibodies titers were shown to correlate inversely with the magnitude of viral shedding, the vSSC and the CLIv risk [32, 185, 186, 191, 192]. The cellular component of immune memory functions to reduce the duration of a subsequent vURTI caused by the same or related virus. Expectedly, this should be accompanied by a lesser recruitment of accessory inflammatory responses and thus a decreased vSSC and CLI risk, although this has not been conclusively demonstrated in humans.

Constitutional factors

Prospective studies reported that individuals with a history of frequent CLIs were highly likely to continue to experience frequent CLIs at later times [27, 193–196]. For example, Ball and colleagues [195] prospectively followed 858 children from birth to age 13 years. Parental recall data for child CLIs in the previous year were collected at 2, 3, 6, 8, 11 and 13 years of age. Children with more than 3 CLIs/year at 2 or 3 years of age were more likely to have frequent CLIs at the later assessment times when compared to children with infrequent CLIs at 2 or 3 years of age. This relationship held after controlling for confounding variables such as gender, ethnicity, maternal education, breast-feeding, number of persons in the household, smoking exposure and presence of pets in the household. Factors that could contribute to this CLI constitution are listed below.

Immunology

Higher than expected frequencies of deficiencies in the humoral and cellular components of the adaptive immune system were reported for patients with a history of frequent CLIs. For example, Cedzynski and colleagues [197] reported that of 335 patients aged 1–16 years with a history of recur-

rent CLIs, 93 (28%) had defects in the humoral immune response, 66 (20%) had disturbances in cellular immunity and 19 (6%) had both humoral and cellular abnormalities. These data suggest that children with functional immune deficiencies are at greater risk for re-infection with the same viral strain and for an exaggerated vSSC interpretable as a CLI during established vURTIs.

In persons exposed to a novel virus, a first line of defense against infection is the innate immune system. While local levels of nonspecific antiviral chemicals and other components of the innate immune system are expected to participate in protection from all vURTIs [198, 199], there are few data supporting this expectation for humans. However, a number of published studies suggest a role for the constitutional production of certain components of innate immunity as modulators of CLI risk. The majority of these studies focused on the interferons, a family of host-produced antiviral proteins that up-regulate epithelial cell resistance to virus infection [200], and reported that lower stimulated leukocyte production of interferon was associated with a higher frequency of CLIs in children [195, 201–203]. In contrast, Becker and colleagues [204] focused on ICAM-1, the epithelial cell receptor for the major RV subgroup (and other viruses), and reported an inverse relationship between CLI risk and ICAM-1 serum levels [205]. Because circulating ICAM-1 can serve as a decoy for RV attachment, they argued that protection was afforded by lowering the probability of RV attachment to epithelial cells.

Allergy and asthma are chronic diseases characterized by an altered Th1/Th2 balance of adaptive immunity [206]. Adequate Th1 function is required to eradicate viral infections and this suggests that allergic/asthmatic individuals may express a greater vSSC and thus be at greater risk for CLIs when compared to 'normal' individuals. Indeed, subtle differences between allergic and non-allergic subjects in the immune response to experimental RV, but not influenza virus, infection have been reported [207, 208]. However, the results of an experimental RV challenge study of 10 allergic and 10 non-allergic adult volunteers did not evidence between-group differences in the vSSC or in the CLIv frequency. This lack of effect was replicated in a second study that compared the upper and lower respiratory tract responses to RV infection between 11 allergic-asthmatic subjects and 10 non-allergic, non-asthmatic control subjects. No between-group differences were noted for the vSSC, cellular response, cytokine response or lower airway response to infection [209]. In a study that evaluated the possible effect of allergen priming on CLIv risk, allergic adult subjects were challenged with either allergen or placebo (10/group) three times in the week before experimental exposure to RV. No between-group differences in infection rate, vSSC magnitude, cellular response and local cytokine production were documented [210]. The results for these experimental studies are consistent with those reported for a study of natural RV infection in asthmatic and control subjects [211]. There, 76 cohabitating couples with one allergic-asthmatic and

one healthy member were followed by daily diary for upper and lower respiratory symptoms, twice daily peak expiratory flow measurement and bimonthly collection of nasal secretions for RV detection. There were no between-group differences in rvURTI or CLI incidences or in the rvSSC.

Genetics

A possible genetic contribution to CLI risk is suggested by data collected during the Seattle Virus Watch where the spread of vURTIs in families was studied using nasopharyngeal virus cultures and data on CLIvs were collected from diaries [27]. Fox and colleagues reported that some families were characterized by a CLIv with every documented rvURTI, while others had no CLIvs despite frequent rvURTIs and concluded that a 'familial' factor, either environmental or genetic, controlled CLIv risk. While no studies have used twin methodologies to estimate the heritability of vURTIs or CLIs, there is evidence that genetic factors contribute to a 'CLI constitution' by affecting the vURTI risk, the CLIv risk and the risk of vURTI complications.

Human leukocyte antigens (HLAs) are encoded by genes of the major histocompatibility complex and play a prominent role in regulating the immune response to infection. Past studies reported that HLA genotype influences the humoral response to vaccination [212], while other studies attempted to associate HLA genotypes with resistance to different infectious diseases [213]. Coetzee and colleagues [214] genotyped 59 adult female members of the Bantu-speaking Tswana and collected retrospective data on the number of CLIs experienced in the previous year. HLA-B allele frequency was a significant predictor of CLI incidence but not of the number of total illnesses in the previous year. The more common HLA-B alleles in that population were associated with a lesser CLI incidence.

Mannose-binding protein (MBP) is a member of a host-produced family of collectins that plays a prominent role in innate immune defense. The gene coding for MBP is polymorphic in the population, with different genotypes being related to different levels of MBP production [215]. A number of studies investigated the role for these polymorphisms as a modifier of CLI susceptibility [216]. For example, Koch and colleagues [217] genotyped 252 children <2 years of age for MBP polymorphisms and followed the children for 2 years by weekly assessments of illness. MBP mutations associated with lesser levels of MBP production were significantly more frequent in children at high risk for CLIs, an effect that was more evident in children younger than 17 months of age.

As mentioned, the immune/inflammatory response during a vURTI is orchestrated by the synthesis of pro-inflammatory and anti-inflammatory cytokines [46]. Other studies showed that polymorphisms in the genes coding for many of these cytokines affect their synthesis [218]. Recent work focused on a possible role for these polymorphisms in determining CLI risk. Nieters and colleagues [214] genotyped 111 adults for polymorphisms in the

TNF-α (-308 G/A), IL-2 (-330 T/G), IL-10 (-1082 G/A, -819 T/C, -592 A/C), IL-6 (-174 G/C) and IFN-γ (+874 A/T) genes and assessed the frequency of CLIs by yearly interview over 2 consecutive years. They found significant associations between the IL-2 and IL-6 genotypes and CLI incidence. In a later study of 29 adults experimentally exposed to RSV and genotyped for the TNF-α, IL-10, IL-6 and IFN-γ polymorphisms, Gentile and colleagues [219] reported a significant association between the IL-6 genotype and the vSSC, and this was reproduced in a study of 31 adults experimentally exposed to RV (Doyle, unpublished). IL-6 is a cytokine whose local level during experimental vURTIs caused by RV, influenza virus and RSV correlates with the vSSC [46, 113, 220] and these results suggest that IL-6 gene polymorphisms affect CLIv risk by modifying the objective vSSC.

Other work focused on a possible role for these polymorphisms in determining the frequency of complications during a vURTI. Gentile and colleagues [221] genotyped 77 hospitalized infants <6 months of age with bronchiolitis secondary to confirmed RSV infection for TNF-α, IL-10, IL-6 and IFN-γ polymorphisms. They reported a significant association between the IL-6 genotype and length of hospital stay, between the IFN-γ genotype and presentation with otitis media and between the IL-10 genotype and presentation with pneumonia. Alper and colleagues [222] prospectively followed 230 children over the typical cold season for nasopharyngeal virus detected by PCR, CLIs by daily parental diary and otitis media by weekly otoscopy. All children were genotyped for the TNF-α, IL-10, IL-6 and IFN-γ polymorphisms. IL-10 and TNF-α genotypes were significant predictors of otitis media during rvURTIs and IL-10 genotype was a significant predictor of otitis media during rsvURTIs.

Personality

There is a growing body of evidence that an individual's personality influences basal immunity and illness risk [223], has a moderate heritability [224, 225] and is relatively stable over time [226]. Two early virus challenge studies reported that persons scoring high in introversion at entry developed a greater vSSC [112] and shed more virus [112, 227] after experimental RV exposure. Cohen and colleagues [41] measured each of the Goldberg Big 5 personality traits (extraversion, agreeableness, conscientiousness, neuroticism and openness to experience) in 276 adult subjects, exposed all subjects to RV and followed them for the development of a CLIv. Only extraversion was a predictor of CLIv risk with those scoring lower on that measure (higher on introversion) being at greater risk. In a second study, the same investigators explored whether extraversion, agreeableness and a variable combining these two traits (termed sociability) were associated with CLIv risk. There, they collected pre-exposure data for virus-specific antibody titers, demographics, health practices, social ties, salivary cortisol and urinary catecholamines in 334 healthy adults, measured the three traits and exposed

all subjects to RV [133]. Increases in extraversion, agreeableness and their combination were all associated with decreasing CLIv risk. Although these traits were associated with more and higher-quality social interactions, participation in health-enhancing behaviors and better emotional regulation, controlling for those variables did not affect their relationship with CLIv risk.

Feldman and colleagues used pathway models to reanalyze the data collected in the Cohen and colleagues' study of the Big 5 Factors [41] with a focus on baseline symptoms and the subjective vSSC bias [38]. The analyses showed that neuroticism was positively correlated with unfounded symptoms both before and after virus exposure, that openness to experience was positively correlated with unfounded, post-exposure symptoms in those with a CLIv and that conscientiousness was positively correlated with unfounded, post-exposure symptoms in those without a documented CLIv. In a second study of 86 subjects experimentally exposed to either RV or influenza A virus, Cohen and colleagues [228] reported that a different measure of neuroticism, trait negative affect, was directly associated with an upwardly biased subjective vSSC.

As mentioned, negative emotional style or neuroticism was shown to be associated with greater unfounded symptoms before and after experimental virus exposure [38, 228]. In two more recent studies, Cohen and colleagues evaluated the effect on the provoked vSSC, vURTI risk and CLIv risk of a positive emotional style characterized by typically experiencing positive emotions such as "happy", "pleased" and "relaxed". The first study enrolled 334 adults, assessed positive and negative emotional styles, exposed all subjects to RV and followed the subjects for the development of a vURTI and a CLIv. The results showed that greater positive emotional style was associated with a lesser CLIv risk but not a lesser vURTI risk, that positive emotional style was associated with a downwardly biased subjective vSSC, that negative emotional style was associated with an upwardly biased subjective vSSC and that the effect of positive emotional style on CLIv risk was independent of negative emotional style [229]. In that study, data were also collected on nasal levels of three pro-inflammatory cytokines, IL-1β, IL-6, and IL-8. The temporal pattern for expression of all three cytokines tracked the vSSC, and lower positive emotional style was associated with greater levels of these cytokines and a greater vSSC. Controlling for IL-6 but not for IL-1β or IL-8 substantially decreased the relationship between positive emotional style and the vSSC, indicating the possibility that IL-6 mediated the association [220]. The relationships between positive emotional style and both the vSSC and CLIv risk were replicated in a second study that exposed 193 adult subjects to either influenza or RV. That study also showed that the relationship was independent of the personality traits of optimism, extraversion, mastery, self-esteem and purpose [39].

While emotional style is a measure of general disposition, mood reflects more transient emotional states. A number of studies have shown that

negative moods can affect immunologic function [230] and that mood is adversely affected during a CLI [231–233]. In one study, Cohen and colleagues [228] assessed state negative affect (negative moods) on the day before virus challenge, exposed all subjects to influenza or RV and assessed the provoked subjective and objective vSSC. They reported that persons with higher negative mood scores had a greater, but unbiased, subjective vSSC when compared to those with lesser negative mood scores.

Conclusions

The development of a CLI requires four antecedent events: exposure to an upper respiratory virus at a potentially infectious dose, infection with the virus, the development of a vSSC and interpretation of the vSSC as a CLI. Factors that modulate CLI risk can moderate any of these sequential events. An ideal study of CLI risk factors would characterize the conditional probabilities of each of these sequential events for each potentially causal virus but this is clearly not feasible given that the 'denominators' (e.g.. CLIs/vSSCs/infections/exposures) for the rate calculation are difficult to estimate with accuracy. Nonetheless, it is possible to present hypothetical pathways for the action of some of the CLI risk factors suggested in the above review.

Virus exposure requires that a virus be circulating in a population, a precondition that is affected by climate, season, meteorological and other factors. Given the existence of a virus reservoir, the probability of exposure increases in proportion to the frequency of contacts with infected individuals (with or without a CLI). This is enhanced under community structures characterized by crowding (community, home, day care, school, work, hospital environments) and, perhaps, can be affected by certain personality characteristics. Given exposure to a virus, the probability of infection will depend on the functional status of the innate immune system, on the past experience of the individual with respect to the specific virus, and on the presence of immune memory as reflected in the specific antiviral antibodies. This will be affected by age given the increasing exposure to a greater repertoire of vURTI viruses with advancing age and by genetic polymorphisms and other factors that moderate the innate and adaptive immune response. Given a vURTI, whether or not an infected person expresses a vSSC depends on the extant immunocompetence of the host, which will determine the degree of inflammatory recruitment during the infection and on the propensity of the host to develop an inflammatory response. It is expected that a large number of the identified factors moderate immunocompetence including age, genetic background, past history of exposure to related viruses (cellular memory), social environment, diet, sleep efficiency, exercise frequency and intensity, tobacco use, mood states, some personality traits, childhood SES, perceived SES and both physical and psychological

stress. Some of these factors such as poor sleep efficiency, strenuous exercise/work, childhood and perceived SES and crowding may operate in part by acting as stressors (be nested within the stress effect), while others such as certain personality traits, social support and physiological reactivity to acute stressors may operate by moderating the stress response (interact with the stress response). Moderate alcohol consumption, certain cytokine polymorphisms, exercise and other factors may act by affecting the propensity of the host to develop an inflammatory response, while others such as tobacco smoke exposure, mold (in allergic persons) and cold environments may act to prime the inflammatory response provoked by a vURTI. Finally, there are factors that most probably operate by modifying the interpretation of the vSSC as a CLI. For example, it is possible that air pollution, household mold and tobacco consumption increase the basal SSC with the effect of enhancing the vSSC and transforming subclinical vURTIs into CLIs. Personality factors can modify the vSSC threshold for CLI assignment and/or distort the basal SSC and the vSSC and affect the probability of assigning a CLI to a specific objective vSSC.

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