

# Mechanisms of symptoms of the common cold and influenza

*The symptoms of colds and flu are well known by everyone, but the mechanisms causing the symptoms are poorly understood despite a great increase in our knowledge of the viruses involved.*

**A**cute upper respiratory tract infection (URTI) with cold and influenza (flu) viruses is the most common disease of mankind, yet our understanding of the mechanisms that generate the familiar symptoms is poor. It is important to understand the symptoms of URTI, as early diagnosis of influenza is essential for any therapy and for isolation of infected cases. There is also evidence that the immune response that generates the symptoms may also be responsible for much of the morbidity and mortality associated with emerging infections such as pandemic influenza.

## Is it a cold or flu?

The common cold and flu are syndromes of familiar symptoms caused by viral infection of the upper respiratory tract. It is difficult to define the syndromes because of great variation in the severity, duration and types of symptoms that may be experienced by those affected. Rhinoviruses account for 30–50% of all colds. Coronaviruses are the second most common agent and account for 10–15% of colds. Influenza viruses account for 5–15% of colds, and colds viruses such as respiratory syncytial virus (RSV) are responsible for much flu-like illness, demonstrating that there is considerable overlap in aetiology and symptomatology between the common cold and flu syndromes.

The common cold syndrome is a short mild illness, with early symptoms of headache, sneezing, chilliness and sore throat, and later symptoms of nasal discharge, nasal obstruction, cough and malaise. The severity of symptoms peaks within 2–3 days of infection, with a mean duration of symptoms of 7–10 days, although some symptoms may persist for more than 3 weeks. Colds in the adult are rarely associated with fever (Eccles, 2005).

The influenza syndrome typically has a sudden onset and is characterized by fever, headache, cough, sore throat, myalgia, nasal congestion, weakness and loss of appetite. The best predictors for influenza are cough and fever, as this combination of symptoms has been shown to have a positive predictive value of around 80% in differentiating influenza from a population suffering from flu-like symptoms.

Avian influenza virus has been reported to attach to receptors in the lower airway. This may explain why H5N1 viruses at present rarely infect and spread between

humans, although they can replicate efficiently in the lungs and cause lower airway symptoms such as cough (Shinya et al, 2006).

## Symptomatology

The immune response to infection, rather than damage to the airway, may be the main factor generating the symptoms of URTI; this may explain the severe symptoms associated with exposure to novel respiratory viruses (Kobasa et al, 2004). Experimental rhinovirus infections are not associated with any morphological changes in the nasal epithelium of infected volunteers, apart from a significant increase in polymorphonuclear leucocytes early in the course of the infection (Winther et al, 1984).

A complex mix of pro-inflammatory cytokines and mediators generates the symptoms of URTI (Eccles, 2000). The triggering of symptoms can be divided into two components, as shown in *Figure 1*: a local response to cellular damage that causes the generation of mediators such as bradykinin and prostaglandins; and a systemic response caused by cytokines released from macrophages and neutrophil granulocytes.

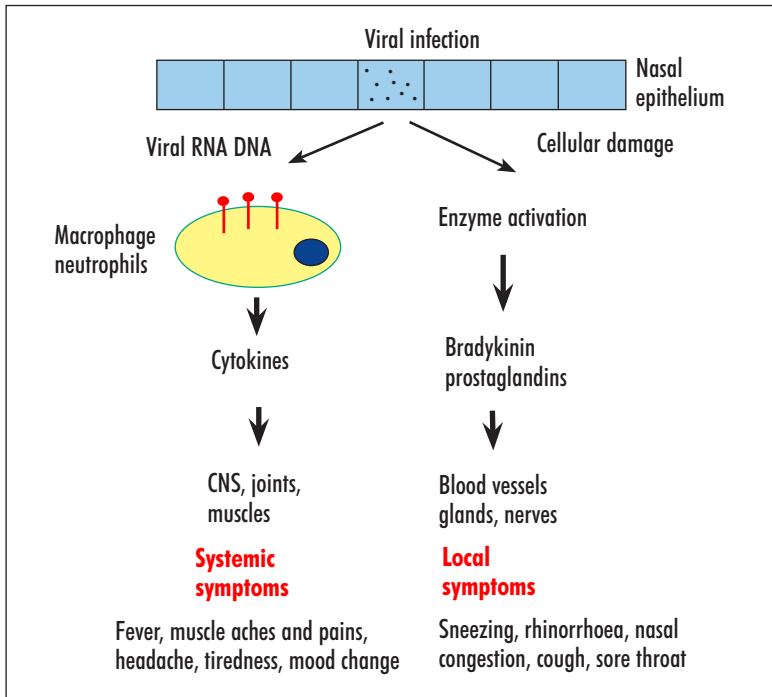
The inflammatory mediators bradykinin and prostaglandins are believed to play a major role in generating the local symptoms of URTI such as sore throat and nasal congestion (Eccles, 2000). Cytokines are believed to be responsible for the systemic symptoms such as fever (Conti et al, 2004).

The mechanisms that generate the symptoms of URTI are the main topic of this review. Each symptom will be discussed in turn.

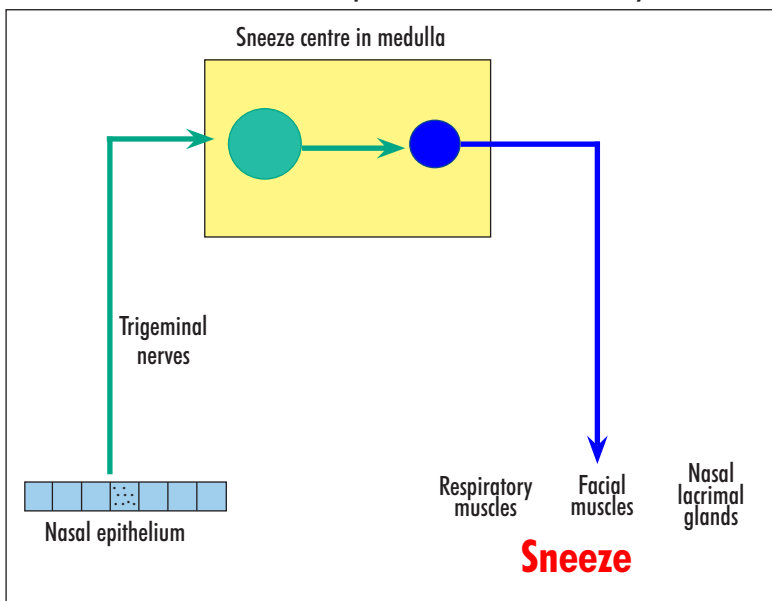
## Sore throat

Sore throat is often the first symptom of URTI and may be related to early viral infection of the nasopharynx rather than the nasal epithelium. The sensation of throat irritation in URTI may be caused by the formation of bradykinin in the airway, as intranasal administration of bradykinin in healthy volunteers has been shown to cause symptoms of rhinitis and a sore throat (Proud et al, 1988). Throat irritation may develop into more severe

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**Figure 1.** Viral infection triggers symptoms by two pathways. Local symptoms are caused by bradykinin and prostaglandins generated in the nasal epithelium. Systemic symptoms are caused by cytokines released from macrophages and neutrophil granulocytes when viral RNA and DNA combine with toll-like receptors on the surface of the leucocytes.



**Figure 2.** Sneezing is caused by stimulation of trigeminal sensory nerves in the nasal epithelium. The trigeminal nerves provide a sensory input to the ‘sneeze centre’ in the medulla. This triggers reflex activation of the nasal and lacrimal glands to cause rhinorrhoea, the facial muscles to cause closure of the eyes and grimace, and the respiratory muscles to cause inspiration followed by an explosive expiration.

sore throat pain associated with nasopharyngitis, pharyngitis or tonsillitis, and these conditions may be associated with secondary bacterial infection. The symptom of sore throat is most likely to be caused by the actions of prostaglandins and bradykinin on sensory nerve endings in the airway.

**Sneezing**

Sneezing is mediated solely by the trigeminal nerves that supply the nasal epithelium and the anterior part of the nasopharynx with sensory fibres. The sneeze response may be mediated via histamine-1 (H1) receptors on the trigeminal nerves, as intranasal administration of histamine causes sneezing. A model of the sneeze reflex is shown in *Figure 2*. The sneeze centre coordinates the inspiratory and expiratory actions of sneezing via respiratory muscles, and lacrimation and nasal congestion via parasympathetic branches of the facial nerve. Eye closure during sneezing indicates a close relationship between the protective reflexes of the nose and eyes. Sneezing activates parasympathetic pathways to nasal glands, and anticholinergics such as ipratropium and first-generation antihistamines have been shown to inhibit sneezing (Eccles et al, 1995).

**Runny nose**

Nasal discharge associated with URTI is a complex mixture derived from glands, goblet cells, plasma cells and plasma exudates from capillaries (Eccles, 1983). A watery nasal secretion is an early symptom of URTI and is often accompanied by sneezing. This early phase of nasal secretion is triggered by irritation of the trigeminal nerves and is derived from nasal glands under parasympathetic cholinergic control. Anticholinergic medication such as ipratropium inhibits nasal secretions in the first 4 days of a common cold (Hayden et al, 1996). A protein-rich plasma exudate derived from subepithelial capillaries is a later cause of nasal discharge and is not inhibited by anticholinergic agents (Eccles, 1983).

**Nasal congestion**

Nasal congestion is caused by dilatation of large veins in the nasal epithelium (venous sinuses) in response to the generation of vasodilator mediators of inflammation such as bradykinin and prostaglandins (Eccles, 2003). These veins are well developed at the anterior end of the inferior turbinate and nasal septum where congestion of the veins in the narrow nasal valve region causes obstruction of the nasal airway. One side of the nose may become completely obstructed in the common cold, with the blockage alternating from one side to the other over a period of 2–4 hours as an exaggerated form of the normal nasal cycle of airflow. A computed tomography (CT) scan of a patient with URTI is shown in *Figure 3*; this demonstrates the asymmetry of congestion of the inferior turbinate associated with the nasal cycle.

**Sinus pain**

The paranasal sinuses surround the nasal airway, and URTI is usually a form of rhinosinusitis (Gwaltney et al, 1994). A fluid level in the maxillary sinus, as shown in *Figure 3*, is a common finding in patients with URTI, yet

these patients will not have clinical sinusitis. Sinus pain may be related to pressure changes in the sinus air space. Obstruction of the ostia of the paranasal sinuses causes gas absorption from the sinuses and 'vacuum maxillary sinusitis'. The ostium of the maxillary sinus is shown in *Figure 3* and there is a tendency to obstruction on the more congested side of the nose. Sinuses with patent ostia may also be painful, indicating that the generation of inflammatory mediators within the sinus may be sufficient to trigger the sensation of pain by stimulation of pain nerve fibres.

### Watery eyes

Watery eyes (epiphora) is a common symptom of URTI (Annamalai et al, 2003). Inflammation of the nasolacrimal duct causes obstruction of drainage, accumulation of tears and the symptom of watery eyes. Obstruction of the duct may be caused by swelling of the veins in the duct, as illustrated in *Figure 4*. The mechanism of nasolacrimal duct congestion is similar to that of nasal obstruction, as the network of veins in the duct connects with the venous network in the inferior turbinate.

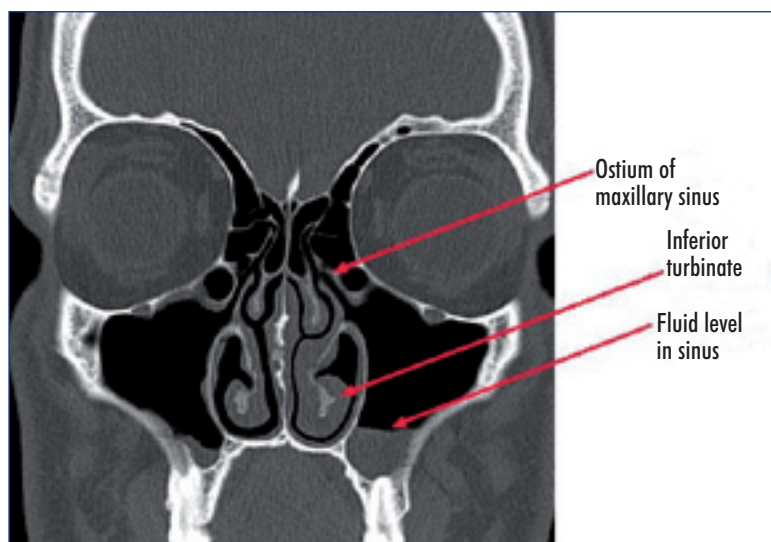
### Cough

Cough is a common symptom of URTI and may persist for three or more weeks (Jones and Stewart, 2002). It is the largest single cause of consultation in primary care (Morice, 2002). Cough is mediated exclusively by the vagus nerve, which means that it is initiated in the airway by stimulation of sensory nerves at the level of the larynx or below. A model of cough control is shown in *Figure 5*. The vagus nerve also supplies the external ear, oesophagus and abdominal organs, and cough can be elicited from stimulation of sensory nerves in these areas, as with cough associated with gastro-oesophageal reflux (Morice, 2002).

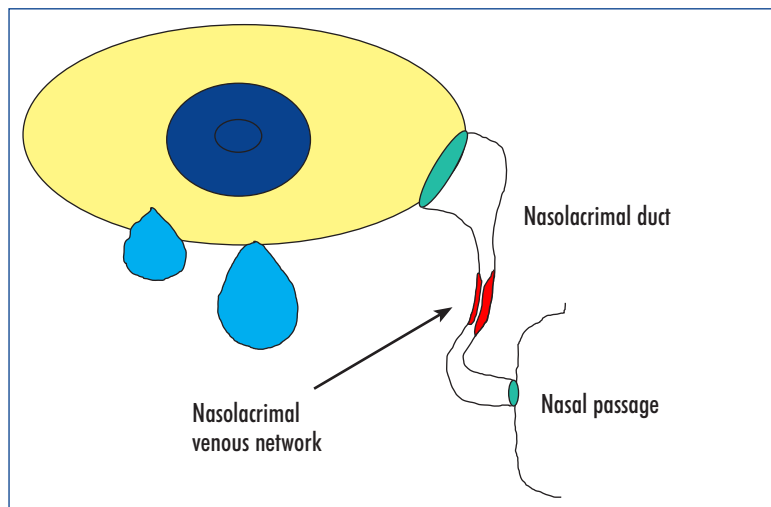
Cough associated with URTI is usually a dry unproductive cough that serves no useful function and may cause loss of sleep and exhaustion. It is believed to be caused by hyperreactivity of the cough reflex resulting from the effects of inflammatory mediators on sensory nerve endings in the airway.

### Headache

The mechanism of headache associated with URTI is unknown, but it may be caused by cytokines released from immune cells in response to viral infection (Smith, 1992). The administration of cytokines involved in the immune response to infection, such as tumour necrosis factor (TNF) and interferons, has been shown to produce headache in humans (Smith, 1992). The mechanism of cytokines-induced headache is unknown, but it is interesting that it is accompanied by symptoms such as fatigue, anorexia, malaise, nausea and depression – all of which are commonly associated with URTI.



**Figure 3.** A 2 mm-thick coronal computed tomographic scan of the nose in a person with the common cold. A fluid level is seen in the maxillary sinus. Note the asymmetry of congestion of the nasal turbinates because of the nasal cycle.



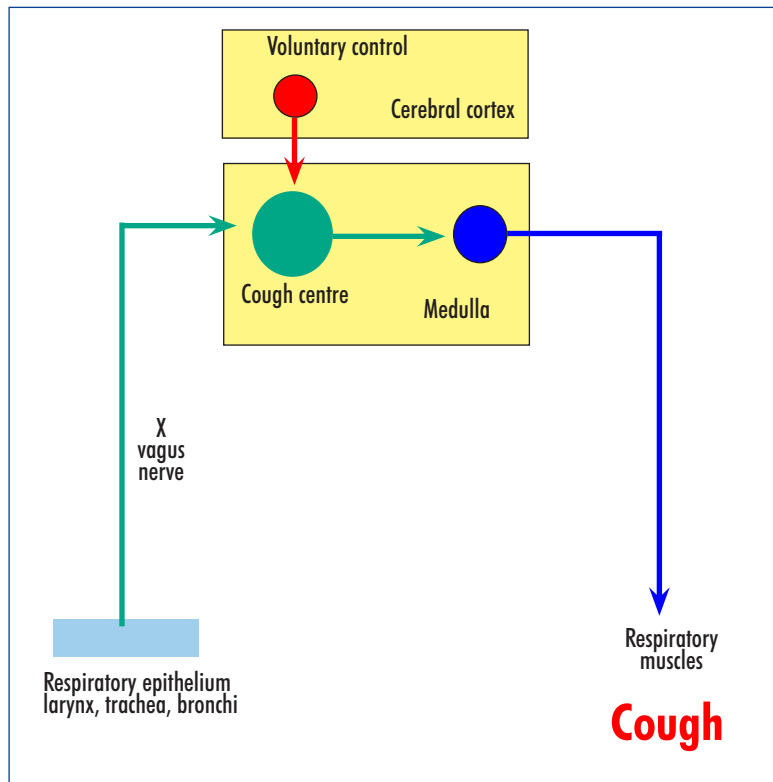
**Figure 4.** Watery eyes (epiphora) caused by congestion of the veins in the nasolacrimal duct.

### Chilliness and fever

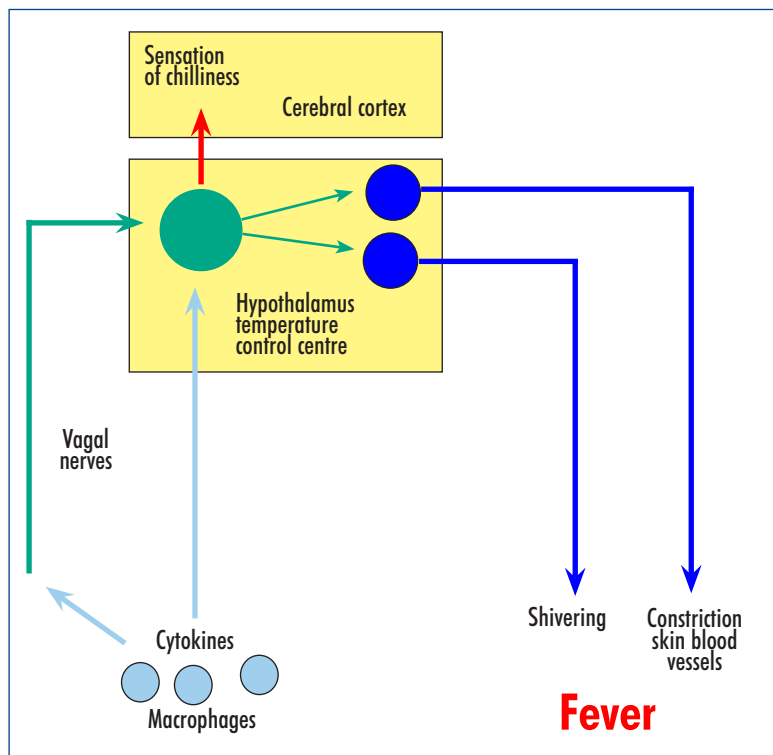
Common cold in the adult is rarely accompanied by fever. The sensation of chilliness may be unrelated to any change in skin or body temperature, as it still develops when a normal skin temperature is maintained (Guieu and Hellon, 1980). The sensation of chilliness may be a central sensation closely linked to the control of shivering and fever.

Fever is usually associated with novel or severe viral infections, especially emerging viral infections where the virus is novel to the host. Cytokines released from macrophages and other leucocytes in response to infection have pyretic and antipyretic effects (Conti et al, 2004). Interleukin-1 (IL-1) and interleukin-6 (IL-6) are believed to be the most important fever-inducing cytokines (Leon, 2002). Cytokines are believed to cross the blood–brain barrier and interact with the peripheral vagus nerve endings to signal the temperature control centre of the

**Figure 5.** Cough associated with upper respiratory tract infection is caused by hyperreactivity of cough receptors in the airway. Cough can also be initiated and inhibited by voluntary control, indicating some control of cough from higher centres such as the cerebral cortex.



**Figure 6.** Fever is caused by cytokines released from macrophages and other immune cells. The cytokines may act on vagal nerve endings or enter the brain to cause a resetting of the temperature control centre in the hypothalamus. The hypothalamus then initiates shivering and constriction of skin blood vessels, and also a sensation of chilliness that is perceived at the level of the cerebral cortex.



hypothalamus to increase the thermal set point. The hypothalamus then initiates shivering, constriction of skin blood vessels, and a sensation of chilliness, as illustrated in *Figure 6*. Fever is a primitive response found in all animals and the rise in body temperature may help to counteract infection.

**Psychological effects, malaise and mood changes**

The symptoms of URTI such as nasal congestion, runny nose and cough may cause discomfort, attention deficit and mood changes, but there is increasing evidence that the psychological changes associated with URTI may also be caused by the effects of cytokines on the central nervous system (Mahoney and Ball, 2002). Cytokines, including TNF, IL-1, IL-2 and IL-6, have been reported to induce the syndrome of ‘sickness behaviour’ with anhedonia, cognitive dysfunction, anxiety/irritability, psychomotor slowing, anergia/fatigue, anorexia, sleep alterations and increased sensitivity to pain (Capuron and Miller, 2004). The mood depression and lack of drive may aid recovery from URTI by inhibiting activity and thereby conserving energy.

**Anorexia**

Loss of appetite is a common finding in URTI, and has entered the folklore as advice to ‘feed a cold and starve a fever’. Decreased food and water consumption are the most common signs of infection associated with fever (Exton, 1997). Anorexia may be caused by cytokines released from leucocytes in response to infection. In support of the folklore advice to starve a fever, the evidence indicates that acute anorexia in response to infection is beneficial and that it is an important behavioural response to help overcome infection. Anorexia may help to eliminate infection by saving energy that would otherwise be used in finding food, and by reducing the availability of micronutrients such as iron and zinc, which are essential for the growth of pathogens.

**Muscle aches and pains**

Myalgia is a symptom of the acute phase response to infection. There is evidence that this symptom is caused by the effects of cytokines on skeletal muscle (Baracos et al, 1983). TNF was initially referred to as ‘cachetin’ because of its role in causing muscle wasting or ‘cachexia’. The breakdown of muscle protein in response to URTI can be viewed as beneficial as it mobilizes proteins and amino acids that can be converted in the liver to opsonins and other components of the immune response.

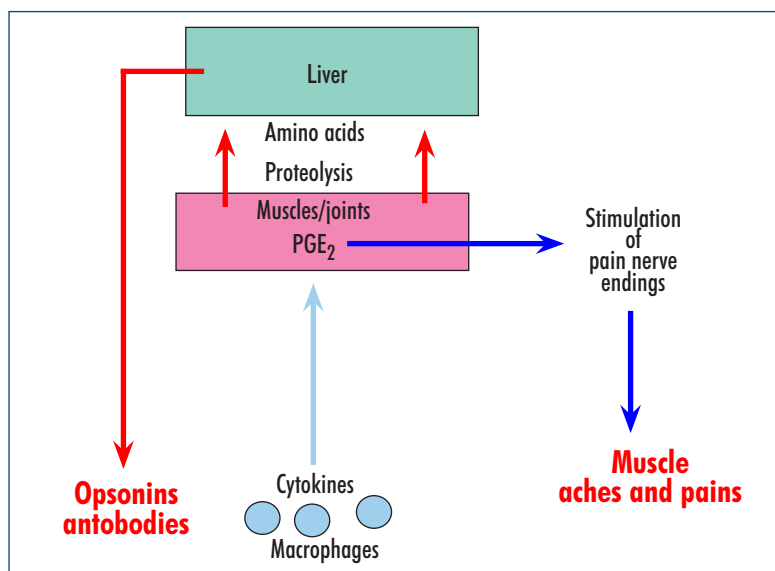
Fever associated with URTI is usually accompanied by other systemic symptoms such as myalgia; there is evidence that both fever and myalgia are caused by the formation of prostaglandin E<sub>2</sub> in response to circulating cytokines, as shown in *Figure 7*.

## Conclusions

Symptoms of the common cold and influenza are generated by the immune response to infection. Some of these symptoms, such as fever and anorexia, may aid recovery from infection, but if the immune response is exaggerated by some special property of the virus such as a novel antigenic surface then the immune response may itself be responsible for much morbidity and mortality. An understanding of how the immune response generates symptoms is important for the treatment of mild infections such as the common cold, and is vital for controlling the severe symptoms caused by exposure to emerging infections such as avian influenza. **BJHM**

*Conflict of interest: none.*

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**Figure 7. Muscle aches and pains are caused by the breakdown of muscle and joint proteins by prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), which also stimulates pain nerve endings. PGE<sub>2</sub> production is stimulated by cytokines released from macrophages and neutrophils in the nasal epithelium.**

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## KEY POINTS

- There is much overlap between the symptoms of colds and influenza.
- Cough and fever are more often associated with influenza than with colds.
- The immune response, rather than tissue damage, may be responsible for influenza morbidity and mortality.
- Symptoms are caused by local mediators (bradykinin and prostaglandins) and by systemic mediators (cytokines).
- Fever, chilliness, anorexia, myalgia and mood changes are caused by cytokines and these symptoms may aid recovery from infection.
- Sore throat, sinus pain, nasal discharge, watery eyes, nasal congestion and cough are caused by local mediators.