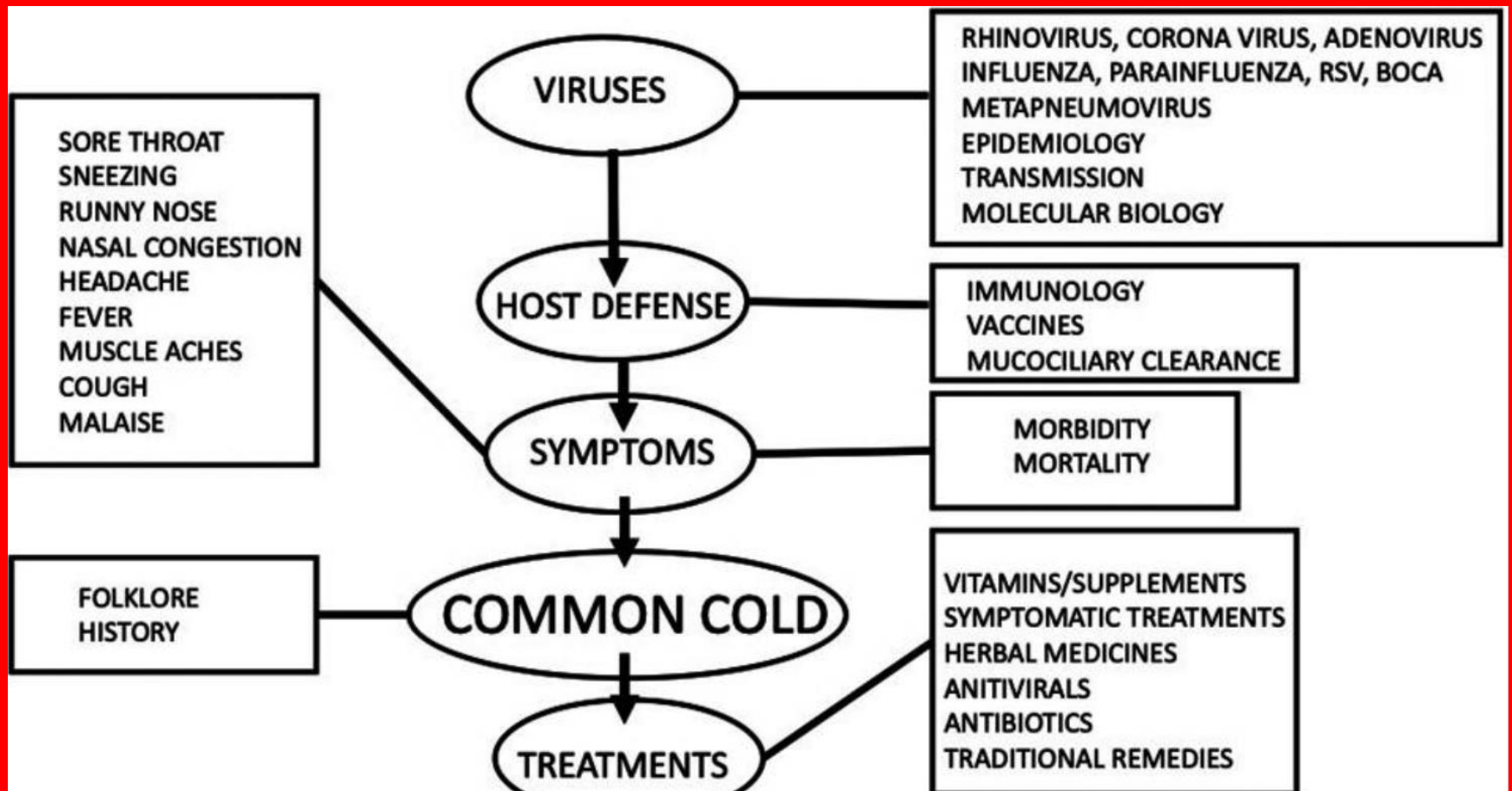


Common cold

- The common cold is a unique human disease, as it is arguably the most common disease and because of the large number of respiratory viruses causing colds it is one of the most complex of human diseases. This review discusses the respiratory viruses and notes that all these viruses may cause the illness complex recognised as the common cold. The common cold is discussed as part of the “iceberg concept” of disease which ranges from asymptomatic infection to severe illness and death. The factors influencing the incidence of colds are discussed: crowding and sociability, stress, smoking and alcohol, immune status, sex, age, sleep, season, chilling, nutrition and exercise. The mechanism of symptoms related to the innate immune response is explained and symptomatic treatments are tabulated. Morbidity associated with common cold is discussed and possible vaccines.

Definition of common cold

- A common cold is defined by the National Institute for Health and Care Excellence (NICE) as “a mild, self-limiting, upper respiratory tract infection characterized by nasal stuffiness and discharge, sneezing, sore throat, and cough” ([1](#)). The term “common cold” is widely used in the medical literature, but it has been argued that the common cold is more of a cultural concept rather than a clinical entity as the disease is usually self-diagnosed and treated by the patient ([2](#)). The term common cold has been used for centuries, and it is often associated with a belief that exposure to cold causes the symptoms of disease ([3](#)). It is only since the discovery in the 1950's that respiratory viruses such as rhinoviruses ([4](#)) cause the common cold that there has been a scientific explanation for this disease. “All known respiratory viruses are able to produce the illness complex recognised as the common cold” ([5](#)). But the illness complex or syndrome of symptoms that is recognised by the patient as a common cold is only part of what is often called the iceberg of virus infection as illustrated in [Figure 2](#). Most respiratory virus infections result in a sub-clinical or asymptomatic infection which is not noticed by the host as the virus is cleared in a few days by the immune system. The iceberg concept of infection is illustrated by a study on 214 healthy individuals (age 3–63 years) ([6](#))



- . Nasopharyngeal swabs and symptom scores were taken twice a week for two years. Of 4,215 samples collected, 737 were positive for one or multiple respiratory viruses (influenza viruses, respiratory syncytial viruses, human rhinoviruses, coronaviruses, adenoviruses, parainfluenza viruses, human metapneumovirus) and amongst the positive results, 69%–74% of the samples were classified as asymptomatic. The iceberg concept of viral infection predicts that after asymptomatic infections the next most common syndrome is an acute self-limiting illness the “common cold”, with symptoms such as sore throat, runny nose, nasal congestion, cough and sneezing as illustrated in [Figure 2](#). The common cold is often referred to as a “head cold” meaning the symptoms are located in the upper airways, whereas more severe “flu-like illness” as illustrated in [Figure 1](#) involves systemic symptoms such as fever, muscle aches and pains and malaise. On infection with a respiratory virus, factors such as old age, low immune deficiency and poor nutrition may allow more severe respiratory illness such as bronchiolitis or pneumonia and less commonly result in death represented by the tip of the iceberg. Infections occur frequently and they are usually milder after several infections. Each infection does not lead to the induction of protective immunity. The common cold can therefore be considered as part of a spectrum of disease caused by respiratory viruses as illustrated in [Figure 2](#).

Ascending
severity of disease



Threshold of symptom severity
for self diagnosis as a common cold



Common cold viruses

- *As stated above, all respiratory viruses may cause symptoms recognised by the patient as a common cold ([5](#)), and viruses that are not classified as respiratory viruses may also cause common cold symptoms when they infect the upper airways such as measles viruses ([7](#)) and enteroviruses ([8](#)), and some bacterial infections may also cause common cold symptoms ([9](#)). [Table 1](#) lists the different groups of respiratory viruses. Rhinoviruses are the most common cause of common cold as they are found in more than half of upper respiratory tract infections and can be considered as the most common infection of humans world-wide ([8](#)). [Table 1](#) lists the respiratory viruses known at present, but it is likely that new viruses await discovery. The metapneumovirus was discovered in 2001 by researchers in the Netherlands who identified the virus in stored nasopharyngeal samples from children, and it was later determined that this virus had been in circulation for some 65 years and that nearly every child would have been infected by metapneumovirus by the age of five ([10](#)). Human bocavirus was discovered in 2005 from nasopharyngeal samples in children and has now been shown to cause common cold in children (*

VIRUS GROUP	ANTIGENIC TYPES
Rhinoviruses	>156 types
Coronaviruses	5 types
Parainfluenza virus	5 types
Respiratory syncytial virus	2 types
Influenza virus	3 types ^a
Adenovirus	57 types
Metapneumovirus	2 types
Other viruses: enteroviruses, bocavirus	

Common cold viruses

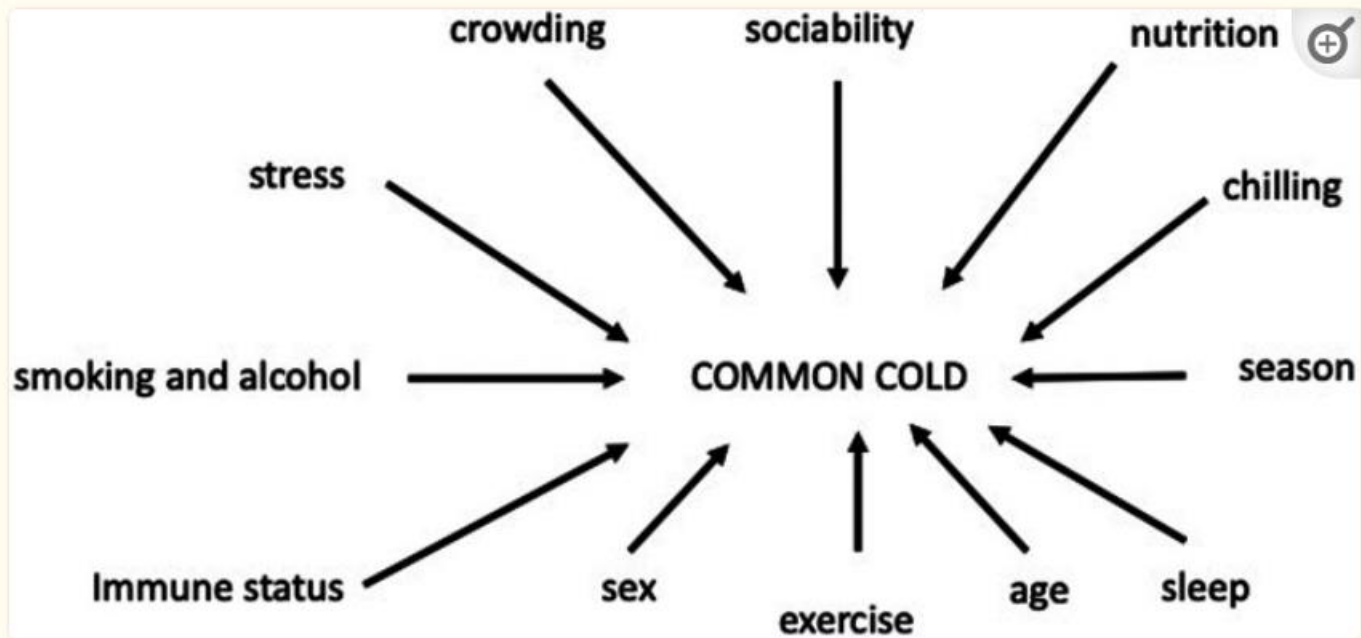
Table 1

Respiratory viruses.

Virus	Abbreviation	Nucleic acid	Classification	Structure
Rhinovirus	HRV	RNA	Species A, B, C with 100 serotypes	Non-enveloped icosahedral capsid
Coronavirus Seasonal	HCoV	RNA	Types OC43, 229E, NL63, HKU1	Enveloped
Coronavirus Pandemic	SARS, MERS SARS-CoV2	RNA	Variants such as Omicron	Enveloped
Respiratory syncytial virus	HRSV	RNA	Groups A and B	Enveloped
Parainfluenza virus	HPIV	RNA	Types 1, 2, 3, 4	Enveloped
Influenza virus	Flu	RNA	Types A, B, C, D	Enveloped
Adenovirus	ADV	DNA	51 serotypes	Non-enveloped icosahedral capsid
Metapneumovirus	HMPV	RNA	Groups A and B	Enveloped
Bocavirus	HBoV	DNA	2 lineages	Non-enveloped icosahedral capsid

Risk factors

- *The common cold is the most common human disease and the factors influencing susceptibility to developing common cold symptoms have been discussed for thousands of years, and form a very large literature of science and folk-lore ([12](#)). The Greeks and Romans explained common cold in terms of the so-called humoral pathology explained by Hippocrates with chilling of the body causing a disturbance of the humors and flow of mucus from the nose ([12](#)). The role of chilling as a predisposing factor to common cold persisted through to the seventeenth century and Richard Lower an eminent physician in London, UK published a treatise entitled De Catarrhalis ([3](#)) and concluded “Finally if one wishes to prevent this evil altogether nothing is more useful as a precaution than to be well protected against external cold and make sure of proper perspiration, even (should the situation demand it) by moving to a hot and dry climate. On these measures depend largely the preservation of our health and the prevention of catarrhs.” Chilling of the body surface as a cause of common cold symptoms or as a means of increasing susceptibility to infection persisted throughout the nineteenth and twentieth centuries ([13](#)) and even in the present is still proposed as a mechanism that may influence susceptibility to infection and common cold although with poor evidence and scientific explanation*



[Figure 3](#)

Factors that may influence susceptibility and incidence of common cold.

Crowding, sociability

- *Humans are infected by respiratory viruses that originate from the respiratory tract of other humans and are transmitted in respiratory mucus by aerosols generated by coughing and sneezing and by fomites such as commonly touched surfaces ([15](#)). It is self-evident that transmission of viruses will be more likely in crowds of human beings when they are close together such as in schools, colleges, cinemas, theatres, public transport, etc. ([16](#)) and social distancing and closure of crowded places and events has been used as a means of controlling spread of SARS-CoV-2 virus during the recent pandemic. Using data collected from 626 participants in England and Wales UK it was shown that spending time in underground trains, supermarkets, theatres, cinemas, concerts, restaurants or attending parties increased the risk of acquiring circulating acute respiratory infections ([16](#)). It may be assumed that sociable persons who have an active social life and have many contacts with other persons have an increased risk of common cold but studies report that the opposite may be the case with sociable persons having greater resistance to respiratory infection ([17](#)). In a study on 334 participants in Pittsburgh USA a questionnaire was used to determine measures of sociability and then the participants were challenged with a rhinovirus. Increased sociability was associated in a linear fashion with decreased probability of developing a cold and this association was independent of baseline immunity to the virus ([17](#)). Sociability was associated with better sleep and diet and more positive and less negative emotions, but analysis failed to support any of these as potential mediators and the mechanism of how sociability influences susceptibility to infection is still unknown.*

Stress

- *Stress is understood generally but there are disagreements about a scientific or clinical definition of stress. Stress has been defined as when external demands (stressors) exceed the capacity of the organism to adapt to conditions and cause detrimental psychological and biological changes ([18](#)). Long-term psychological stress has a negative impact on the immune system and mucosal immunity and suppresses the production of secretory immunoglobulin A (sIgA) ([19](#)). Psychological stress has been shown to be a risk factor for common cold ([18](#), [20](#)). In a one year study carried out in a Spanish university the relationship between stressful life events and occurrence of common cold was investigated among 1,149 subjects aged between 23 and 68 years with 46% females, and 365 cases of common cold ([18](#)). The study found a moderate correlation between stress and incidence of common cold and concluded that the findings suggest that psychological stress is a risk factor for common cold ([18](#)). Studies on the relationship between psychological stress and common cold are difficult because stress can also be associated with changes in diet, behaviour, smoking, alcohol ingestion etc. which may also influence the risk for common cold.*
- *There is some evidence that release of cortisol hormones associated with stress may compromise the immune response and make subjects more susceptible to developing common cold symptoms after infection ([21](#)).*

Smoking and alcohol

- *Smoking increases the risk of respiratory infection by damage and irritation of the respiratory epithelium and alteration of the structural, functional and immunologic host defences ([22](#)). Ingestion of alcohol in moderation is reported to decrease susceptibility to developing a cold by having a beneficial effect on the immune system ([23–25](#)). The effects of smoking and alcohol consumption on the incidence of common cold were studied by exposing 391 volunteers to respiratory viruses ([24](#)). In this study it was reported that smokers were more likely to develop infections after exposure to virus and also to develop illness compared to non-smokers and that taking up to three or four alcoholic drinks a day was associated with decreased risk of developing a cold in non-smokers ([24](#)).*

Immune status

- *The immune status of a subject can be considered as the presence of antibodies (immunoglobulins) against a specific respirator virus. When an infant is born it does not have a mature immune system and depends on immunity derived from the mother via immunoglobulins transferred to the infant via the placenta and breast milk ([26](#)). This maternal protection declines in the first year as the infant ceases breast feeding as immunoglobulins have a relatively short half-life. The immunity transferred to the infant via breast milk is dependent on exposure of the mother to respiratory viruses and during the COVID-19 pandemic circulation of common respiratory viruses was greatly decreased due to lockdown and isolation of the general population and this resulted in lower antibody levels in maternal milk for respiratory viruses such as RSV, influenza and coronaviruses ([27](#)). Antibody immunity against respiratory viruses such as RSV is short lived, and this explains the waning maternal and infant immunity against RSV during the COVID-19 pandemic when RSV almost disappeared from circulation, and may also explain the resurgence of RSV infections in many countries once COVID-19 restrictions were lifted ([28](#)).*

- *Parenthood has been reported to decrease the chance of developing common cold symptoms when challenged with a common cold virus and there was a clear increase in protection with having more children in the family ([29](#)). It may be assumed that parenthood increases exposure to common cold viruses and parents acquire greater immunity than non-parents but this does not appear to be the case as the resistance to developing cold symptoms was independent of pre-challenge viral-specific immunity (viral antibody titre to the challenge virus) ([29](#)).*
- *Respiratory infections and the common cold occur throughout life, and the success of these viruses is due to several factors; the large number of serotypes of viruses such as rhinoviruses, and antigenic drift in viruses such as influenza and rhinoviruses ([30](#), [31](#)). Recent exposure to a respiratory virus confers short lived immunity to that virus but reinfection may occur when antibody titres decline and when the virus evolves into new variants which may have a greater capacity for infection as has been observed with the many variants of SARS-CoV-2 during the recent pandemic ([32](#)).*

Sex and age

- *Sex differences in respiratory viral pathogenesis have been reviewed by Ursin and Klein ([33](#)). In general males are more susceptible to severe outcomes than females at younger and older ages. During the reproductive years from puberty to menopause females are at greater risk than males for severe outcomes from respiratory virus infections ([33](#)). It is not surprising that males and females differ in their immune responses as they have major differences in sex hormones and sexual characteristics.*
- *There are sex differences in the perception of common cold symptoms as even after adjustment for other variables it has been reported that men are significantly more likely to “over rate” their symptoms in comparison to women ([34](#)).*
- *Women are almost twice as likely to develop a cold compared to men when children are sick with a common cold in the family and this because women have more contact with children than men ([35](#)).*
- *Age*
- *The incidence of common cold varies throughout life as immunity to respiratory viruses is acquired by repeated exposure to infection, with infants starting life with little immunity and high incidence of colds, and adults having fewer colds than infants due to previous exposure to viruses. The incidence of common cold is inversely related to age with infants having 6–8 colds a year compared to adults having 2–4 colds a year ([36](#)).*
- *Age also affects the severity of disease with the extremes of age, infancy and old age, having more severe outcomes from disease than the middle range of adults. This difference is related to the immature immune system in infants and the waning immunity associated with old age. RSV infections are a major cause of bronchiolitis and hospital admissions for infants, and also cause severe respiratory infections in the elderly, but may only cause mild common cold symptoms in older children and adults ([37](#), [38](#)).*

Sleep and Season

- *“Sleep quality is thought to be an important predictor of immunity and in turn susceptibility to the common cold” (39). In a study that challenged subjects with rhinovirus it was found that there was an inverse graded association of average sleep duration prior to the challenge and susceptibility to developing common cold symptoms after virus challenge (39). Those subjects with less than seven hours sleep were almost three times more likely to develop a cold than those with eight or more hours sleep (39). This finding has been confirmed in another study which reported that shorter sleep duration prior to rhinovirus challenge was associated with increased susceptibility to the common cold (40). The impact of sleep on immune markers is not fully understood, and this is not surprising considering the complexity of the immune response to infection, but some studies have demonstrated significant changes in immune markers such as decrease in the mitogen proliferation of lymphocytes after sleep deprivation (41).*
- *The seasons of Spring, Summer, Autumn and Winter are determined by changes of day length in the Northern and Southern hemispheres and by changes such as rainfall in the Tropics where day length does not vary. Respiratory virus infections are present throughout the year, but the incidence of infection does vary with season with more symptomatic infections present in Winter and during the rainy season (42, 43). The seasonality of respiratory infections and common cold and flu is part of folk-lore and culture and many different causes for this seasonality have been proposed. Dowell and Ho (44) nicely summarised our understanding of the seasonality of respiratory disease in this quote*
- *“Nearly every important respiratory pathogen of human beings exhibits distinct seasonal variations, yet after hundreds of years of observing and documenting this phenomenon modern science has only superficial observations and largely untested theories about the underlying causes. Is it the cold? Dry air? Crowding together of people indoors in winter? Where do pathogens such as influenza and respiratory syncytial virus (RSV) go in the summertime? Do they migrate across the equator and return the following winter, or do they remain present at low levels in human or animal populations until environmental or host conditions are suitable for re-emergence?”*
- *One of the main changes with season is that inspired air is colder in Winter compared to Summer and a hypothesis has been put forward that breathing cold air inhibits local defences against infection in the upper airway by slowing muco-ciliary clearance and slowing the activity of leukocytes (45). Discussion of all the different factors that may influence the seasonality of respiratory infections would be too great a task for the current review and therefore the reader is directed to some of the literature on this topic (42–48).*

Chilling and Nutrition

- *There is a widely held folklore that respiratory infections are caused by chilling or exposure to draughts and damp, that in some way penetrate the body to cause illness. Common cold is believed to occur after “going outside with wet hair”, “getting one's feet wet” and “getting caught in the rain” (49). Laboratory experiments involving challenge with common cold viruses and chilling have failed to demonstrate any effect of cold exposure on susceptibility to infection (50–52). However, these laboratory experiments have been criticised as not representing a “real life” situation when subjects may be harbouring a sub-clinical infection which can be converted into a clinical infection by chilling of the body surface (53). The idea that sub-clinical respiratory infections could be converted to clinical infections was first proposed by Mudd and Grant (54) who demonstrated that chilling of the body surface caused an intense ischaemia and cooling of the pharynx and tonsils and that this reflex vasoconstriction of the airway epithelium could decrease resistance to infection and allow a sub-clinical infection to become symptomatic. Support for this mechanism of chilling is put forward in a review by Eccles (55) and by a review of the relevant literature by Mourtzoukou and Falagas (56).*
- *It is self-evident that poor nutrition with deficiency of calories protein and vitamins etc. will have an impact on general health and the functioning of the immune system and resistance to infection. Nutrients support epithelial integrity, restoration and maintenance. Malnourished children in developing countries are particularly susceptible to morbidity and mortality associated with acute respiratory infection (56). A review of the literature highlights that discussions on nutrition and susceptibility to common cold are dominated by studies on the possible benefits of vitamins C and D in the diet.*
- *The role of vitamin C in preventing and treating the common cold has been controversial since the dual Nobel laureate Linus Pauling published a book in 1970 claiming that vitamin C prevents and alleviates symptoms of common cold (57). The claims in the book were widely criticised as based on opinion rather than scientific evidence but the idea that vitamin C was a cure for the common cold became widely accepted by the general public. Numerous clinical trials have been conducted on the effects of vitamin C on common cold and in 2013 a meta-analysis of 29 trials concluded “The failure of vitamin C supplementation to reduce the incidence of colds in the general population indicates that routine vitamin C supplementation is not justified” and “Regular supplementation trials have shown that vitamin C reduces the duration of colds, but this was not replicated in the few therapeutic trials that have been carried out.”*
- *Vitamin D like Vitamin C has become accepted by the general public as a preventive treatment for common cold but scientific evidence to support this treatment in healthy adults is controversial with some reports showing no benefit (58, 59) and others reporting benefit, especially in those subjects with vitamin D deficiency (60, 61).*

Exercise

- *Moderate exercise has been claimed to have beneficial effects on the immune system and this is associated with fewer days of sickness with common cold whereas severe exercise can have adverse effects on the immune system and increase the incidence of common cold in athletes ([62](#)). However a meta-analysis of eleven trials could not determine whether exercise is effective at altering the occurrence, severity or duration of acute respiratory infections and therefore the role of moderate exercise on common cold incidence still requires more research before it can be accepted that exercise reduces the risk of catching a cold ([63](#)).*

Mechanism of symptoms of common cold

- *Viral infection of the upper respiratory tract triggers a local immune innate response in the infected epithelium and this response is responsible for generating all the symptoms of common cold. Prodromal symptoms at the first signs of a cold or flu include symptoms that may become more severe later in the course of the infection such as throat irritation, sneezing, chilliness, fever, myalgia, headache and tiredness. The innate immune response triggers systemic and local symptoms as illustrated in [Figure 4](#).*

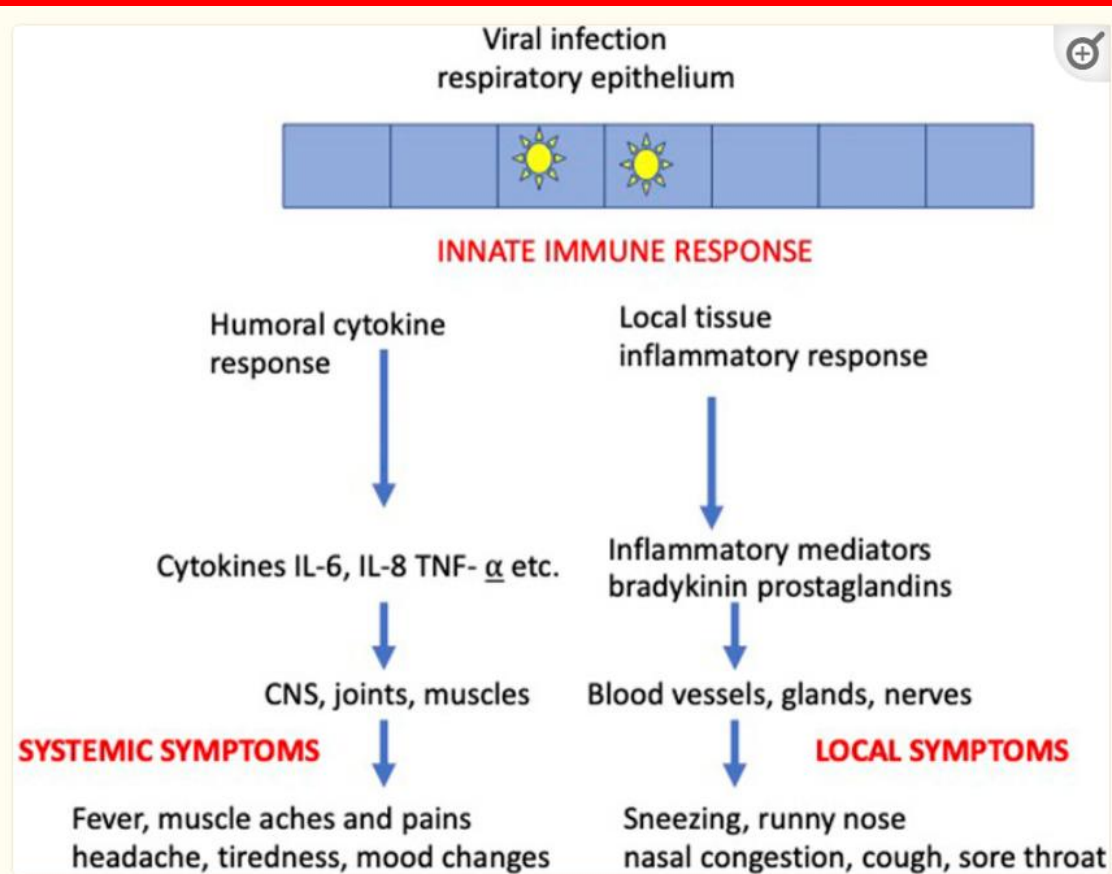


Figure 4

symptoms

- *Incubation periods vary for the different viruses that cause the common cold. ⁷⁴ The incubation period for rhinovirus is typically 2 to 4 days. The common cold can manifest with a wide variety of symptoms based on the causative virus and the age and immune status of the host. Common cold symptoms often begin with a sore or scratchy throat. Rhinorrhea and sneezing typically follow and persist for several days, after which nasal congestion and cough become the dominant symptoms. ⁷⁵ Mucus color often changes from clear to yellow or green during the course of a cold. This does not represent the development of a bacterial infection but is a result of myeloperoxidase and other enzymes produced by neutrophils. ⁷⁶ The mean duration of symptoms is 7 to 10 days, but nasal congestion and cough can persist for weeks. Other symptoms that may be experienced include headache, hoarseness, chilliness, and malaise. Fever is uncommon in adults but common in children*

Treatments for common cold

- *Treatments for common cold can be considered as falling into three categories; (1) use when healthy for supporting the immune system, (2) use at first signs of symptoms with an antiviral effect, (3) use during a cold with symptom relief.*
- *The most common treatments of the common cold are in category 3. For symptom relief and the different symptomatic treatments are listed in [Table 2](#) and have been reviewed by Eccles ([74](#)). These medicines are marketed as over the counter (OTC) medicines that are freely available to consumers as single medicines or as multi-symptom medicines containing several actives.*

Table 2

Symptomatic treatments for common cold.

Symptom	Treatment class	Medicines
Fever	Analgesic, antipyretic	Paracetamol (acetaminophen), ibuprofen, aspirin
Headache	Analgesic, antipyretic	As above
Muscle aches and pains	Analgesic, antipyretic	As above
Sore throat pain	Analgesic, antipyretic	As above
Sinus pain	Analgesic, antipyretic	As above
Nasal congestion	Sympathomimetics	Oxymetazoline, xylometazoline, phenylephrine, pseudoephedrine
Runny nose	Anticholinergics and sedating antihistamines	diphenhydramine, chlorpheniramine, doxylamine etc.
Cough	Antitussives and sedating antihistamines	Dextromethorphan, diphenhydramine
Sneezing	Sedating antihistamines	Diphenhydramine, chlorpheniramine, doxylamine etc.

SYMPTOM	ETIOLOGY	TREATMENT	EXAMPLES
Sore throat	Bradykinin?	Analgesics, topical anesthetics	NSAIDs
			Acetaminophen
			Benzocaine lozenges
Rhinorrhea	Nasal glandular secretions	Anticholinergics	Diphenhydramine
			Doxylamine
			Ipratropium nasal spray
Nasal obstruction	Engorgement of nasal venous sinuses	Adrenergic agents	Pseudoephedrine
			Oxymetazoline nasal spray

Accurate difference between flu and COVID

Accurate difference between flu and COVID	<u>testing</u> is needed someone has both the flu and COVID-19 at the same time
Similarities	<ul style="list-style-type: none"> تب سرفه خلط آبریزش بینی گلودرد تهوع و استفراغ بدون اسهال بیشتر با فلو لرز سرفه قطاری تنگی نفس اسهال فقدان حس بویایی و چشایی) 38% to 55% جشایی و ۴۰ درصد بویایی ندارند و نسبتاً اختصاصی برای کووید است) درد سینه بیشتر با کوید سر درد درد عضلانی و خستگی هر دو
How Long Symptoms Appear After Exposure and Infection	<ul style="list-style-type: none"> Flu: from 1 to 4 days after infection. COVID-19: from 2 to 14 days after infection.
How Long Someone Can Spread the Virus	<ul style="list-style-type: none"> Flu: contagious for about 1 day before they show symptoms. remain contagious for about 7 days COVID-19: begin spreading the virus 2-3 days before and spread the virus another 8 days after their symptoms began.

Accurate difference between flu and COVID	<u>testing</u> is needed someone has both the flu and COVID-19 at the same time
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spread	<ul style="list-style-type: none"> • COVID-19 spreads more easily • the virus that causes COVID-19 is generally more contagious than flu viruses
People at Higher Risk for Severe Illness	<ul style="list-style-type: none"> • Overall, COVID-19 seems to cause more serious • Serious COVID-19 illness resulting in hospitalization and death can occur even in healthy people
Post infection problems	<ul style="list-style-type: none"> • symptoms that can last weeks or months after first being infected with the virus that causes COVID-19 or can appear weeks after infection
Complications	<ul style="list-style-type: none"> • Secondary bacterial infections are more common with influenza than with COVID-19. • Most flu will recover on their own in a few days to two weeks, but some people will experience severe <u>complications</u>. • Diarrhea is more common in young children with flu than in adults with flu. • <u>Covid 19</u>: Blood clots in the veins and arteries of the lungs, heart, legs or brain

Accurate difference
between flu and COVID

testing is needed someone has both the flu and COVID-19 at the same time

- **Multisystem Inflammatory Syndrome in Children**
Ongoing **fever PLUS** more than one of the following:
 - Stomach pain
 - Bloodshot eyes
 - Diarrhea
 - Dizziness or lightheadedness (signs of low blood pressure)
 - Skin rash
 - Vomiting

laboratory analyses

- وجود موارد ذیل به نفع کووید است تا آنفلانزا
- ترومبوسیتوپنی کمتر از ۱۵۰ هزار
 - $WBC < 5000$
 - $LDH > 500$
 - $Ferritin > 500$
- در سی تی اسکن: وجود consolidation و پلورال افیوژن به نفع آنفلانزا است و grand glass به نفع کووید