Colds and Influenza: A Review of Diagnosis and Conventional, Botanical, and Nutritional Considerations

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Abstract

The common cold is the leading cause of doctor visits in the United States and annually results in 189 million lost school days. In the course of one year the U.S. population contracts approximately 1 billion colds. Influenza infection is still a leading cause of morbidity and mortality, accounting for 20-25 million doctor visits and 36,000 deaths per year in the United States. Conventional therapies for colds and flu focus primarily on temporary symptom relief and include over-the-counter antipyretics, anti-inflammatories, and decongestants. Treatment for influenza also includes prescription antiviral agents and vaccines for prevention. This article reviews the common cold and influenza viruses, presents the conventional treatment options, and highlights select botanicals (*Echinacea spp.*, *Sambucus nigra*, larch arabinogalactan, *Astragalus membranaceous*, *Baptisia tinctoria*, *Allium sativa*, *Panax quinquefolium*, *Eleutherococcus senticosus*, *Andrographis paniculata*, olive leaf extract, and *Isatis tinctoria*) and nutritional considerations (vitamins A and C, zinc, high lactoferrin whey protein, N-acetylcysteine, and DHEA) that may help in the prevention and treatment of these conditions. (*Altern Med Rev* 2007;12(1):25-48)

Introduction

The common cold, also referred to as acute viral nasopharyngitis, is a mild, self-limiting infectious disease that can be caused by more than 100 different viruses. Of these, rhinoviruses and coronaviruses are responsible for approximately 50-70 percent of all colds.[1,2] Colds were known to man even in ancient Egypt where they were depicted in hieroglyphs. The Greek physician Hippocrates described the disease as early as the 5th century BC. In 1914, Walter Kruse, a German professor, demonstrated that viruses, not bacteria, cause the common cold,[3] but the finding was not widely accepted until the 1920s when Alphonse Dochez confirmed it in chimpanzees and humans. The term "cold" was likely derived from ancient physicians who described "cold conditions" and "warm conditions" that were dependent on or caused by cold or warm environments. In modern times the misnomer has persisted, possibly due to the viruses' effect on thermogenesis. People are thought to associate the shivering from a viral-induced fever with shivering from being in a cold climate.[4]

Although generally benign in symptomology, cold viruses are the most common infectious diseases humans contract and result in significant costs to the economy in lost workdays and school attendance. Adults average 2-4 colds per year and children 6-10, depending on age and exposure.[5] A 2003 study found common colds resulted in more than 100 million physician visits annually, at a cost of $7.7 billion. At least

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one-third of these patients received an antibiotic, even though they have no effect on viral infections, not only adding to the cost but also contributing to the development of antibiotic resistance. The study also found Americans spend nearly $3 billion annually on over-the-counter drugs that may not provide any symptom relief. In addition, an estimated 189 million school days are missed due to colds, which consequently result in 126 million missed workdays by parents who stay home to care for sick children.[6]

Influenza is an acute respiratory illness caused primarily by the influenza virus (serotypes A and B). It occurs worldwide and is responsible for considerable morbidity and mortality. The first report of what was likely an influenza epidemic was noted in 1173-1174,[7] and the first definitive report occurred in 1694.[8] During the 18th century, data on flu epidemics increased considerably, with comprehensive reports appearing in the 19th century.[7,9-11] Influenza A viruses were first isolated in the laboratory from human specimens in 1933,[12] and in 1957 the virus was made available for laboratory analysis.[13] Subsequent studies have demonstrated the influenza virus mutates rapidly (antigenic drift), creating difficulties each year for researchers trying to develop effective vaccines.[14]

Influenza – usually more severe than the common cold – typically causes fever, headache, muscle aches, and a more significant cough; however, mild cases of influenza are similar to colds. Of the two serotypes, influenza A occurs more frequently and is more dangerous. Although most epidemics and pandemics are caused by influenza A, both A and B serotypes frequently co-circulate during yearly outbreaks. Although influenza B is usually less severe, in children the clinical presentation may be similar to that of influenza A.[15] Influenza-like illness is clinically similar to true influenza but is caused by a virus other than influenza A or B (e.g., the respiratory syncytial virus).[16]

In the United States, influenza epidemics typically occur during the winter months; the influenza "season" stretches from fall to spring in the Northern Hemisphere, with peak activity from December through early March. Between 1990 and 1999, 36,000 deaths per year were attributed to influenza in the United States.[17,18] In influenza epidemic years, 10 percent or more of the population is typically infected, with about 50 percent of those infected showing symptoms.[19] Although influenza viruses infect every age group, children have the highest infection rates. Serious illness and death rates are highest among the elderly, young children under age two, and those with medical conditions placing them at increased risk for influenza complications.[17]

Because of the potential severity and epidemic/pandemic possibilities, the Advisory Committee on Immunization Practices (ACIP) recommends annual immunizations for persons at high risk for influenza-related complications, persons who live with or care for persons at high risk, and health care workers. The objective is that immunizations will prevent hospitalization and/or death and reduce influenza-related respiratory illnesses, decrease physician visits among all age groups, prevent otitis media among children, and decrease work absenteeism.[17]

Incidence and Etiopathology

Common Cold

Although acute upper respiratory tract infections can be attributed to several different viral agents, over 50 percent are caused by rhinoviruses. Coronaviruses account for 10-20 percent, followed by influenza viruses (10-15%) and adenoviruses (5%).[20,21]

Rhinoviruses belong to the Picornaviridae family, (i.e., "pico" for small and "RNA" because they are RNA viruses). Other Picornaviridae family members include enteroviruses and hepadnaviruses (such as hepatitis A); there are over 100 different rhinovirus serotypes.[20]

Rhinovirus infections are typically limited to the nasopharynx but may also affect the middle ear and sinuses. Rhinoviruses grow in a fairly narrow temperature range (33-35° C/91.4-95° F), a range accommodated by the upper respiratory tract. The lower respiratory tract, however, is warmer and consequently inhospitable to the virus. Because rhinoviruses cannot tolerate an acidic environment, the warmer temperature and acidic environment of the stomach render these viruses unlikely to cause gastrointestinal infections.

Although rhinovirus infections can occur anytime, they are more prevalent in the fall and spring; whereas, coronaviruses seem to occur more often in the winter and early spring.[20] Approximately 70-80 percent of exposed individuals present with symptoms.[20] The virus is spread by direct person-to-person contact,

contact with contaminated surfaces (e.g., telephone receivers, stair rails, etc.), and inhalation of large-particle aerosols.

Rhinoviruses bind to intercellular adhesion molecule 1 (ICAM-1) receptor sites on the epithelium of the nasopharynx. Typically the infected areas tend to be isolated, dispersed foci that account for a relatively small portion of epithelium.[22] Infected cells release interleukin-8 (IL-8), a strong chemo-attractant that stimulates the release of inflammatory mediators, such as kinins and prostaglandins. Presence of these substances can increase vasodilation, vascular permeability, and exocrine gland secretion, ultimately leading to classic cold symptoms such as nasal congestion, rhinorrhea, and sneezing. Higher concentration of IL-8 translates to greater intensity of symptoms.[20]

Medical evidence suggests that, despite commonly held beliefs, exposure to cold temperature or getting chilled or overheated does not increase susceptibility to infection. Furthermore, upper respiratory tract abnormalities (e.g., enlarged tonsils or adenoids) are not thought to place an individual at greater risk of contracting a cold. However, studies have demonstrated that psychological stress and allergic conditions affecting the nose and throat influence susceptibility to infection.[23]

Influenza

Although there are three classified serotypes of influenza viruses (A, B, and C), only the previously mentioned A and B types are associated with the human disease most commonly referred to as "the flu." These viruses are divided into various subgroups based on antigenic characteristics. For instance, influenza A viruses are typically divided into two general subtypes that correspond to two different antigens on the surface of the virus: hemagglutinin and neuramidase. Hemagglutinin antigen (HA) is a glycoprotein that allows the virus to bind to cellular sialic acid and fuse with the host membrane. Neuramidase antigen (NA), on the other hand, breaks down sialic acid, allowing the virus to disperse from the infected cell.

Point mutations occur in influenza A and B viruses, resulting in the frequent emergence of new viral strains (antigenic drift). Consequently, antibodies generated to the previous strain have limited protection against an infection of a new variant, placing the body in a constant game of "catch-up" with the virus.

Influenza epidemics are usually associated with a single serotype. However, it is possible for different influenza viruses to appear sequentially in one location or to have multiple influenza strains infect the same area simultaneously.[24] In the United States, an epidemic occurs every 2-3 years, most often caused by influenza A viruses.[24] Influenza B viruses typically produce milder disease and do not undergo antigenic drift as rapidly as influenza A viruses.[25]

Signs and Symptoms

Common Cold

Cold symptoms occur within 1-2 days after inoculation, and peak 2-4 days later, although some accounts report symptoms presenting less than 24 hours after exposure.[20] Symptoms often start with a tickle or soreness in the throat, followed by sneezing, runny nose, nasal congestion, and general malaise. Temperature is usually normal. Nasal discharge is clear, watery, and can be quite profuse initially, subsequently turning more mucoid and purulent. If a cough is present it is generally mild and may persist up to two weeks. A simple, uncomplicated cold usually resolves within 10 days.

Influenza

The incubation period for an influenza infection is 1-4 days. Mild cases of the flu present very much like a common cold (e.g., sore throat, rhinorrhea); mild conjunctivitis may also occur. However, in a typical flu presentation an individual rapidly experiences chills and high fever, prostration, cough, body aches and pains, headache (particularly behind the eyes), increased sensitivity to light, and generalized malaise. Respiratory symptoms include sore throat, coryza, and a productive or non-productive cough. Children may also experience nausea, vomiting, or abdominal pain; infants may present with a sepsis-like syndrome.

Acute symptoms usually subside within 2-3 days, although fever may last up to five days. The illness typically resolves after 3-7 days if no complications are present. However, cough and general malaise can last for weeks. Table 1 compares the characteristics of influenza and the common cold.

Potential Complications

Common Cold

Although most rhinovirus infections are self-limiting, they can act as a secondary insult to the upper respiratory tract in the presence of conditions such as asthma, cystic fibrosis, chronic bronchitis, or any lower respiratory tract illness in infants, elderly, smokers, or immune-compromised patients. The presence of purulent sputum or significant lower respiratory tract symptoms can be indications of more than a simple rhinoviral infection.

One study of 533 individuals (ages 60-90) revealed chronic medical conditions increased the likelihood of lower respiratory complications from rhinovirus infections by 40 percent. Smokers had a 47-percent increased risk of developing complications.[26] Diagnosis of bronchitis usually involves pulmonary function tests, chest x-ray, and possibly a sputum culture.[27]

Viral pneumonia is another potential complication. Usually the pneumonia is mild and resolves without treatment within a few weeks, but some cases are more serious and can require hospitalization. As with bronchitis, populations at risk for developing severe viral pneumonia are those with impaired immune systems, chronic medical conditions, impaired lung function, young children (especially those with heart defects), and the elderly. Diagnosis of viral pneumonia

Table 1. A Comparison of Common Cold and Influenza Characteristics

Feature	Colds	Flu
Etiological Agent	>100 viral strains; rhinovirus most common	3 strains of influenza virus: influenza A, B, and C
Site of Infection	Upper respiratory tract	Entire respiratory system
Symptom Onset	Gradual: 1-3 days	Sudden: within a few hours
Fever, chills	Occasional, low grade (<101° F)	Characteristic, higher (>101° F), lasting 2-4 days
Headache	Frequent, usually mild	Characteristic, more severe
General aches, pains	Mild, if any	Characteristic, often severe and affecting the entire body
Cough, chest congestion	Mild-to-moderate, with hacking cough	Common, may become severe
Sore throat	Common, usually mild	Sometimes present
Runny, stuffy nose	Very common, accompanied by bouts of sneezing	Sometimes present
Fatigue, weakness	Mild, if any	Usual, may be severe and last 2-3 weeks
Extreme exhaustion	Never	Frequent, usually in early stages of illness
Season	Year around, peaks in winter months	Most cases between November and February
Antibiotics helpful?	No, unless secondary bacterial infection develops	No, unless secondary bacterial infection develops

may require blood tests, chest x-ray, and possibly nasopharyngeal or sputum cultures.[27]

A viral infection can also travel to the sinuses or ears and cause excessive mucus secretion. Sinus openings or ear canals can become blocked as mucus accumulates, becoming a breeding ground for bacteria and other organisms. Even if a bacterial infection does develop, antibiotics may not speed recovery of an ear or sinus infection and the infection will usually resolve on its own. It is estimated 80 percent of children with otitis media get better without antibiotics.[28] There is minimal convincing evidence that children prescribed antibiotics for otitis media have shorter symptom duration, fewer recurrences, or better long-term outcomes than those who do not receive antibiotics.[29] Despite this, in the case of ear infections in young children who are very uncomfortable and crying, physicians will often prescribe an antibiotic to placate a stressed parent, even if the physician suspects a viral agent. Unfortunately, over-prescribing systemic antibiotics (particularly penicillin derivatives such as amoxicillin) has resulted in significant antibiotic resistance for the two bacterial pathogens most commonly isolated from the nasopharynx of children with otitis media – *Streptococcus pneumoniae* and *Haemophilus influenza*.[30]

Table 2. Populations at High Risk for Developing Influenza Complications

- Adults ≥65 years
- Children under age 2 years
- Pregnant women
- Residents of long-term care facilities
- Individuals with cardiovascular disease
- Individuals who required regular medical follow-up or hospitalization during the preceding year due to chronic metabolic disorders (e.g., diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (e.g., HIV)
- Individuals suffering from any condition that may compromise respiratory function, the handling of respiratory secretions, or that can increase the risk of aspiration
- Children and adolescents on long-term aspirin therapy (due to risk of Reye's Syndrome)

Although bacterial sinus infections secondary to the common cold usually resolve within two weeks with self-care, antibiotics are often prescribed when a bacterial infection develops. Diagnosis is typically via exam of sinuses and ears with a fiber-optic scope, sinus x-rays, or nasal swab cultures.[27]

Influenza

In addition to the complications observed with the common cold, influenza can on rare occasions result in encephalitis. When the virus enters the bloodstream it can localize in the brain, causing inflammation of brain tissue and membranes. In an effort to fight off the infection, white blood cells invade the brain tissue, causing cerebral edema and destruction of nerve cells, bleeding within the brain, and brain damage. Symptoms can include fever, severe headache, neck stiffness, drowsiness, muscle weakness, or seizures.[31]

Certain population groups have been identified as high risk for influenza and its potential complications. These groups are considered top priority for attention when it comes to prophylactic and treatment measures and are identified in Table 2.

Diagnosis

Because the signs and symptoms of the common cold occur so often, most people are familiar with them and are able to self-diagnose. When a health care provider is seen, diagnosis will likely be via recent patient history, fiber-optic scope examination of the ear, nose, and throat, lymph node palpation, and stethoscope evaluation of the lungs. The provider also determines whether symptoms of more serious respiratory illnesses such as pneumonia or bronchitis are present. Although no laboratory tests are available to detect cold viruses because of myriad viral agents, throat cultures, blood tests, or x-rays can rule out a secondary infection.

Influenza diagnosis based on clinical symptoms alone can be difficult because infections caused by other viral agents, including adenovirus, respiratory syncytial virus, rhinovirus, and parainfluenza viruses, can present with the same early symptoms. Diagnosis involves a recent patient history, checking body temperature, fiber-optic examination of ears, nose and throat, and stethoscopic evaluation of the lungs. During outbreaks of respiratory illnesses in nursing homes, dormitories,

or other closed communities, laboratory testing for influenza can help confirm influenza as the cause of the outbreak.[32]

Preferred samples for influenza testing include nasopharyngeal swab or nasal swab, wash, or aspirate; sample collection should take place within a few days of symptom onset. Results from rapid influenza tests are available in 30 minutes or less, but viral culture can take 3-10 days. Most of the rapid tests are >70-percent sensitive for detecting influenza and >90-percent specific. Viral culture of respiratory samples is the only way to determine which influenza A or B strain is causing illness. Viral culture also allows researchers and epidemiologists to watch for outbreaks of influenza and influenza-like illness in order to develop vaccines for the coming year.[32]

Conventional Prevention and Treatment

Over-the-Counter Treatments

Because colds and influenza are usually self-limiting, treatment tends to focus on reducing symptom duration and intensity and minimizing risk of complications.

For the common cold, a warm and comfortable environment and rest and hydration are often all that is needed. If additional intervention is necessary, over-the-counter anti-inflammatory agents, analgesics, and nasal/oral decongestants can be used for temporary symptom relief.

Potential drawbacks do exist to symptom suppression by over-the-counter medications. For instance, nasal decongestants (e.g., pseudoephedrine, phenylephrine) dry nasal secretions. Although this is the desired effect, an excessively dry mucosa can increase risk of infection, not only in the nasopharynx but the sinuses as well. In addition, when nasal decongestants are used for an extended period of time (more than five consecutive days) and then discontinued, a rebound effect of worsened symptoms can occur due to mucosal dependence on the drug.[33] Furthermore, use of decongestants are contraindicated in patients with cardiovascular disease, hypertension, diabetes, prostatic hypertrophy, and thyroid conditions because decongestants can increase blood pressure, exacerbate thyroid symptoms, and cause difficulty in urination.

Because influenza is often accompanied by a fever, an antipyretic (most frequently aspirin or acetaminophen) is often added to over-the-counter analgesics, antihistamines, and anti-inflammatory agents used for symptom relief. When treating children, however, using aspirin should be avoided because of concerns linking its use to Reye's syndrome.

Fever is an important clinical indicator and is generally a healthy reaction by the body to combat infection and regain homeostasis. Although a low-grade fever (37.2-38.3° C/99-101° F) can facilitate healing, fevers are commonly suppressed for the purpose of patient comfort. Body temperature can rise to 41° C/105.8° F without harm.[34] There are, however, instances when a fever can place the patient at risk and use of antipyretics may be indicated. Several non-pharmacological therapies, such as tepid baths and body sponging, may be employed as alternatives.

Antiviral Agents

Antiviral drugs limit the ability of the influenza virus to infect respiratory epithelial cells and can offer modest symptomatic relief. Although treatment is generally recommended for high-risk patients who develop influenza-like symptoms, there is no evidence these drugs decrease the risk of serious complications in these patients.[24,35] Furthermore, they must be administered within 48 hours of symptom onset to be effective. Although antiviral medications can be used to prevent influenza infection, immunization is the preferred measure for prophylaxis in the conventional medical model. In the United States, four antiviral agents are available for use against influenza: amantadine (Symmetrel®), rimantadine (Flumadine®), zanamivir (Relenza®), and oseltamivir (Tamiflu®).

Amantadine and Rimantadine

Amantadine and rimantadine reduce the duration of uncomplicated influenza A infection by inhibiting virus penetration or uncoating. Adamantine derivatives were the first effective antiviral agents for treatment of influenza. Although some reports claim amantadine or rimantadine can prevent 70-90 percent of influenza A illness, the drugs must be taken from 10 days to six weeks for effectiveness,[36] and are not effective against influenza B infections.

Resistance to amantadine and rimantadine can develop rapidly, rendering the drugs ineffective. Approximately 30 percent of treated individuals start shedding resistant variants 2-5 days after beginning treatment.[36] Although the drug resistance that develops during treatment does not affect the efficacy of treatment for the patient, it can result in transmission of a resistant virus to contacts.[21] To reduce the potential for drug resistance, treatment should be stopped after 3-5 days (or 1-2 days after symptoms resolve).

Side effects such as nervousness and/or insomnia occur in 10 percent of individuals receiving amantadine and two percent receiving rimantadine, and are more prominent in the elderly and in those with CNS disease or impaired renal function. Other possible adverse effects include anorexia, nausea, and constipation.[24] In patients with impaired renal function, dosage is decreased according to creatinine clearance. Rimantadine dosage should not exceed 100 mg/day in patients with hepatic dysfunction.

Zanamivir and Oseltamivir

Zanamivir and oseltamivir are newer anti-influenza drugs that can reduce the duration of uncomplicated influenza A and B infections. These drugs are neuramidase inhibitors, meaning they essentially block the activity of the neuramidase enzyme on the surface of the influenza virus, consequently preventing the spread of the virus to uninfected cells.

Drug resistance with neuramidase inhibitors is also a concern, although not to the same extent as the adamantine derivatives. Fewer adverse side effects are associated with neuramidase inhibitors compared to the adamantine counterparts. Clinical trials on zanamivir and oseltamivir show headache and gastrointestinal disturbance to be the most common side effects (oseltamivir produced occasional nausea and vomiting), with occurrence comparable to that of placebo.[37-40] Although neuramidase inhibitors work on both influenza A and B and are associated with fewer side effects, they are significantly more expensive than adamantine derivatives. Because zanamivir is only available as an orally inhaled powder, it can cause bronchospasm and should be avoided in patients with underlying reactive airway disease.[24,36,41]

Influenza Vaccinations

Although antiviral medications offer preventive support, conventional medicine regards vaccination as the standard of care for preventing influenza and its complications.[25]

Vaccines are typically modified each year to include the most prevalent strains from the previous season: usually two influenza A viruses (e.g., H3N2 and H1N1) and one B virus, as the vaccine is only effective against three particular strains in any given season. When the vaccine contains the same hemagglutinin antigen and/or neuramidase antigen as the strains in the community, vaccination can decrease infections by 70-90 percent in healthy adults under age 65.[24] There are, however, several hundred strains of influenza circulating at any time, and healthy adults are not the population in most need of vaccination.

Interestingly, vaccines appear to be less effective in institutionalized elderly patients. According to the Centers for Disease Control (CDC), even when the match between the vaccine and the circulating virus is close, the efficacy rate of the flu vaccination drops to 30-40 percent for institutionalized individuals over age 65.[32]

A report on the influenza vaccination effect on seasonal mortality in the elderly revealed that, although in the United States the number of individuals age 65 and older getting flu vaccinations increased from 15-50 percent before 1980 to 65 percent in 2001, the actual rate of flu-related deaths did not decline.[42]

Vaccine-induced immunity decreases with antigenic drift; therefore, prior vaccinations provide less or no protection as the viruses mutate. Furthermore, vaccination offers no protection against antigenic shift, which occurs when two different strains of influenza combine to form a new subtype having a mixture of the surface antigens of the two original strains.

Two forms of influenza vaccines are available for administration, an inactivated influenza vaccine and a live attenuated influenza vaccine (LAIV), both of which are antigenically equivalent to the annually recommended strains. Because both vaccines use influenza viruses initially grown in embryonated hens eggs, they may contain trace amounts of residual egg protein and are contraindicated in patients with a history of anaphylactic reactions to chicken or egg protein.[24,25]

Although inactivated influenza vaccines containing killed viruses do not produce signs or symptoms of influenza virus infection, LAIV has the potential to produce mild flu-like signs or symptoms. In the United States, the LAIV is administered intranasally to healthy individuals, ages 5-50 years. The vaccine should not be given to patients in high-risk groups, pregnant women, household contacts of immune-deficient patients, or children receiving chronic aspirin therapy. Children, ages 5-8 years, not previously vaccinated with the LAIV, should receive a second dose at least six weeks after the first dose.

The most common adverse effects associated with flu vaccines range from localized pain at the injection site (for the inactivated vaccine) to rhinorrhea, fever, fatigue, painful joints, and headache.[24,25,43] Guillain-Barre syndrome has been reported as a possible serious adverse effect occurring within two weeks of vaccination.[43] Although some studies assess the risk at 10 cases per million persons vaccinated,[44] it is recommended that individuals with a history of Guillain-Barre syndrome not be vaccinated.[32]

In an interesting blend of conventional treatment and alternative therapies, a small randomized, controlled, eight-week study was conducted on 41 adult participants exploring the alterations in brain and immune function produced by mindfulness meditation. Brain activity was measured before, immediately after, and four months after an eight-week clinical training program in mindfulness meditation. At the end of the eight-week period, subjects in both the experimental and control groups were inoculated with influenza vaccine. Results of the study revealed significant increases in left-sided anterior brain activation and antibody titers to the influenza vaccine in meditators versus non-meditators, indicating meditation might improve one's response to flu vaccines.[45]

Alternative Treatments for Cold and Flu

Nutritional Considerations

Vitamin C

Since the 1940s, numerous studies have suggested high doses of vitamin C both prevent and reduce the effects of the common cold. And, ever since Linus Pauling – a highly respected, two-time Nobel prize winner – advocated large doses of vitamin C in his 1970 bestseller, *Vitamin C and the Common Cold*, interest in vitamin C for treating colds and other viruses has skyrocketed.

A meta-analysis of 29 controlled trials investigated the benefits of ≥200 mg vitamin C daily for the common cold in 11,077 subjects.[46] The meta-analysis revealed vitamin C prophylaxis does appear to reduce the duration and severity of colds, but not the incidence. However, regarding incidence, in a subgroup of six studies in which subjects were under significant physical stress from exercise training in cold northern climates (soldiers, skiers, or marathon runners), subjects on vitamin C prophylaxis demonstrated a 50-percent reduction in incidence of the common cold.[47] The 29-trial meta-analysis also examined the effect of vitamin C prophylaxis on cold duration (n=9,676 colds). Doses of ≥200 mg daily shortened cold duration in children by 14 percent and eight percent in adults. The effect of prophylactic vitamin C on cold severity was examined in several of the trials, (7,045 respiratory episodes) and those taking vitamin C experienced slightly fewer "at home" days than those not taking vitamin C, suggesting a less severe infection.[46] Table 3 summarizes the prevention studies from this meta-analysis for which full text was available.

The meta-analysis also evaluated the efficacy of vitamin C taken at the onset of cold symptoms (for treatment rather than prevention) and found no statistically significant benefit in cold duration or severity,[46] with the exception of one large trial that reported a reduction in duration with 8 g vitamin C at symptom onset.[55] Table 4 summarizes the treatment studies from this meta-analysis for which full text was available.

Table 3. Summary of Vitamin C Studies for Prevention of the Common Cold[48-65]

Year	Authors	Subjects	Type of Study	Duration of Trial	Dosage	Outcome Measured	Outcome
1942	Cowan	363 college students	SBC	2 years	200 mg daily	incidence	No effect on incidence
1944	Dahlberg	2,525 Army personnel	SBC	57 days	200 mg daily for 24 days, then 50 mg daily	incidence, duration	No effect on incidence or duration
1956	Franz	89 medical students & nurses	SBC	3 months	205 mg daily	incidence	No effect on incidence
1961	Ritzel	279 children at ski school	RCT	2 weeks	1 g daily	incidence, duration	Decreased incidence; no effect on duration
1972	Anderson	818 adults	RCT	3 months	4 g daily for 3 days, then 1 g daily	incidence, duration, severity	Significantly decreased incidence and severity
1972	Charleston	90 adults	SBC	15 weeks	1 g daily	incidence, duration	Decreased incidence; slightly decreased duration
1973	Wilson	421 boarding-school children	RCT	9 months	200 mg daily	duration, severity	Decreased severity in girls only
1974	Anderson	2,349 adults	RCT	3 months	250 mg-2 g daily; 3 dosage arms	incidence, duration, severity	No effect on incidence; small effect on duration and severity
1974	Coulehan	641 Navaho children	RCT	14 weeks	1-2 g daily; 2 dosage arms	incidence, duration	No effect on incidence; shortened duration
1975	Carson	263 adults	RCT	40 days	1 g daily	incidence	No effect on incidence
1975	Karlowski	190 adults	RCT	9 months	3 g daily	duration	Slightly decreased duration
1976	Coulehan	868 Navaho children	RCT	15-18 weeks	1 g daily	incidence, duration	No effect on incidence; shortened duration
1976	Elwood	688 adults	RCT	100 days	1 g daily	incidence, duration	Slight decrease in incidence and duration
1977	Ludvigsson	615 school children	RCT	3 months	1 g daily	incidence, duration, severity	No effect on incidence; shortened duration and severity
1977	Miller	44 twin children	RCT	5 months	500 mg-1 g daily; 3 dosage arms	duration, severity	Significantly decreased duration in a subgroup; no effect overall
1979	Pitt	674 Marines	RCT	8 weeks	2 g daily	incidence, duration, severity	No effect on incidence or duration; possible decrease in severity
1981	Carr	95 pairs of adult & adolescent twins	RCT	100 days	1,070 mg daily	incidence, duration, severity	Significantly decreased incidence, duration, and severity
1998	Himmelstein	92 marathon runners & sedentary controls	RCT	2 months	1 g daily	incidence, duration, severity	No benefit on any parameter in marathon runners

* Trials shown are those for which full text was available in English. Several other trials were included in the Douglas meta-analysis.
SBC = Single-blind, randomized, controlled
RCT = Double-blind, randomized, controlled

The following is a summary of meta-analysis conclusions.[46]

Prophylaxis trials (vitamin C given to prevent colds):

Cold incidence: Among all trials included in the meta-analysis (29 total with 11,077 participants) the pooled relative risk (RR) of developing a cold while taking prophylactic vitamin C was 0.96 (95% CI 0.92-1.00) – not a significant difference when compared to placebo. However, in a subgroup of six trials involving 642 soldiers, skiers, and marathon runners exercising in cold climates, individuals on vitamin C prophylaxis had only a 50-percent chance of developing a cold compared to subjects exercising in cold climates and not taking vitamin C (pooled RR: 0.50).

Cold duration: In trial comparisons involving 9,676 respiratory episodes, adults on vitamin C prophylaxis experienced an eight-percent reduction in cold duration compared to placebo, while children on prophylaxis experienced a 15-percent reduction in cold duration compared to placebo.

Cold severity: Pooled analysis of trial comparisons involving 7,045 respiratory episodes among adults and children revealed a modest, yet statistically significant, decrease in cold severity in those taking vitamin C prophylaxis. The main outcomes measured were missed school or work days and mean symptom severity score. However, results were inconsistent and parameters used to measure severity varied greatly among the trials.

Table 4. Summary of Vitamin C Studies for Treatment of the Common Cold[55,58,66-70]

Year	Authors	Subjects	Type of Study	Duration of Trial	Dosage	Outcome Measured	Outcome
1950	Cowan	367 college students	RCT	1st 48 hrs. of symptoms	6 g daily	duration, severity	No significant effect on duration or severity
1974	Anderson	1,760 adults	RCT	1 day	4-8 g daily	duration, severity	No overall effect
1975	Anderson	622 adults	RCT	15 weeks	500 mg weekly; 1.5 g 1st day of symptoms; 1 g days 2 to 5	duration, severity	No effect on duration; significant decrease in severity
1975	Karlowski	190 adults	RCT	Undefined symptomatic period	3 g daily	duration, severity	Small effect on duration and severity
1977	Elwood	1,082 adults	RCT	3-4 days	3 g daily	duration	Small effect on duration in subgroup of men
1977	Tyrell	1,524 adults	RCT	2.5 days	4 g daily	duration, severity	No overall effect
2001	Audera	149 adults	RCT	3 days	1-3 g daily (±flavonoids)	duration, severity	No overall effect

* Trials shown are those for which full text was available in English. Several other trials were included in the Douglas meta-analysis.
RCT = Double-blind, randomized, controlled trial

Therapeutic trials (vitamin C given at onset of a cold):

Cold duration: In an analysis of seven trials involving 3,294 respiratory episodes, vitamin C provided no significant benefit to duration of cold symptoms compared to placebo.

Cold severity: No statistically significant effect of vitamin C on cold severity was observed in treatment groups compared to placebo when four trials involving 2,753 respiratory episodes were analyzed.

One drawback to trials using high-dose vitamin C is that gastrointestinal side effects make it difficult to keep the trials double-blind. Consequently, any effective trial using therapeutic doses of 2-10 g daily is met with skepticism by the conventional medical community.[71] Some of the studies in the meta-analysis showing little or no effect used vitamin C dosages considered "small" by vitamin C advocates (100-500 mg per day).

Another factor is the plasma half-life of high-dose vitamin C, which is approximately 30 minutes.[72] This suggests most studies are methodologically flawed because vitamin C, when not dosed frequently enough, would be expected to show only minimal benefit. The Vitamin C Foundation (formed by a group of highly-regarded physicians and researchers specializing in orthomolecular medicine and headed by Abram Hoffer, MD, PhD) recommends very high doses of vitamin C for the common cold – an initial dosage of up to 8 g every 20-30 minutes.[73] Unfortunately, oral doses of this magnitude are not feasible for most people due to gastrointestinal symptoms, with supplementation often being discontinued. Vitamin C supplementation in large, divided doses over several days is likely to be the most effective at alleviating symptoms or shortening cold duration.

In the case of influenza, few clinical trials have examined the efficacy of vitamin C. In a controlled trial of 226 patients with influenza A, 114 patients received 300 mg vitamin C daily, while 112 patients served as controls; outcomes measured were development of pneumonia and duration of hospital stay. Pneumonia was reported in two cases in the treatment group and 10 in the control group, while hospital stays for influenza or related complications averaged nine days in the vitamin C group and 12 days in the control group.[74]

A two-year, controlled trial of 715 students (ages 18-32) examined the effect of high-dose vitamin C in preventing and relieving the symptoms of viral-induced respiratory infections (colds and flu). In the control group of 463 students, those reporting symptoms were treated with decongestants and pain relievers. The 252 students in the treatment group were divided into those reporting symptoms and those who were asymptomatic. Symptomatic individuals were given hourly doses of 1 g vitamin C for the first six hours, and then 1 g three times daily until symptoms subsided; asymptomatic students received 1 g three times daily throughout the test period. In the test group, vitamin C administration resulted in an 85-percent decrease in cold and flu symptoms compared to the control group. The results of this study are difficult to interpret, however, as the study period was not clearly defined and data did not separate the incidence of colds versus the flu.[75]

Zinc

Zinc plays an important role in maintaining healthy immune function. Human studies have observed even a mild zinc deficiency can elicit changes in immune status, such as defective natural killer (NK) cell function, decreased interleukin-2 production, and anergy.[76]

Zinc supplementation has long been considered an effective means of reducing the duration of the common cold. In a randomized study, 200 healthy children were assigned to receive either oral zinc sulfate (15 mg elemental zinc) or placebo daily for seven months, with an increase to 15 mg twice daily at the onset of a cold. The mean number of colds in the zinc group was statistically significantly fewer than the placebo group (1.2 versus 1.7 colds per child, respectively; p=0.003), while mean cold-related school absences was 0.9 days for the zinc group versus 1.3 days in the placebo group.[77]

Several trials have examined the use of zinc lozenges for colds, with mixed results (Table 5).[78-84] One placebo-controlled, seven-day study observed 65 individuals who took either a loading dose of 46 mg zinc (two zinc gluconate lozenges) followed by 23 mg zinc (one lozenge) or placebo every two wakeful hours until symptoms were absent for six hours. After seven days 86 percent of the zinc group were symptom-free compared to 46 percent of the placebo group (p=0.0005).[78]

Table 5. Zinc Lozenges for Treatment of the Common Cold

Study (year)	Sample Size	Zinc Form	Dosage of Zinc	Study Length	Findings
Kurugol Z, et al. (2006)	200 (n=100 in tx group) school-age children	zinc sulfate syrup	15 mg daily prophylactic; 15 mg twice daily after onset of cold and until symptoms resolved	7 months	Mean no. colds per child: 1.2 (Z) vs 1.7 (P); (p=0.003) Mean no. cold-related absences per child: 0.9 days (Z) vs 1.3 days (P); (p=0.04) Shorter duration of cold symptoms in zinc group vs placebo; (p<0.0001)
McElroy BH, Miller SP (2003)	134 (n=134 in tx group) school-age children; retro. data used as placebo	zinc gluconate glycine lozenges	13.3 mg (1 lozenge) daily as a prophylactic measure; 53.2 mg (4 lozenges) daily at onset of cold signs and/or until symptoms resolved	10/2001-05/2002; pre-1999 records used as placebo data	Mean no. of colds per child: 1.28 (±1.03) (Z) vs 1.7 (±1.9) (P); (p<0.05) Mean duration (days) of cold per child: 6.9 (±3.1) (Z) vs 9.1 (±3.5) (P); (p=0.001)
McElroy BH, Miller SP (2002)	496 (n=119 in tx group) school-age children	zinc gluconate glycine lozenges	13.3 mg (1 lozenge) daily as a prophylactic measure	review of cases from 01/1998-08/2001	Median no. of colds per year: 0.0 vs 1.3; (p<0.001)
Prasad AS, et al. (2000)	48 (n=25 in tx group) adults	zinc acetate lozenges	12.8 mg (1 lozenge) every 2-3 hours	Initiated within 24 hours of onset and continued until symptoms resolved	Mean duration (in days) of cold: 4.5 (±1.6) (Z) vs 8.1 (±1.8) (P); (p<0.01)
Turner RB, Cetnarowski WE (2000)	273 (n=204 in tx groups)* adults w/ induced colds	zinc gluconate glycine lozenges; zinc acetate lozenges (two different potencies)	13.3 mg (1 zinc gluconate lozenge) x 6/d (n=69); 11.5 mg (1 zinc acetate lozenge) x 6/d (n=70); 5 mg (1 zinc acetate lozenge) x 6/d (n=65) *n=69+70+65=204	From onset of cold up to 14 days	Median duration (in days) of cold: zinc gluconate lozenges: 2.5 (Z) vs 3.5 (P); (p=0.035) zinc acetate lozenges: Neither potency had any significant effect. Effect on severity of cold: No difference between zinc preparations and placebo
	281 (n=208 in tx groups)** adults w/ natural colds	zinc gluconate glycine lozenges; zinc acetate lozenges (two different potencies)	13.3 mg (1 zinc gluconate lozenge) x 6/d (n=68); 11.5 mg (1 zinc acetate lozenge) x 6/d (n=68); 5 mg (1 zinc acetate lozenge) x 6/d (n=72) ** n=68+68+72=208	From onset of cold up to 14 days	Effect on duration or severity of cold: No difference between zinc preparations and placebo
Macknin ML, et al. (1998)	249 (n=124 in tx groups) school-age children	zinc gluconate glycine lozenges	10 mg (1 lozenge) three times daily during school hours; Children grades 1-6: 20 mg (2 lozenges) on school nights and 100 mg (5 lozenges) per day on weekends Children grades 7-12: 30 mg (3 lozenges) on school nights and 110 mg (6 lozenges) per day on weekends	From within 24 hours of onset of cold until symptoms absent for 6 hours	No significant difference between zinc group and placebo
Eby GA, et al. (1984)	65 (n=37 in tx group) adults and school-age children	zinc gluconate glycine lozenges	46 mg (2 lozenges) loading dose followed by 23 mg (1 lozenge) every 2 wakeful hours until symptoms absent for 6 hours	7 days	After 7 days, 86% of zinc group were asymptomatic vs 46% of placebo group; (p=0.0005). Zinc lozenge shortened the duration of cold by 7 days.

One study involving 48 adults found zinc acetate lozenges (12.8 mg zinc per lozenge) taken every 2-3 hours while awake reduced the duration of cold symptoms compared to placebo (4.5 versus 8.1 days).[84]

In a seven-month, phase IV trial, 134 school children were given 13.3 mg zinc (one zinc gluconate lozenge) daily as a preventive and 53.2 mg zinc (four zinc gluconate lozenges) daily at cold onset until symptoms resolved. Previously collected data was used as a control. Average cold duration of the zinc group was 6.9±3.1 days versus 9.0±3.5 days for the control group.[80]

Several studies have concluded, however, that zinc lozenges fare no better than placebo.[81-83] One study involving two arms (273 adults with induced colds; 281 adults with natural colds) examined the effects of zinc gluconate (13.3 mg zinc) or zinc acetate (5 or 11.5 mg zinc) lozenges compared to placebo. The treatment groups took six lozenges daily of their respective preparation from cold onset until symptoms resolved, for a maximum of 14 days. The subjects with induced colds

taking zinc gluconate demonstrated a median duration of illness of 2.5 days compared to 3.5 days in the placebo group (p=0.35); no significant change was noted in symptom severity compared to placebo. The zinc acetate group yielded no significant change in cold duration or symptom severity compared to placebo. In the experimental arm involving subjects with natural colds, none of the zinc groups yielded any significant change in duration of cold and/or severity of symptoms compared to placebo.[82]

In another study, the efficacy of zinc gluconate lozenges (10 mg zinc per lozenge) compared to placebo was examined in 249 school children. Lozenges were dosed at one lozenge five times daily (grades 1-6) or six times daily (grades 7-12) from cold onset until symptoms were absent for six hours. No significant differences were noted between the zinc and placebo groups.[83]

A meta-analysis of the effect of zinc gluconate lozenges for the common cold analyzed eight randomized, clinical trials. Although the researchers cited limitations to their analysis (e.g., dependence on the validity of the studies and the fact that their analysis was limited to a single variable [presence of "any" cold symptom after seven days of treatment]), the authors found weak evidence for the efficacy of zinc gluconate lozenges in reducing cold duration.[81]

Differences in zinc preparations, including form (zinc gluconate versus zinc acetate), amount (elemental zinc per lozenge; ranges from 5-23 mg), and composition of the lozenge have been identified as possible explanations why study results are inconsistent.[79,85]

Intranasal zinc preparations are often sold as over-the-counter cold remedies. However, studies have not shown this route of administration to be as effective as lozenges. Two placebo-controlled trials found intranasal zinc gluconate slightly reduced the duration of cold symptoms.[86,87] In one study, 78 adults took 2.1 mg zinc daily (one spray in each nostril four times daily) or placebo for 10 days from cold onset. Mean duration of cold was 4.3 days in the zinc group versus six days in the placebo group (p=0.002).[86] Similarly, another study observed 213 adults taking either 2.1 mg zinc (one spray in each nostril every four hours) or placebo from cold onset until symptoms resolved. Duration of cold was 2.3 days in the zinc group versus nine days in the placebo group (p<0.05).[87]

These findings contrast with two other placebo-controlled studies that found no benefit from zinc nasal spray.[88,89] One study followed 91 individuals with induced colds using either zinc gluconate nasal spray (one spray in each nostril five times daily) or placebo for three days before the challenge and six days after.[88] The second study involved 160 adult participants taking 0.044 mg zinc (zinc sulfate nasal spray) or placebo daily from cold onset until symptoms resolved or up to 14 days.[89] In both cases, the respective researchers concluded that changes in cold duration or symptom severity were no different between the zinc and placebo groups. Table 6 summarizes the studies of zinc nasal spray.

In an interesting footnote, several cases report individuals experiencing loss of the sense of smell (anosmia) after using intranasal zinc as a cold remedy.[90]

Zinc at doses of 30 mg and above can cause stomach upset, nausea, and/or vomiting, which can be reduced when taken with food. Prolonged excessive zinc intake can result in copper deficiency, as documented in a case of zinc gluconate supplementation at 850-1,000 mg per day for one year. Signs and symptoms included fatigue, dyspnea on exertion, anemia, neutropenia, pallor, and orthostatic pulse changes.[91]

Vitamin A

Clinical trials examining vitamin A to boost immunity and treat respiratory infections have yielded conflicting results. The majority of studies have been conducted in children malnourished, underweight, and/or deficient in vitamin A. No consistent benefit has been observed in healthy children or adults with viral-induced respiratory infection.[92,93] One study analyzed the effect of 50,000-100,000 IU vitamin A given as a single dose to children under age five years with pneumonia, a potential cold/flu complication. No significant differences were reported between the treatment and placebo groups with respect to duration of respiratory symptoms.[94]

N-acetylcysteine

N-acetylcysteine (NAC), an ester of the amino acid L-cysteine, is a potent antioxidant.[95] It has been used for over 30 years to treat bronchitis and other lung conditions due to its expectorant and mucolytic properties.[96,97] In a 1988 randomized controlled trial,

Table 6. Zinc Nasal Spray for Treatment of the Common Cold

Study (year)	Sample Size	Zinc Form	Dosage of Zinc	Study Length	Findings
Mossad SB (2003)	78 (n=40 in tx group) adults	zinc gluconate nasal spray (33mmol/L)	2.1 mg/day (1 spray in each nostril 4x/day)	Initiated 24-48 hrs from onset of cold until symptoms resolved or up to 10 days	Mean duration (in days) of cold: 4.3 (Z) vs 6 (P); (p = 0.002) Significant reduction of total symptom scores started from second day of the study; Adverse effects (mainly nasal stinging) similarly reported in both zinc and placebo groups
Belongia EA, et al. (2001)	160 (n=81 in tx group) adults	zinc sulfate nasal spray	0.044 mg/day (2 sprays in each nostril 4x/day)	Initiated at onset of cold until symptoms resolved or up to 14 days	Effect on duration or severity of cold: No difference between zinc preparations and placebo
Turner RB (2001)	91 (n=41 in tx group) adults w/ induced colds	zinc gluconate nasal spray (33mmol/L)	2.1 mg/day (1 spray in each nostril q4h 5x/day)	Initiated 3 days before viral challenge and for 6 days after	No effect on total symptom score, rhinorrhea, nasal obstruction, or proportion of infected volunteers who developed colds compared to placebo
Hirt M, et al. (2000)	213 (n=108 in tx group) (adults)	zinc gluconate nasal spray (33 mmol/L)	2.1 mg/day (1 spray in each nostril q4h)	Initiated within 24 hrs from onset of cold until symptoms resolved	Shorter time to resolution of symptoms in zinc group vs placebo: 2.3 days (Z) vs 9.0 days (P); p<0.05

91 patients with chronic bronchitis were given 300 mg NAC or placebo twice daily for six months. Over the four winter months, subjects in the NAC group experienced a 65-percent reduction in sick leave days from bronchitis exacerbation (173 days versus 456 days in the placebo group), indicating less severe infection in the NAC group.[98]

A larger trial involving 262 elderly subjects investigated the effect of oral NAC prophylaxis on the occurrence and severity of influenza-like episodes and influenza A infection during the cold and flu season. Subjects received 600-mg NAC tablets or placebo twice daily for six months. Over the six-month period, the number of subjects with influenza-like episodes in the NAC group averaged 29 percent, compared to 51 percent in the placebo group. In regard to severity of influenza-like episodes, 72 percent of those in the NAC group who became ill reported mild episodes, 26 percent reported moderate episodes, and two percent reported severe episodes. In the placebo group 48 percent reported mild episodes, 47 percent moderate episodes, and six percent severe episodes, indicating that a greater percent of the placebo group experienced a severe infection. Of the 262 subjects in the study, 65 became infected with influenza A virus. Although infection rates between placebo and NAC groups were similar, only 25 percent of the NAC group who became infected with influenza A was symptomatic compared to 79 percent in the placebo group.[99]

Dehydroepiandrosterone (DHEA)

Influenza is particularly dangerous to older people with weakened immune systems. Age-associated DHEA deficiency may be partially responsible for an age-related decline in immune function.[100,101] One study demonstrated a metabolite of DHEA enhanced

T-helper cell activation and protected mice from a lethal influenza virus infection.[102] Other studies have shown DHEA and its metabolites have powerful immune-enhancing and antiviral effects.[103-105] In elderly men, administration of 50 mg DHEA daily resulted in significant increases in number of monocytes and B-lymphocytes, a 62-percent increase in B-cell activity, a 40-percent increase in T-cell activity, and significant increases in both NK-cell numbers and activity.[101] DHEA may be a hormone to consider for prevention of colds and flu, particularly in the elderly; most studies of DHEA for immune enhancement in the elderly used 50 mg daily.

High Lactoferrin Whey Protein

Whey protein supplementation appears to enhance the immune system,[106] scavenge free radicals,[107] and exhibit antimicrobial activity.[108] Lactoferrin is a peptide fraction of whey with documented antibacterial, antimycotic, antiviral,[109] and immune-modulating effects. Studies have shown lactoferrin is an iron-binding protein[110] that is present in exocrine secretions, including tears, nasal exudates, saliva, and bronchial mucus.[111] Lactoferrin is also a major constituent of circulating polymorphonuclear neutrophils (PMNs)[112] and is released on degranulation in septic areas.[113]

To date, no clinical trials have been conducted on the use of high lactoferrin whey protein to prevent or treat colds or flu, but because of its demonstrated antiviral, antibacterial, and anti-inflammatory properties, it may be of benefit in alleviating the symptoms or complications of these viral infections. The primary function of lactoferrin is to scavenge free iron in fluids and inflamed areas,[114] suppressing free radical-mediated damage and decreasing the availability of the metal to invade microbial and neoplastic cells. Lactoferrin has also been shown to bind to viral receptor sites and inhibit *in vitro* growth of several viruses, including HIV, *Herpes simplex* 1 and 2, hepatitis C, and human cytomegalovirus.[112]

Botanicals for the Prevention and Treatment of Colds and Flu

Echinacea (*Echinacea spp*)

Various species of Echinacea have been identified for generations by traditional herbalists as invaluable medicinal plants.[115,116] Although traditional herbalists used Echinacea for various conditions, from alopecia to cancer, its modern application is primarily for immune support. Today, Echinacea is arguably the most recognized herbal supplement for prevention and treatment of colds and flu. Despite this long history in traditional herbal medicine, or perhaps because of it, Echinacea has come under much scientific scrutiny to determine its effectiveness for colds and flu.

Different species of Echinacea demonstrate immuno-supportive properties. Both *Echinacea purpurea* and *Echinacea angustifolia* appear to activate nonspecific cellular and humoral immunity and the complement system.[117-121] Polysaccharides from *E. purpurea* have been shown *in vitro* to preferentially stimulate the mononuclear immune system and release of interleukin-1 (IL-1).[117] Similarly, *in vitro* studies on arabinogalactans from *E. purpurea* have been observed to induce a dose-dependent release of tumor necrosis factor-alpha (TNF-α) from peritoneal macrophages.[117] In another study, glycoproteins known as arabinogalactan-proteins isolated from *E. pallida* demonstrated marked immunomodulatory effects by stimulating IgM production and proliferation of lymphocytes in mice.[122]

A randomized, double-blind, placebo-controlled trial observed 48 adult female participants over a period of four weeks to determine the immunological activity of various Echinacea preparations and larch arabinogalactan versus placebo.[123] Of the various preparations used in the study, complement properdin (a protein in serum used as a marker for assessing immune response) increased by 21 percent over placebo in participants taking a combination extract of *E. purpurea* and *E. angustifolia* and by 18 percent in subjects taking a combination of *E. purpurea*, *E. angustifolia*, and larch arabinogalactan. The other forms did not provoke a significant response.

Clinical studies have shown mixed results regarding Echinacea's effect on reduction and duration of symptoms associated with common cold, influenza, and other acute respiratory infections. One randomized, double-blind, placebo-controlled study involving 282

adults examined the effect of an Echinacea formulation (0.25 mg/mL alkamides, 2.5 mg/mL chicoric acid, and 25 mg/mL polysaccharides=1 unit) or placebo for seven days from cold onset. The dosage was 10 units on the first day of cold symptoms, followed by four units per day for the next seven days. Total daily symptom severity scores, recorded on a 10-point scale (0=minimum; 9=maximum), were 23.1-percent lower in the Echinacea group compared to placebo ($p<0.01$).[124]

In a related placebo-controlled trial on 150 adults using the same Echinacea formula (dosage=eight 5-mL units on the first day and three units daily on subsequent days for the next seven days), researchers observed decreased daily symptom scores and increases in the number of total white blood cells, monocytes, neutrophils, and NK cells in the Echinacea group versus placebo.[125]

In another placebo-controlled, blinded study assessing changes in cold duration, 80 adult participants were randomly assigned to take *E. purpurea* herb extract or placebo at the onset of cold symptoms until symptoms subsided. The median duration of illness was six days in the Echinacea group compared to nine days in the placebo group ($p=0.0112$).[126]

Conversely, some studies have reported no statistically significant improvement from Echinacea for the common cold.[127-130] For example, in a randomized, double-blind, placebo-controlled trial, 148 college students were given an encapsulated mixture of unrefined *E. purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) or placebo; 1 g doses were taken six times on the first day of a cold and three times daily on each subsequent day for a maximum of 10 days. There were no significant differences in severity or duration of symptoms between the Echinacea and placebo groups.[131] In another placebo-controlled trial, 128 adults were administered 100 mg *E. purpurea* or placebo three times daily until cold symptoms were relieved, up to a maximum of 14 days, with no statistical difference observed between the two groups.[130]

There is a clear controversy within the established scientific community regarding the efficacy of Echinacea. Differences in study results might be associated with the preparation used in a given study (*E. purpurea*, *E. angustifolia*, or *E. pallida*, or a combination), the part of the plant used, and the method of extraction. Nevertheless, there is sufficient evidence to warrant further investigation of Echinacea for immune support.

Elderberry (*Sambucus nigra*)

Sambucus nigra is a member of the Caprifoliaceae or honeysuckle family. Extracts of the berries are used primarily as antiviral agents for colds, influenza, and Herpes virus infections. Research demonstrates *Sambucus nigra* possesses immune-modulating and antioxidant properties.[132,133] Constituents of the berries include the flavonoids quercetin and rutin, anthocyanins identified as cyanidin-3-glucoside and cyanidin-3-sambubioside,[134] the hemagglutinin protein *Sambucus nigra* agglutinin III (SNA-III),[135] cyanogenic glycosides including sambunigrin,[136,137] viburnic acid, and vitamins A and C.[133]

The antiviral properties of elderberry were first studied by Mumcuoglu, an Israeli virologist, who demonstrated elderberry constituents neutralize the activity of the hemagglutinin spikes found on the surface of several viruses, including influenza A and B and the Herpes virus. When these hemagglutinin spikes are deactivated, the viruses can no longer pierce cell walls or enter the cell and replicate.[138] Elderberry extracts also exert an immune-modulating effect by enhanced cytokine production, which activates phagocytes and facilitates movement to inflamed tissues.[139] Elderberry anthocyanin flavonoids also possess significant antioxidant potential.[140] Although no clinical trials have been conducted, the German Commission E reports that constituents of Sambucus provide effective relief for colds, fevers, and catarrh.[141] Anecdotal reports indicate elderberry extracts can shorten the duration or lessen the severity of the common cold, particularly when used in combination with vitamin C and zinc.

Two randomized, double-blind, placebo-controlled studies demonstrate the elderberry extract, Sambucol, effectively inhibits both influenza A and B strains when given orally to patients in the first 48 hours of influenza symptoms. In one study, 27 individuals (23 with laboratory confirmation of influenza B) experiencing typical early flu symptoms were given Sambucol ($n=15$) or placebo ($n=12$) daily for three days – two tablespoons (30 mL) for children or four tablespoons (60 mL) for adults – and symptoms were monitored for six days. Serum from all subjects was analyzed for antibodies to influenza A and B at the initial dose and during the convalescent phase. While differences in antibody titers between the two groups did not reach statistical

significance, a trend in favor of the treatment group was observed. Clinically however, significant improvement in flu symptoms was observed in 14 of 15 subjects in the treatment group two days after initial dosing, with complete symptom resolution in 13 of 15 subjects after three days. In the placebo group, complete symptom resolution was only achieved by 4 of 12 subjects within three days and 5 of 12 subjects after five days.[142]

In a second study, 60 patients (ages 18-54 years) experiencing early influenza symptoms were given 15 mL (1 tablespoon) Sambucol or placebo syrup four times daily for five days; symptoms were monitored for eight days. In the treatment group, the majority of patients reported "pronounced improvement" after an average of 3-4 days, while the placebo group required 7-8 days to reach the same level of improvement.[143]

Garlic (*Allium sativa*)

Although clinical research examining garlic's effect on colds and flu is minimal, one study did evaluate an allicin-containing garlic supplement on cold incidence and duration in 146 volunteers. Subjects received one capsule daily for 12 weeks between November and February, and symptoms were assessed via a symptom diary using a five-point scale. In the garlic-supplemented group, 24 colds were reported compared to 65 in the placebo group; the treatment group experience shorter duration of cold symptoms compared to placebo – 1.5 versus 5.0 days, respectively.[144]

Panax quinquefolium

Panax quinquefolium (North American ginseng) has been shown in controlled trials to reduce the incidence, duration, and severity of colds and flu in both ill and healthy individuals. A four-month study that commenced at the beginning of cold and flu season evaluated 323 healthy adults (ages 18-65 years) with a history of at least two colds the previous year. Those in the treatment group received two 200-mg capsules daily of a standardized extract of *P. quinquefolium* containing 80-percent poly-furanosyl-pyranosyl-saccharides, while the placebo group received 200 mg rice powder (encapsulated) twice daily. Outcomes measured were number of colds, symptom severity, and total number of symptomatic days. In patients taking the ginseng extract the mean number of reported colds was reduced by 9.2 percent, and the risk of developing a cold was reduced by 12.8 percent compared to the placebo group. In addition, the ginseng group reported a 31-percent lower symptom score (severity) and 34.5-percent fewer symptom days (duration) than the placebo group.[145]

In a second study using a proprietary extract containing highly concentrated poly-furanosyl-pyranosyl-saccharides, 43 community-dwelling elderly adults were given 200-mg capsules of the extract or placebo twice daily for four months. One month into the study, all participants received an influenza vaccination. During the first two months, incidence and duration of respiratory infections did not differ significantly between the two groups. During the last two months, however, 32 percent of subjects taking the herbal formula reported an upper respiratory tract infection compared to 62 percent in the placebo group. In addition, the treatment group reported average symptom duration of 5.6 days compared to 12.6 days in the placebo group.[146]

A Combination of *Eleutherococcus senticosus* and *Andrographis paniculata*

A combination of *Eleutherococcus senticosus* and *Andrographis paniculata* was found effective for influenza infections. The combination formula, also known as Kan Jang®, was studied in a pilot trial involving 540 adults with influenza. Subjects (n=71) were given two tablets containing standardized extracts of Andrographis (88.8 mg) and Eleutherococcus (10.0 mg) three times daily for 3-5 days, while individuals using conventional antiviral medications (n=469) – amantadine or other physician-preferred medication – served as the control group. Primary outcome measures were severity of disease (measured by development of complications) and disease duration (measured by number of days on sick leave). In the herbal formula group, 30.1 percent progressed to complicated influenza compared to 67.8 percent in the control group. Likewise, those in the herbal group experienced a shorter duration of symptoms (approximately 6-7 days) compared to 9-10 days in the control group.[147]

A second phase of the trial, involving 66 influenza patients (n=31 herbal treatment; n=35 controls [conventional treatment]) using the same protocol, revealed comparable results. Days on sick leave were significantly fewer in the herbal group (7.2 days) than in

the control group (9.2 days). In addition, 31.4 percent of patients in the herbal-treatment group developed post-influenza complications, while that rate more than doubled to 71.0 percent in the control group. These studies appear to indicate Kan Jang extract is an effective herbal therapy that may be superior to conventional antiviral medications for reducing severity and duration of influenza infections.[147]

Larch Arabinogalactans

Larch arabinogalactans, polysaccharides derived from the wood of *Larix occidentalis* (Western larch), stimulate the immune system by activating phagocytosis and potentiating the effect of the reticuloendothelial system. Because of these properties, larch arabinogalactans may be an effective adjunct for the treatment of colds and flu.[148,149]

Recurrent otitis media is common in pediatric populations and a frequent complication of colds. Improving immune system function might lead to a decrease in both frequency and severity of this common complication. Research has demonstrated larch and other arabinogalactans enhance the immune response to bacterial infection via stimulation of phagocytosis, competitive binding of bacterial fimbriae, or bacterial opsonization. D'Adamo reports a decrease in occurrence and severity of otitis media in pediatric patients supplemented prophylactically with larch arabinogalactan.[148] Larch arabinogalactan's mild taste and excellent solubility in water and juice make it a relatively easy therapeutic tool to employ in pediatric populations.[148]

Olive Leaf Extract

Constituents of the olive tree, *Olea europaea*, have been studied and utilized in folk medicine for centuries. Olive leaf extract, derived from the leaves of the olive tree, contains phenolic compounds, specifically oleuropein, that have demonstrated potent antimicrobial, antioxidant, and anti-inflammatory activity. Oleuropein and derivatives such as elenolic acid have been shown to be effective in *in vitro* and animal studies against numerous microorganisms, including retroviruses, coxsackie viruses,[150] influenza, and parainfluenza 3,[150,151] as well as some bacteria.[152] Research suggests that olive leaf constituents interact with the protein of virus particles and reduce the infectivity and inhibit replication of viruses known to cause colds, influenza, and lower respiratory infection.[150,151,153] Olive leaf extract has also been shown to stimulate phagocytosis, thereby enhancing the immune response to viral infection. Anecdotal reports indicate olive leaf extract taken at the onset of cold or flu symptoms prevents or shortens the duration of the disease. For viral sore throats, gargling with olive leaf tea may alleviate symptoms, possibly by decreasing inflammation and viral infectivity.

Astragalus (*Astragalus membranaceus*)

Astragalus membranaceus has traditionally been used as a tonic and treatment for colds and flu, either alone or in conjunction with other herbs.[154] Astragalus is rich in polysaccharides, flavonoids, multiple trace minerals, and amino acids, all of which contribute to its immuno-supportive properties. Animal studies demonstrated oral administration of Astragalus root extract to mice infected with Japanese encephalitis virus increased survival rates by 30-40 percent compared to 20 percent in the untreated control group.[155] The researchers attribute this to increased phagocytic activity.

In a small, double-blind, placebo-controlled trial participants took oral extracts of *Echinacea purpurea*, *Astragalus membranaceus*, or *Glycyrrhiza glabra* singly, a combination of the three herbs, or placebo twice daily for seven days, to determine whether intake of the herbal tinctures (singly and/or in combination) stimulated activation and/or proliferation of immune cells. Of the herbs tested, Astragalus demonstrated the strongest activation and proliferation of immune cells, particularly CD8 and CD4 T-cells, compared to placebo. Furthermore, the combination herbal formula demonstrated an additive effect regarding activation, but not proliferation, of T-cells.[156]

Baptisia (*Baptisia tinctoria*) in Combination with other Herbs

A randomized, double-blind, placebo-controlled trial of 238 subjects with acute cold symptoms demonstrated that a formula of *Baptisia tinctoria* root (30 mg), *Echinacea purpurea* root (22.5 mg), and *Thuja occidentalis* leaf (6 mg) three times daily for 7-9 days significantly reduced intensity and duration of symptoms compared to placebo. In subjects who suffered from moderate-symptom intensity at baseline, at least 50-percent improvement by day 5 was experienced in

55.3 percent of the treatment group compared to 27.3 percent of the placebo group (p=0.017).[157] Therapeutic benefit of the herbal formula was noted on day 2, reached significance (p=0.05) on day 4, and continued to improve until the end of the treatment.[157]

Isatis (*Isatis tinctoria; Isatis indigotica*)

Both the leaf and root of Isatis have been used for centuries in traditional medicine for the treatment of various infections, including upper respiratory infections, influenza, encephalitis, and gastroenteritis.[158] Isatis is listed in both old and new Chinese pharmacopoeias, and is considered an effective antipyretic and anti-inflammatory.[159] The antimicrobial action of the root is similar in action to berberine.[159] *In vitro* and human studies from China have shown Isatis root extract to be antibacterial, antiviral, and antiparasitic.[158]

Animal studies indicate Isatis polysaccharide increases total white blood cell and lymphocyte counts in peripheral blood, and antagonizes the immuno-suppressive actions induced by hydrocortisone, indicating Isatis is capable of increasing humoral and cellular immune function.[160]

Conclusion

Common cold viruses and influenza infections are leading causes of doctor visits in the United States, afflicting a significant portion of the population. The common cold, although relatively mild in symptomology and severity, accounts for a significant number of lost work or school days. Influenza, although considered a preventable disease, accounts for 36,000 deaths annually in the United States. Although vaccinations and antiviral drugs can be helpful in prevention and treatment of influenza, their scope and effectiveness are limited. Consequently, most conventional interventions for colds and flu involve symptomatic relief with over-the-counter medications. Natural therapeutics in the form of nutritional supplementation and immune-stimulating and antiviral botanicals can support the body's natural defenses, potentially decreasing the incidence of colds and flu, shortening the duration and decreasing the intensity of symptoms, and preventing complications.

References

1. Gwaltney JM Jr. The common cold. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases: Volume 1*. 4th ed. London, UK: Churchill Livingstone; 1995:561-566.
2. Durand M, Joseph M. Infections of the upper respiratory tract. In: Braunwald E, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 15th ed. New York, NY: McGraw-Hill; 2001:187-193.
3. Tyrell D, Fielder M. *Cold Wars: The Fight Against the Common Cold*. New York, NY: Oxford University Press, USA; 2002:253.
4. http://en.wikipedia.org/wiki/Common_cold [Accessed December 12, 2006]
5. Gwaltney JM Jr. Rhinoviruses. In: *Viral Infection of Humans: Epidemiology and Control*. 4th ed. Evans AS, Kaslow RA, eds. New York, NY: Plenum Press; 1997:815-838.
6. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med* 2003;163:487-494.
7. Hirsch A. *Handbook of Geographical and Historical Pathology*. London, UK: New Sydenham Society; 1883.
8. Molineux T. Dr. Molineux's historical account of the late general coughs and colds: with some observations on other epidemic distemper. *Philosophical Transactions of Royal Society of London* 1694;18:105-109.
9. Thompson ES. *Influenza*. London, UK: Percival; 1890.
10. Creighton C. *A History of Epidemics in Britain*. London, UK: Cambridge University Press; 1894.
11. Finkler D. Influenza in twentieth century practice. In: Shipman TL, ed. *An International Encyclopaedia of Modern Medical Science*. London, UK: Sampson Law & Marston; 1899.
12. Smith W, Andrewes CH, Laidlaw PP. A virus obtained from influenza patients. *Lancet* 1933;2:66-68.
13. Chu CM, Shao D, Hou CC. Studies of strains of influenza virus isolated during the epidemic in 1957 in Changchun. *Vopr Virusol* 1957;2:278-281.
14. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. *Br Med Bull* 1979:35:69-75.
15. Immunisation against infectious diseases. In: *The Green Book: Influenza Update*; 2006: Chapter 19. Department of Health. www.dh.gov.uk [Accessed December 13, 2006]

16. NICE (2003c) *Final appraisal determination: oseltamivir and amantadine for the prophylaxis of influenza.* National Institute for Health and Clinical Excellence. www.nice.org.uk [Accessed December 13, 2006]
17. http://www.cdc.gov/flu/professionals/background.htm [Accessed December 14, 2006]
18. http://www.influenza.com/index.cfm?FA=FAQ_5 [Accessed December 14, 2006]
19. Potter CW. A history of influenza. *J Appl Microbiol* 2001;91:572-579.
20. Rajnik M, Murray C, Hospenthal DR. Rhinoviruses. http//www.emedicine.com/MED/topic2030.htm [Accessed December 27, 2006]
21. Beers MH, Porter RS, Jones TV, et al. eds. The Common Cold (Upper Respiratory Infection). *The Merck Manuals Online Medical Library*. Whitehouse Station, NJ: Merck Research Laboratories; http://www.merck.com/mmpe/sec14/ch188/ch188c.html?qt=common%20cold&alt=sh [Accessed December 27 2006]
22. van Kempen M, Bachert C, Van Cauwenberge P. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology* 1999:37:97-103.
23. National Institutes of Health: National Institute of Allergy and Infectious Diseases. http://www3.niaid.nih.gov/healthscience/healthtopics/colds/ [Accessed December 26, 2006]
24. Beers MH, Porter RS, Jones TV, et al, eds. Influenza. *The Merck Manuals Online Medical Library*. Whitehouse Station, NJ: Merck Research Laboratories; www.merck.com/mmpe/sec14/ch188/ch188d.html#sec14-ch188-ch188d-2292 [Accessed December 27, 2006]
25. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2005;54e:1-40. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr54e713a1.htm [Accessed December 12, 2006]
26. Nicholson KG, Kent J, Hammersley V, Cancio E. Risk factors for lower respiratory complications of rhinovirus infections in elderly people living in the community: prospective cohort study. *BMJ* 1996;313:1119-1123.
27. *MedLine Plus Medical Encyclopedia*: http://www.nlm.nih.gov/medlineplus/ency/article/000073.htm) [Accessed December 15, 2006]
28. Marcy SM. General information and practitioner guidelines for otitis media. APUA Newsletter. 1999;http://www.tufts.edu/med/apua/PractitionersAOMguidelines.html. [Accessed January 23, 2007]
29. Froom J, Culpepper L, Jacobs M, et al. Antimicrobials for acute otitis media? A review from the International Primary Care Network. *BMJ* 1997;315:98-102.
30. Brook I, Gober AE. Antimicrobial resistance in the nasopharyngeal flora of children with acute otitis media and otitis media recurring after amoxicillin therapy. *J Med Microbiol* 2005;54:83-85.
31. *MedLine Plus Medical Encyclopedia*: http://www.nlm.nih.gov/medlineplus/ency/article/001415.htm [Accessed December 15, 2006]
32. Advisory Committee on Immunization Practices, Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-10):1-42.
33. MedicineNet, Inc. 1996-2005: http://www.medterms.com/script/main/art.asp?articlekey=4505&pf=3&page=1 [Accessed January 24, 2007]
34. Drwal-Klein LA, Phelps SJ. Antipyretic therapy in the febrile child. *Clin Pharm* 1992;11:1005-1021.
35. Ressel GW. ACIP releases 2002 guidelines on the prevention and control of influenza. Advisory Committee on Immunization Practices. *Am Fam Physician* 2002;66:894,896,899-900.
36. Townsend KA, Eiland LS. Combating influenza with antiviral therapy in the pediatric population. *Pharmacotherapy* 2006;26:95-103.
37. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med* 1997;337:874-880.
38. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J* 2000;19:410-417.
39. GlaxoSmithKline. Relenza (zanamivir) package insert. Research Triangle Park, NC; 2003. http://us.gsk.com/products/assets/us_relenza.pdf [Accessed February 9, 2007]
40. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J* 2001;20:127-133.
41. *Drug Facts and Comparisons*. St. Louis, MO: Wolters Kluwer Health, Inc; 2004:542.
42. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005;165:265-272.
43. Fisher BL. *The Vaccine Reaction*. Vienna, VA: The National Vaccine Information Center; Spring 2004:1-7.

44. Kimmel SR. Vaccine adverse events: separating myth from reality. *Am Fam Physician* 2002;66:2113-2120.
45. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med* 2003;65:564-570.
46. Douglas RM, Hemila H. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev* 2004;4:CD000980.
47. Hemila H. Vitamin C supplementation and respiratory infections: a systematic review. *Mil Med* 2004;169:920-925.
48. Cowan DW, Diehl SH, Baker AB. Vitamins for the prevention of colds. *JAMA* 1942;120:1268-1271.
49. Dahlberg G, Engel A, Rydin H. The value of ascorbic acid as a prophylactic against common colds. *Acta Med Scand* 1944;119:540-561.
50. Franz WL, Heyl HL, Sands GW. Blood ascorbic acid level in bioflavonoid and ascorbic acid therapy of common cold. *J Am Med Assoc* 1956;162;1224-1226.
51. Ritzel G. Critical evaluation of vitamin C as a prophylactic and therapeutic agent in colds. *Helv Med Acta* 1961;28:63-68. [Article in German]
52. Anderson TW, Reid DB, Beaton GH. Vitamin C and the common cold: a double-blind trial. *Can Med Assoc J* 1972;107:503-508.
53. Charleston SS, Clegg KM. Ascorbic acid and the common cold. *Lancet* 1972;1:1401-1402.
54. Wilson CW, Loh HS, Foster FG. Common cold symptomatology and vitamin C. *Eur J Clin Pharmacol* 1973;6:196-202.
55. Anderson TW, Suranyi G, Beaton GH. The effect on winter illness of large doses of vitamin C. *Can Med Assoc J* 1974;111:31-36.
56. Coulehan JL, Reisinger KS, Rogers KD, Bradley DW. Vitamin C prophylaxis in a boarding school. *New Engl J Med* 1974;290:6-10.
57. Carson M, Cox H, Corbett M, Pollitt N. Vitamin C and the common cold. *J Soc Occup Med* 1975;25:99-102.
58. Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold. A prophylactic and therapeutic trial. *JAMA* 1975;231:1038-1042.
59. Coulehan JL, Eberhard S, Kapner L, et al. Vitamin C and acute illness in Navajo school children. *N Engl J Med* 1976;295:973-977.
60. Elwood PC, Lee HP, St Leger AS, et al. A randomized controlled trial of vitamin C in the prevention and amelioration of the common cold. *Br J Prev Soc Med* 1976;30:193-196.
61. Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a preventive medicine against common colds in children. *Scand J Infect Dis* 1977;9:91-98.
62. Miller JZ, Nance WE, Norton JA, et al. Therapeutic effect of vitamin C. A co-twin control study. *JAMA* 1977;237:248-251.
63. Pitt HA, Costrini AM. Vitamin C prophylaxis in marine recruits. *JAMA* 1979;241:908-911.
64. Carr AB, Einstein R, Lai LY, et al. Vitamin C and the common cold: a second MZ Cotwin control study. *Acta Genet Med Gemellol (Roma)* 1981;30:249-255.
65. Cowan DW, Diehl HS. Antihistaminic agents and ascorbic acid in the early treatment of the common cold. *J Am Med Assoc* 1950;143:421-424.
66. Anderson TW, Beaton GH, Corey P, Spero L. Winter illness and vitamin C: the effect of relatively low doses. *Can Med Assoc J* 1975;112:823-826.
67. Elwood PC, Hughes SJ, Leger AS. A randomized controlled trial of the therapeutic effect of vitamin C in the common cold. *Practitioner* 1977;218:133-137.
68. Tyrrell DA, Craig JW, Meada TW, White T. A trial of ascorbic acid in the treatment of the common cold. *Br J Prev Soc Med* 1977;31:189-191.
69. Audera C, Patulny RV, Sander BH, Douglas RM. Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial. *Med J Aust* 2001;175:359-362.
70. Himmelstein SA, Robergs RA, Koehler KM, et al. Vitamin C supplementation and upper respiratory tract infections in marathon runners. *J Exer Physiol Online* 1998;1:1-21.
71. Hemila H. Do vitamins C and E affect respiratory infections? University of Helsinki, Dissertation, Faculty of Medicine, Department of Public Health; 2006.
72. Padayatty SL, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med* 2004;140:533-537.
73. Vitamin C as a cold cure. Vitamin C Foundation. http://www.vitamincfoundation.org/surefire.htm [Accessed June 2006]
74. Kimbarowski JA, Mokrow NJ. Colored precipitation reaction of the urine according to Kimbarowski (FARK) as an index of the effect of ascorbic acid during treatment of viral influenza. *Dtsch Gesundheitsw* 1967;22:2413-2418. [Article in German]
75. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. *J Manipulative Physiol Ther* 1999;22:530-533.
76. Kaplan J, Hess JW, Prasad AS. Impairment of immune function in the elderly: association with mild zinc deficiency. In: *Essential and Toxic Elements in Human Health and Disease*. New York, NY: Alan R. Liss; 1988:309-317.
77. Kurugol Z, Akilli M, Bayram N, Koturoglu G. The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. *Acta Paediatr* 2006;95:1175-1181.

78. Eby GA. Zinc lozenges: cold cure or candy? Solution chemistry determinations. *Biosci Rep* 2004;24:23-39.
79. Hulisz D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc (Wash DC)* 2004;44:594-603.
80. McElroy BH, Miller SP. Effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) against the common cold in school-aged subjects: a retrospective chart review. *Am J Ther* 2002;9:472-475.
81. Jackson JL, Lesho E, Peterson C. Zinc and the common cold: a meta-analysis revisited. *J Nutr* 2000;130:1512S-1515S.
82. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000;31:1202-1208.
83. Macknin ML, Piedmonte M, Calendine C, et al. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998;279:1962-1967.
84. Prasad AS, Fitzgerald JT, Bao B, et al. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;133:245-252.
85. Eby GA. Zinc ion availability – the determinant of efficacy in zinc lozenge treatment of common colds. *J Antimicrob Chemother* 1997;40:483-493.
86. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *QJM* 2003;96:35-43.
87. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000;79:778-780, 782.
88. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001;33:1865-1870.
89. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001;111:103-108.
90. Linus Pauling Institute. http://lpi.oregonstate.edu/infocenter/minerals/zinc/ [Accessed: January 6, 2007]
91. Walsh CT, Sandstead HH, Prasad AS, et al. Zinc: health effects and research priorities for the 1990s. *Environ Health Perspect* 1994;102:S5-S46.
92. Rahman MM, Mahalanabis D, Alvarez JO, et al. Effect of early vitamin A supplementation on cell-mediated immunity in infants younger than 6 mo. *Am J Clin Nutr* 1997;65:144-148.
93. Fitch C, Neville J. Vitamin A and respiratory infections in children. *Nutr Res* 2002;22:795-806.
94. Rodriguez A, Hamer DH, Rivera J, et al. Effects of moderate doses of vitamin A as an adjunct to the treatment of pneumonia in underweight and normal-weight children: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 2005;82:1090-1096.
95. Roes EM, Raijmakers MT, Peters WH, Steegers EA. Effects of oral N-acetylcysteine on plasma homocysteine and whole blood glutathione levels in healthy, non-pregnant women. *Clin Chem Lab Med* 2002;40:496-498.
96. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. *J Int Med Res* 1984;12:198-206.
97. Grassi C, Morandini GC. A controlled trial of intermittent oral acetylcysteine in the long-term treatment of chronic bronchitis. *Eur J Clin Pharmacol* 1976;9:393-396.
98. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *Eur Respir J* 1988;1:351-355.
99. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *Eur Respir J* 1997;10:1535-1541.
100. Dharia S, Parker CR Jr. Adrenal androgens and aging. *Semin Reprod Med* 2004;22:361-368.
101. Khorram O, Vu L, Yen SS. Activation of immune function by dehydroepiandrosterone (DHEA) in age-advanced men. *J Gerontol A Biol Sci Med Sci* 1997;52: M1-M7.
102. Padgett DA, Loria RM, Sheridan JF. Endocrine regulation of the immune response to influenza virus infection with a metabolite of DHEA-androstenediol. *J Neuroimmunol* 1997;78:203-211.
103. Ben-Yehuda A, Danenberg HD, Zakay-Rones Z, et al. The influence of sequential annual vaccination and of DHEA administration on the efficacy of the immune response to influenza vaccine in the elderly. *Mech Ageing Dev* 1998;102:299-306.
104. Danenberg HD, Ben-Yehuda A, Zakay-Rones Z, Friedman G. Dehydroepiandrosterone (DHEA) treatment reverses the impaired immune response of old mice to influenza vaccination and protects from influenza infection. *Vaccine* 1995;13:1445-1448.
105. Degelau J, Guay D, Hallgren H. The effect of DHEAS on influenza vaccination in aging adults. *J Am Geriatr Soc* 1997;45:747-751.
106. Bounous G, Batist G, Gold P. Immunoenhancing property of a dietary whey protein in mice: role of glutathione. *Clin Invest Med* 1989;12:154-161.

107. Tong LM, Sasaki S, McClements DJ, Decker EA. Mechanisms of the antioxidant activity of a high molecular weight fraction of whey. *J Agric Food Chem* 2000;48:1473-1478.
108. Min S, Harris LJ, Krochta JM. Antimicrobial effects of lactoferrin, lysozyme, and the lactoperoxidase system and edible whey protein films incorporating the lactoperoxidase system against *Salmonella enterica* and *Escherichia coli* O157:H7. *J Food Sci* 2005;7:332.
109. Orsi N. The antimicrobial activity of lactoferrin: current status and perspectives. *Biometals* 2004;17:189-196.
110. Rodriguez-Franco DA, Vazquez-Moreno L, Ramos-Clamont Montfort G. Antimicrobial mechanisms and potential clinical application of lactoferrin. *Rev Latinoam Microbiol* 2005;47:102-111. [Article in Spanish].
111. van der Strate BW, Beljaars L, Molema G, et al. Antiviral activities of lactoferrin. *Antiviral Res* 2001;52:225-239.
112. Valenti P, Berlutti F, Conte MP, et al. Lactoferrin functions: current status and perspectives. *J Clin Gastroenterol* 2004;38:S127-S129.
113. Ward PP, Uribe-Luna S, Conneely OM. Lactoferrin and host defense. *Biochem Cell Biol* 2002;80:95-102.
114. Conneely OM. Antiinflammatory activities of lactoferrin. *J Am Coll Nutr* 2001;20:389S-395S.
115. Felter HW, Lloyd JU. *King's American Dispensatory, Volume 1*. 18th ed. Sandy, OR: Eclectic Medical Publications; 1983:671-677.
116. Ellingwood F. *American Materia Medica, Therapeutics and Pharmacognosy, Volume 2*. Sandy, OR: Eclectic Medical Publications; 1983:358-376.
117. Bauer R, Wagner H. Echinacea species as potential immunostimulatory drugs. *Econ Med Plant Res* 1991;5:253-321.
118. Willard T. *Textbook of Advanced Herbology*. Alberta, Canada: Wild Rose College of Natural Healing Ltd; 1992:85-86.
119. Blumenthal M. *The Complete German Commission E Monographs*. Austin, TX: American Botanical Council; 1998:122-123.
120. Murray MT. *The Healing Power of Herbs*. 2nd ed. Rocklin, CA: Prima Publishing; 1995:92-107.
121. Murray MT, Pizzorno J. *Encyclopedia of Natural Medicine*. 2nd ed. Rocklin, CA: Prima Publishing; 1998:159-160.
122. Classen B, Thude S, Blaschek W, et al. Immunomodulatory effects of arabinogalactan-proteins from Baptisia and Echinacea. *Phytomedicine* 2006;13:688-694.
123. Kim LS, Waters RF, Burkholder PM. Immunological activity of larch arabinogalactan and Echinacea: a preliminary, randomized, double-blind, placebo-controlled trial. *Altern Med Rev* 2002;7:138-149.
124. Goel V, Lovlin R, Barton R, et al. Efficacy of a standardized Echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2004;29:75-83.
125. Goel V, Lovlin R, Chang C, et al. A proprietary extract from the Echinacea plant (*Echinacea purpurea*) enhances systemic immune response during a common cold. *Phytother Res* 2005;19:689-694.
126. Schulten B, Bulitta M, Ballering-Bruhl B, et al. Efficacy of *Echinacea purpurea* in patients with a common cold. A placebo-controlled, randomised, double-blind clinical trial. *Arzneimittelforschung* 2001;51:563-568.
127. Grimm W, Muller HH. A randomized controlled trial of the effect of fluid extract of *Echinacea purpurea* on the incidence and severity of colds and respiratory infections. *Am J Med* 1999;106:138-143.
128. Turner RB, Bauer R, Woelkart K, et al. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med* 2005;353:341-348.
129. Schwarz E, Parlesak A, Henneicke-von Zepelin HH, et al. Effect of oral administration of freshly pressed juice of *Echinacea purpurea* on the number of various subpopulations of B- and T-lymphocytes in healthy volunteers: results of a double-blind, placebo-controlled cross-over study. *Phytomedicine* 2005;12:625-631.
130. Yale SH, Liu K. *Echinacea purpurea* therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004;164:1237-1241.
131. Barrett BP, Brown RL, Locken K, et al. Treatment of the common cold with unrefined Echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:939-946.
132. Lust J. *The Herb Book*. Reading, PA: Cox and Wyman Ltd.; 1974:174.
133. Duke JA. *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press; 1985:423.
134. Wu X, Cao G, Prior RL. Absorption and metabolism of anthocyanins in elderly women after consumption of elderberry or blueberry. *J Nutr* 2002;132:1865-1871.
135. Mach L, Scherf W, Ammann M, et al. Purification and partial characterization of a novel lectin from elder (*Sambucus nigra* L.) fruit. *Biochem J* 1991;278:667-671.
136. Jensen SR, Nielsen BJ. Cyanogenic glucosides in *Sambucus nigra* L. *Acta Chem Scand* 1973;27:2661-2662.
137. Buhrmester RA, Ebingerla JE, Seigler DS. Sambunigrin and cyanogenic variability in populations of *Sambucus canadensis* L. (Caprifoliaceae). *Biochem Syst Ecol* 2000;28:689-695.

138. Personal communication with Madeleine Mumcuoglu, MD; January 25, 2005.
139. Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. *Immuno Biology 5. The Immune System in Health and Disease*. New York, NY: Garland Publishing; 2001:12-13.
140. Abuja PM, Murkovic M, Pfannhauser W. Antioxidant and prooxidant activities of elderberry (*Sambucus nigra*) extract in low-density lipoprotein oxidation. *J Agric Food Chem* 1998;46:4091-4096.
141. Blumenthal M. *The Complete German Commission E Monograph*; American Botanical Council, Austin, TX; 1998:124.
142. Zakay-Rones Z, Varsano N, Zlotnik M, et al. Inhibition of several strains of influenza virus *in vitro* and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. *J Altern Complement Med* 1995;1:361-369.
143. Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res* 2004;32:132-140.
144. Josling P. Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. *Adv Ther* 2001;18:189-193.
145. Predy GN, Goel V, Lovlin R, et al. Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial. *CMAJ* 2005;173;1043-1048.
146. McElhaney JE, Goel V, Toane B, et al. Efficacy of COLD-fX in the prevention of respiratory symptoms in community-dwelling adults: a randomized, double-blinded, placebo controlled trial. *J Altern Complement Med* 2006;12:153-157.
147. Kulichenko LL, Kireyeva LV, Malyshkina EN, Wikman G. A randomized, controlled study of Kan Jang versus amantadine in the treatment of influenza in Volgograd. *J Herb Pharmacother* 2003;3:77-93.
148. D'Adamo P. Larch arabinogalactan. *J Naturopathic Med* 1996;6:33-37.
149. Slavin J, Feirtag J, Robinson R, Causey J. Physiological effects of arabinogalactan in human subjects. Unpublished research.
150. Renis HE. *In vitro* antiviral activity of calcium elenolate. *Antimicrobial Agents Chemother (Bethesda)* 1969;9:167-172.
151. Soret MG. Antiviral activity of calcium elenolate on parainfluenza infection of hamsters. *Antimicrobial Agents Chemother (Bethesda)* 1969;9:160-166.
152. Tranter HS, Tassou SC, Nychas GJ. The effect of the olive phenolic compound, oleuropein, on growth and enterotoxin B production by *Staphylococcus aureus*. *J Appl Bacteriol* 1993;74:253-259.
153. Privatera JR. *Olive Leaf Extract: A New/Old Healing Bonanza for Mankind*. 1st ed. Covina, CA: Nutriscreen, Inc.; 1996.
154. McKenna D, Hughes K, Jones K. Astragalus. *Altern Ther Health Med* 2002;8:34-40.
155. Kajimura K, Takagi Y, Ueba N, et al. Protective effect of Astragali radix by oral administration against Japanese encephalitis virus infection in mice. *Biol Pharm Bull* 1996;19:1166-1169.
156. Brush J, Mendenhall E, Guggenheim A, et al. The effect of *Echinacea purpurea*, *Astragalus membranaceus* and *Glycyrrhiza glabra* on CD69 expression and immune cell activation in humans. *Phytother Res* 2006;20:687-695.
157. Henneicke-von Zepelin H, Hentschel C, Schnitker J, et al. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double blind, placebo controlled, multicentre study. *Curr Med Res Opin* 1999;15:214-227.
158. Benske D, Gamble A. *Chinese Herbal Medicine Materia Medica*. Seattle, WA: Eastland Press; 1986.
159. Huang KC. *The Pharmacology of Chinese Herbs*. Boca Raton, FL: CRC; 1999:400-401.
160. Xu YM, Lu PC. Experimental studies on immunostimulatory effects of the *Isatis indigotica* polysaccharide. *Zhong Xi Yi Jie He Za Zhi* 1991;11:357-359,325-326. [Article in Chinese]