感染在過敏氣喘病人的角色

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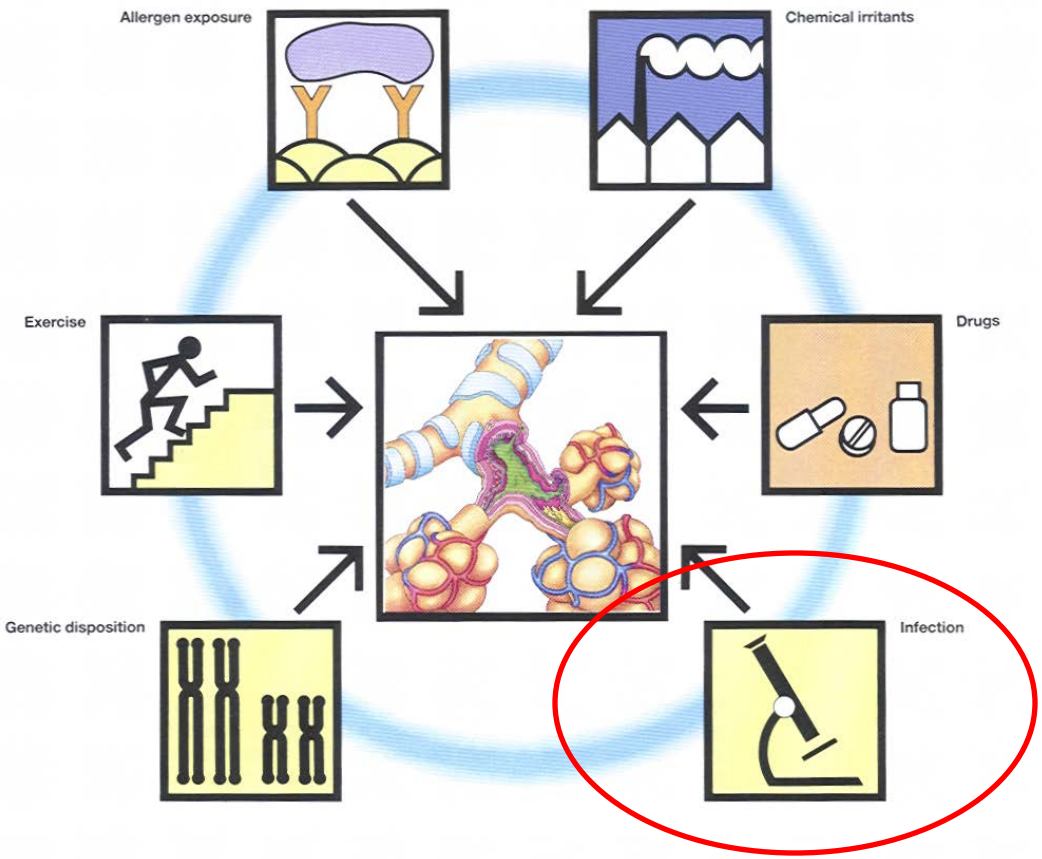
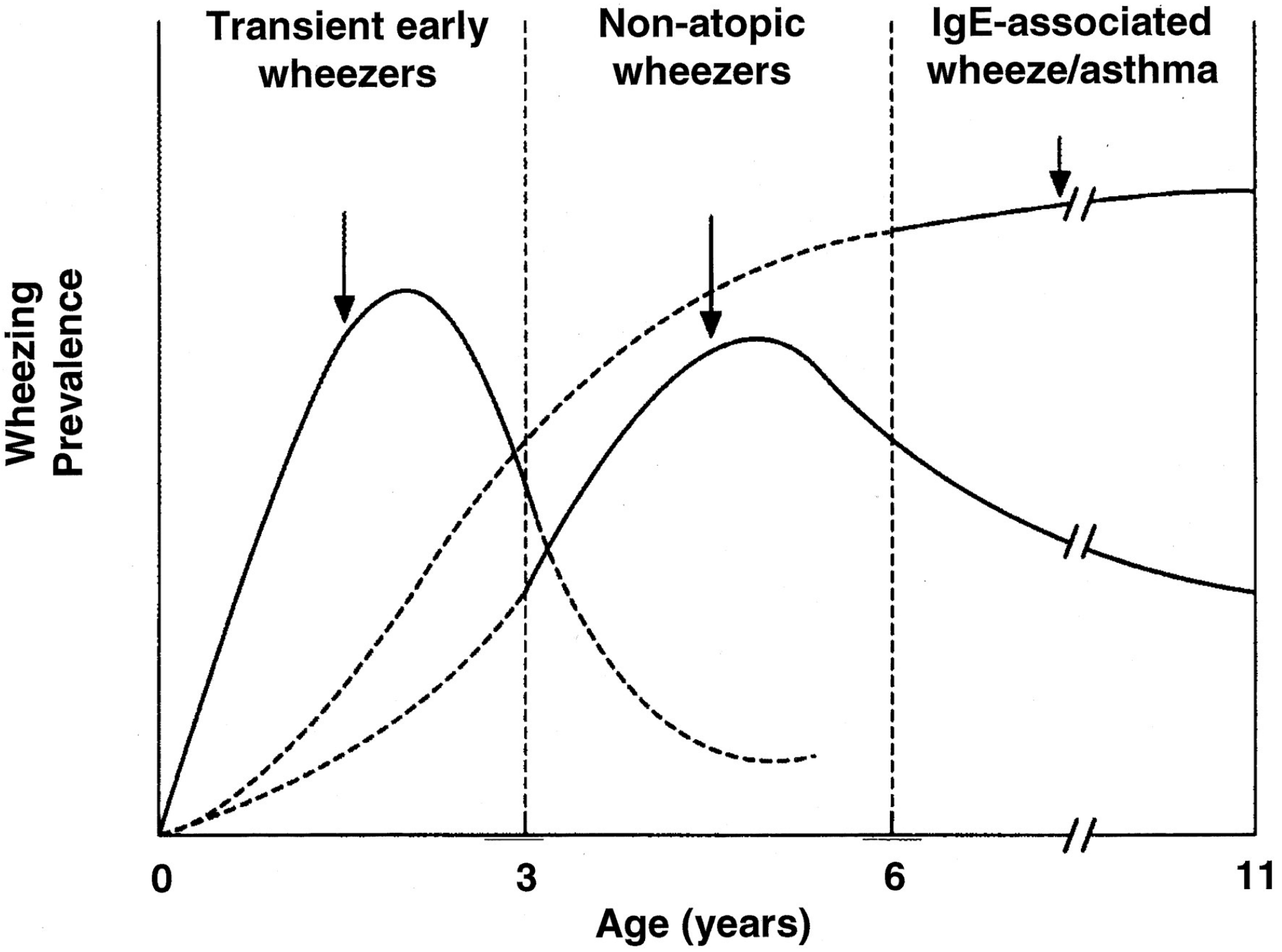


infection

- The causes of asthma are multifactorial.
- there is a strong association between respiratory infections and the risk and pathogenesis of asthma.


Transient early wheezers
Non-atopic wheezers
IgE-associated wheeze/asthma
Wheezing Prevalence
0
3
6
11
Age (years)

Tucson Children's Respiratory Study: wheezing phenotypes and natural history

<table>
<tr><td colspan="2">Never wheezed (51.5%)</td><td colspan="3">Not associated with asthma</td></tr>
<tr><td>Transient early wheezers (19.9%)</td><td>Only wheezed <3 yo</td><td colspan="3">Not associated with asthma (by 22 yo), but theoretical increased risk of COPD</td></tr>
<tr><td rowspan="2">Persistent wheezers (13.7%)</td><td rowspan="2">Wheezed at <3 yo and 6 yo</td><td>40% non-atopic</td><td>“Non-atopic wheezers”</td><td>RSV at <3 yo associated with wheezing up to 11 yo (no significant risk at 13 yo)</td></tr>
<tr><td>60% atopic</td><td rowspan="2">“Atopic wheezers”</td><td rowspan="2">High risk for asthma
• 70% with asthma at 22 yo were persistent or late-onset wheezers
• 49% of subjects with h/o asthma dx or current wheeze by 22 yo
• 31% with active asthma at 22 yo</td></tr>
<tr><td>Late-onset wheezers (15%)</td><td>Wheezed at 6 yo</td><td>Atopic</td></tr>
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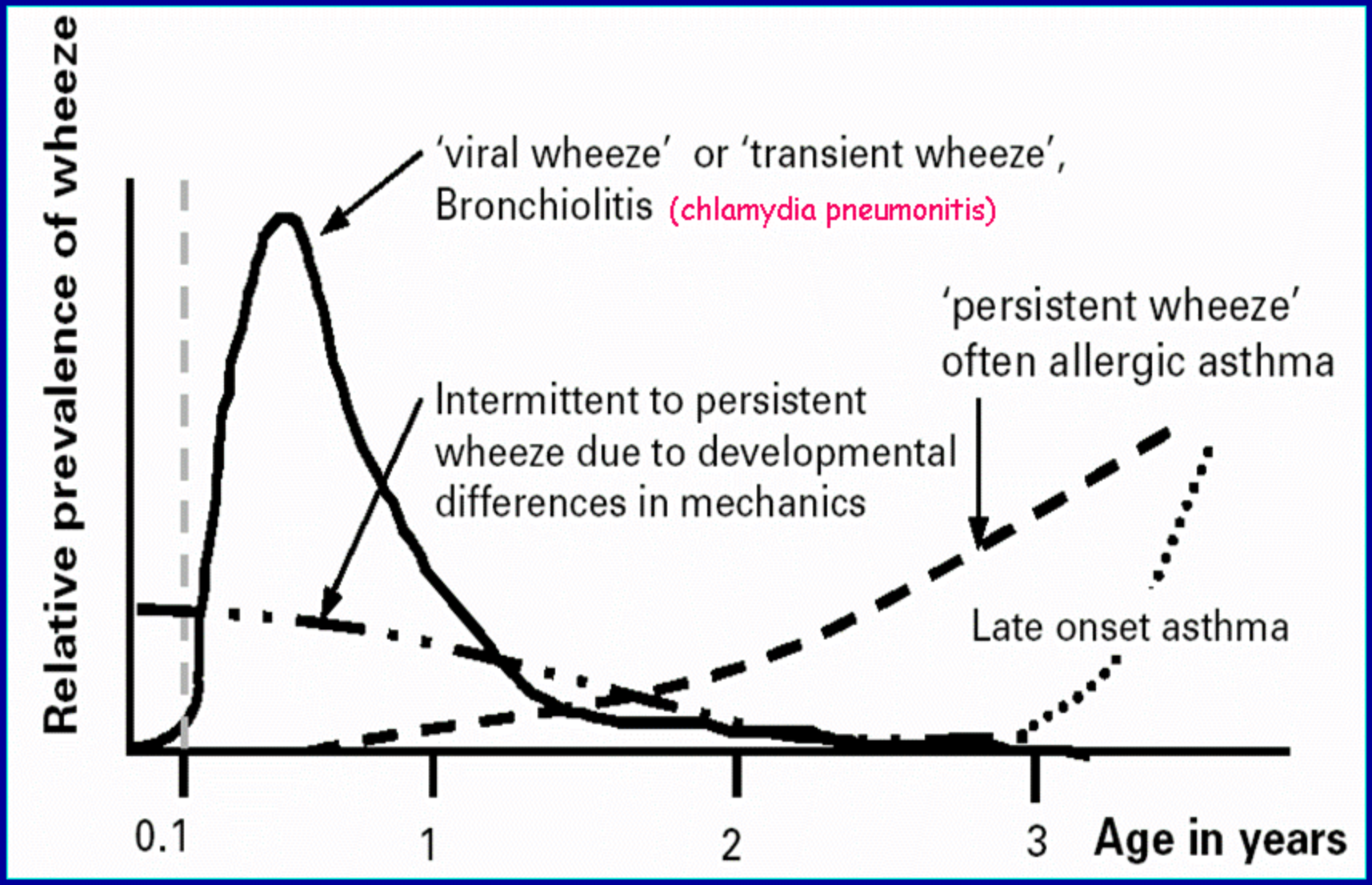
Different phenotype of wheezing at different ages



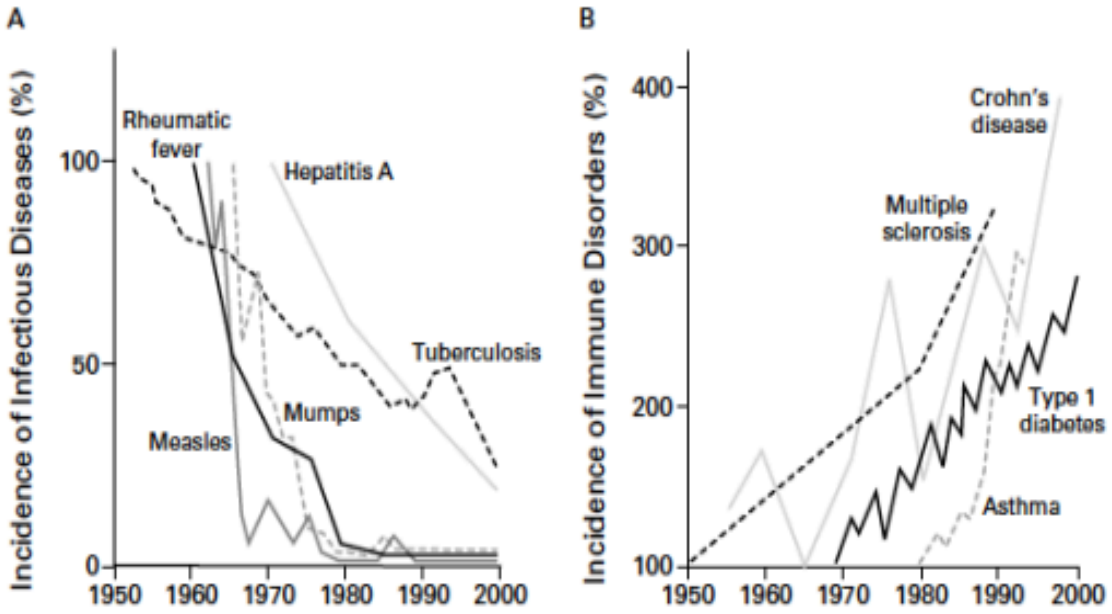


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

The Hygiene hypothesis

- repeated exposure to diverse common infections (in particular, with bacteria, food-borne and orofaecal parasites, and hookworms) and exposure to environmental microbiota during childhood are strongly associated with a healthy maturation of the immune system and with protection from the development of asthma and allergies later in life.

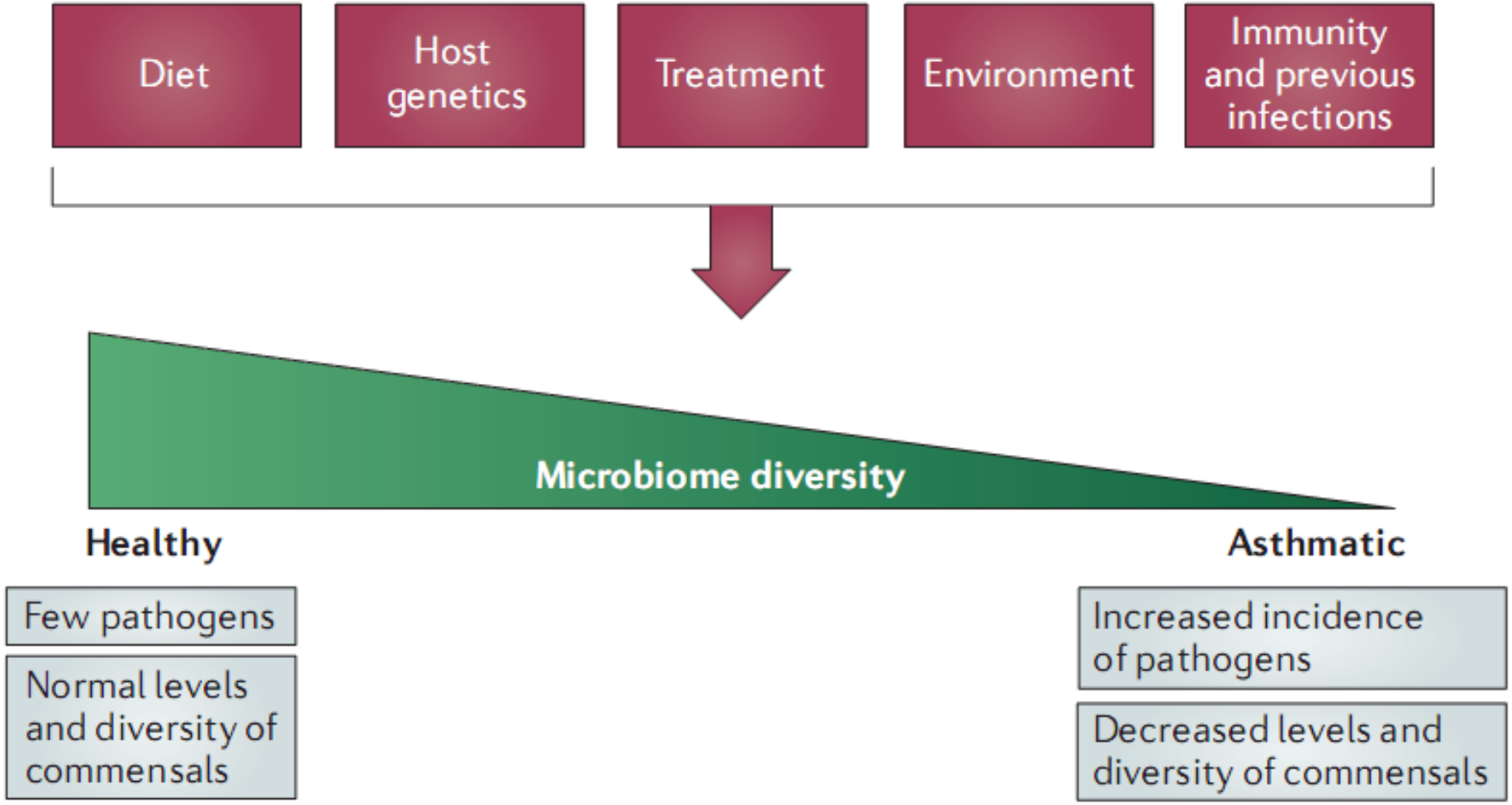


Figure 1 | **The microbiome is influenced by and may determine factors affecting asthma.** The microbiome is regulated by diet, environmental factors (such as smoking and pollution), treatment, host genetics, and previous infections and host immunity. The diversity of the microbiome may in turn affect asthma development, as suggested by the hygiene hypothesis, and may influence the pathogenic species that contribute to stable and severe asthma and asthma exacerbations.

Table 2 | **Current and future treatments for asthma**

Treatment	Notes
Glucocorticoids	• Anti-inflammatory small molecules that bind the cytosolic glucocorticoid receptor and both suppress inflammation and induce anti-inflammatory pathways
β_2 agonists	• Widely used therapies that reduce contraction of airway smooth muscle and result in bronchodilation • Can be short or long acting
Leukotriene receptor antagonists	• Prevent cysteinyl leukotrienes from binding the CysLT1 receptor and inducing airway smooth muscle contraction, mucus secretion and airway inflammation • For example, montelukast
Therapies against T_H2 type cytokines	• Monoclonal antibodies and soluble receptors against IL-4, IL-13 and IL-5 • Reduce circulating levels of T_H2 type cytokines[136–138]
IgE-specific antibodies	• Monoclonal antibodies (for example, omalizumab) • Reduce levels of circulating and cell-bound IgE • A striking effect of this therapy on the incidence of asthma exacerbations has been recently reported[139]
Therapies against TNF	• Soluble TNF receptors or TNF-specific antibodies • Reduce levels of circulating TNF (a major pro-inflammatory cytokine implicated in asthma pathogenesis) • Have shown limited efficacy in asthma treatment, and there are some safety concerns[140]
Vitamin D	• A link between infection risk, asthma and vitamin D has received much attention recently[141–143] • Data suggest an association between vitamin D and asthma risk, but a clear mechanism of how vitamin D prevents asthma is still being sought
Probiotics	• Probiotics with immunomodulatory potential have been applied to allergy and asthma[144–146] as a result of the recent rise in the number of studies advocating a role for microorganisms in asthma and other inflammatory disorders
Pathogen-associated molecular pattern and TLR agonists	• Shown to have a good efficacy as a treatment in animal models of asthma[147,148] • Beginning to appear in clinical trials for allergic rhinitis but have yet to be applied to asthma in humans
IFNs	• Human studies suggest that IFNα has a clinical benefit in stable asthma[149] • IFNβ is currently in a clinical trial for asthma exacerbations • IFNλs reduce allergic airway inflammation in mice[150]

IFN, interferon; IgE, immunoglobulin E; IL, interleukin; TLR, Toll-like receptor; T_H2, T helper 2; TNF, tumour necrosis factor.

Table 1 | **Asthma phenotypes**

Asthma phenotype	Description
Atopic (allergic) asthma	• Reactivity to one or more known allergens (determined by skin prick test) • Higher than normal IgE levels • Specific IgE to allergen (determined by radioallergosorbent assay*) • Eosinophils in the airways (common but not always)
Non-allergic asthma	• No known allergy • No or low serum IgE • No reactivity to allergen (determined by skin prick test or radioallergosorbent assay*)
Mild asthma	• Occasional symptoms, but well controlled by therapy (low-dose glucocorticoids and/or short-acting β_2 agonists)
Stable asthma	• Well-controlled symptoms • No dysregulated lung function or asthma exacerbations
Severe asthma	• Poor control of symptoms despite using maximal therapy (high-dose glucocorticoids and/or β_2 agonists, or other therapies)
Asthma exacerbations	• Mild or severe asthma with sudden symptom onset, often requiring medical consultation or hospitalization and possible oral glucocorticoid intervention
Neutrophilic asthma	• Increased number of neutrophils in bronchoalveolar lavage or sputum samples (can be allergic or non-allergic asthma)
Allergic bronchopulmonary aspergillosis	• Invasive colonization of the airway with *Aspergillus* spp., an opportunistic pathogen; *Aspergillus* growth promotes allergic sensitization to at least 12 known fungal allergens
Virus-induced wheeze or bronchiolitis	• Common in young children (<2 years of age) • Asthma caused by a viral infection, mucus and inflammation in young children, giving a typical 'wheezy' episode • Mild, severe, acute onset or febrile
High T_H2-associated atopic asthma	• T_H2 cell-associated gene expression is typical (for example, expresses *IL13* and IL-13-inducible genes) • Responds well to glucocorticoids • Prone to asthma exacerbations[135]
Low T_H2-associated atopic asthma	• A mixed phenotype of asthma • Less prominent T_H2 type cytokine responses • More refractory to glucocorticoid treatment than patients with high T_H2-associated atopic asthma[135]

IgE, immunoglobulin E; T_H2, T helper 2. *A radioallergosorbent assay is a blood test that is used to quantify allergen-specific IgE antibodies.

Asthma and viral infections

- **In both children and adults, viral infections of the airways may be associated with the development of chronic asthma, as well as with acute disease exacerbations.**
- **With regard to the pathogenesis of asthma and its exacerbations, the most commonly involved viruses include respiratory syncytial virus (RSV), rhinovirus (RV), influenza and parainfluenza viruses, coronavirus, enterovirus, and adenovirus.**
- **Wheezing-associated viral infections are characterized by an age-related distribution. In particular, RSV predominates in children under 3 years of age, whereas RV represents the most frequent cause of infectious respiratory illnesses affecting older children and adults; influenza and parainfluenza viruses affect all age groups.**

- Respiratory infections may significantly affect, via complex cellular and immunological mechanisms, the development and progression of asthma, also including its exacerbations.
- Infections often cause, in asthmatic patients, a worsening of symptoms and a deterioration of pulmonary function.
- Macrolides and fluoroquinolones may represent a useful therapeutic tool in limiting both the duration and severity of asthma exacerbations induced by atypical bacteria like Chlamydiae and Mycoplasms.
- Further progresses may be achieved in asthma therapy if pharmacological and immunological research efforts will provide new molecules and vaccines, able to be really effective against those viruses most commonly involved in inducing and exacerbating such a widespread disease.

Respiratory syncytial virus and rhinovirus infection in infants and bronchiolitis.

- Much evidence points to a relationship between severe lower respiratory infections with human respiratory syncytial virus or human rhinoviruses early in life and the development of recurrent wheeze followed by asthma diagnosis in later childhood.
- Whether these viruses are true causative agents of asthma or (owing to shared risk factors) simply act as markers for an increased risk of asthma development, or even whether both possibilities are true, is unclear and much debated.

BMJ. 1995 May 13;310(6989):1225-9.

Community study of role of viral infections in exacerbations of asthma in 9-11 year old children.

Johnston SL[1], Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, et al.

Author information

- This study supports the hypothesis that upper respiratory viral infections are associated with 80-85% of asthma exacerbations in school age children.

Respiratory syncytial virus and rhinovirus infection in infants and bronchiolitis. (1)

- Much evidence points to a relationship between severe lower respiratory infections with human respiratory syncytial or human rhinoviruses early in life and the development of recurrent wheeze followed by asthma diagnosis in later childhood.
- Serological monitoring shows that RSV infects nearly all children in their first 2 years of life; however, only ~40% of children exhibit clinical signs of infection in the lower respiratory tract. For unknown reasons, some children with bronchiolitis develop recurrent respiratory symptoms.

Respiratory syncytial virus and rhinovirus infection in infants and bronchiolitis. (2)

- lower respiratory infections by RVs are as important as infections by RSV in terms of the risk of later asthma development.
- it is not yet clear whether the inflammation caused by viruses causes long-term respiratory disease or is associated with wheeze and asthma diagnosis because of shared risk factors.

Respiratory syncytial virus and rhinovirus infection in infants and bronchiolitis. (3)

- In a study of 191 palivizumab-treated and 230 control (untreated) premature babies who were followed for 24 months, the rates of recurrent wheeze were about 50% lower in those who had prophylactic treatment with palivizumab.
- palivizumab prophylaxis was shown to be associated with a similar substantial protection against recurrent wheeze in children aged 2–5 years.

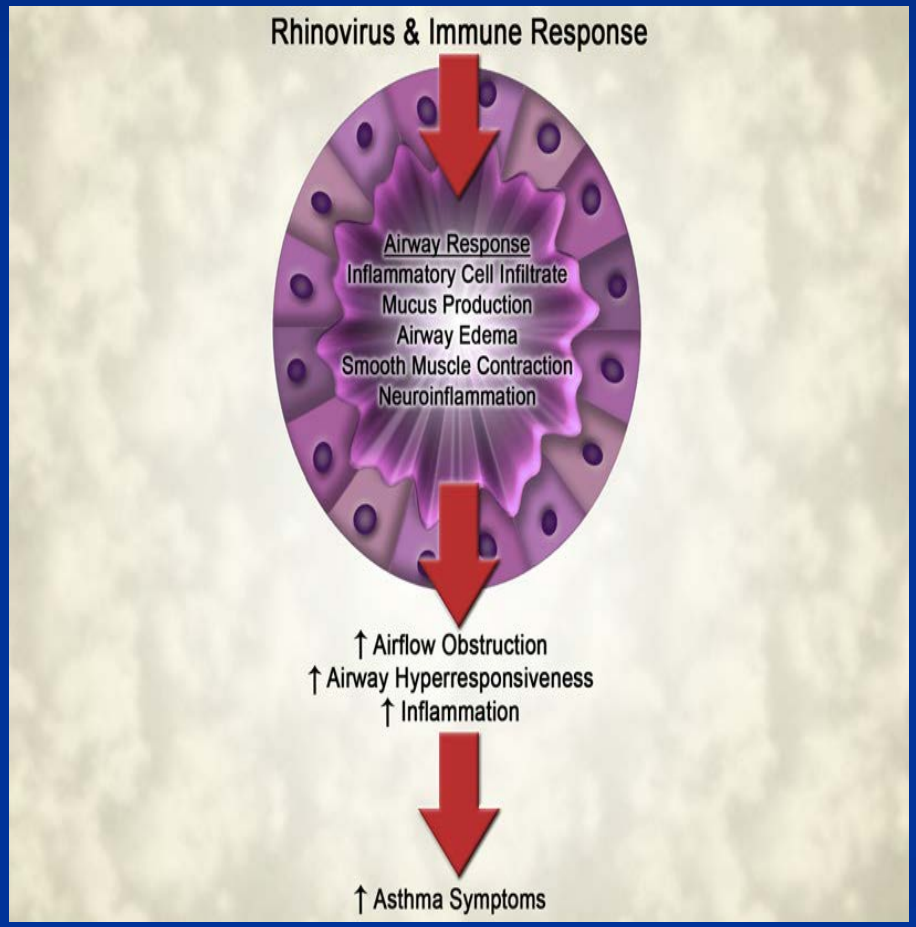
- ***There are two ways viruses can trigger asthma symptoms.***

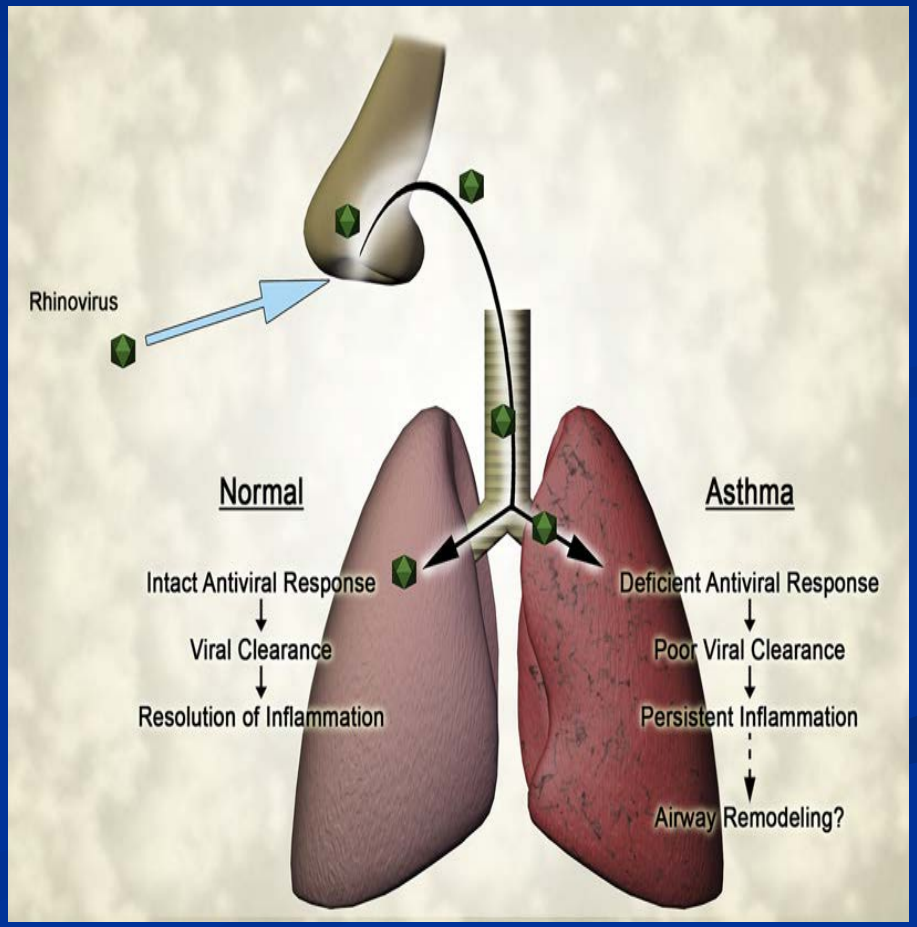
1. **The first type of viral-induced asthma affects people who have no history of asthma, but who develop asthma symptoms--a cough and wheezing--that begin after a viral illness.**
2. **The second type of viral-induced asthma affects children and adults who already have persistent asthma; a viral illness worsens their asthma symptoms. An estimated 40% of asthma exacerbations in adults are caused by a viral illness.**

Host immune responses to rhinovirus: Mechanisms in asthma

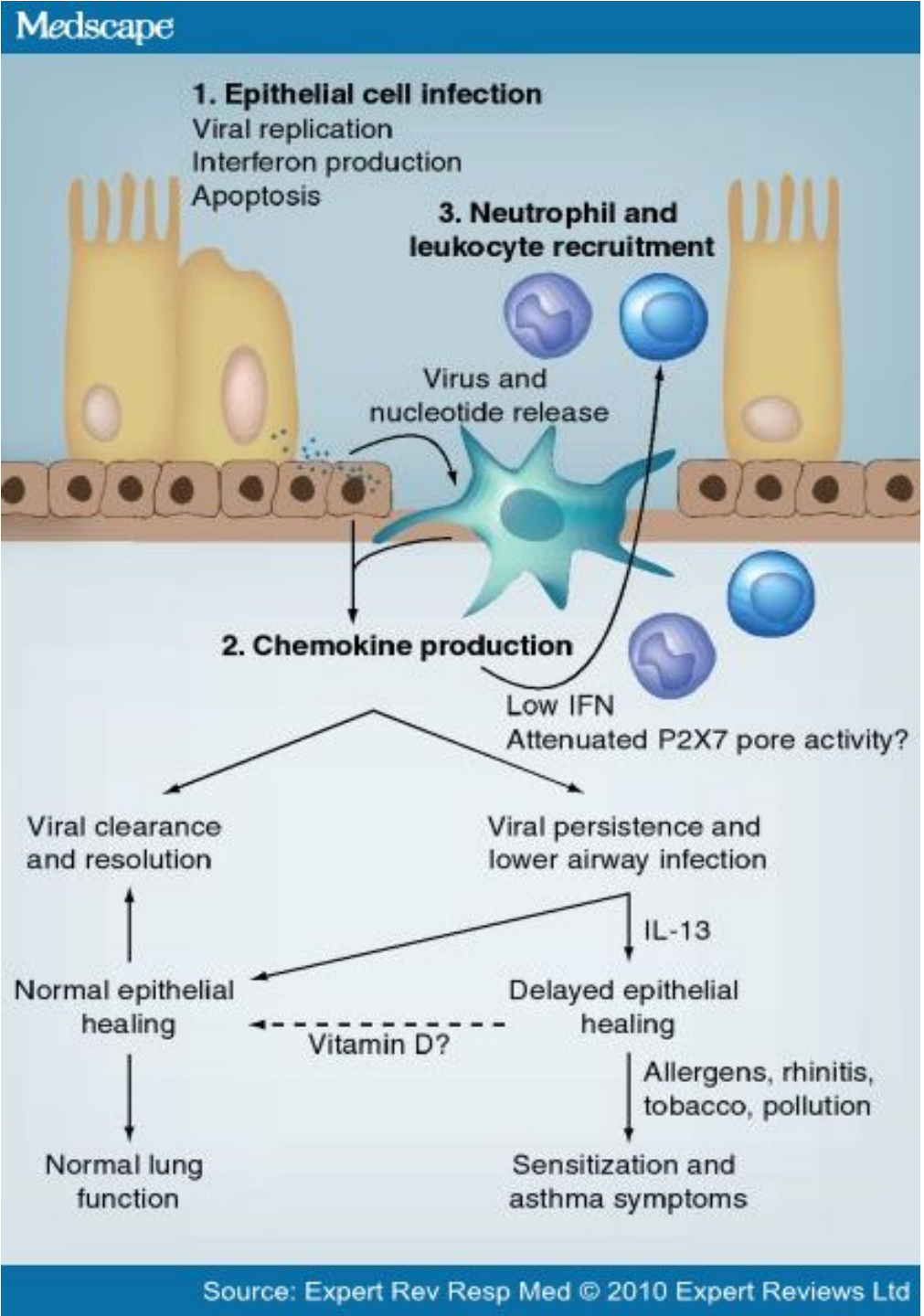
Consequences of immune response to rhinovirus and altered airway responses in asthma

Antiviral response to rhinovirus in a healthy subject vs. a subject with asthma

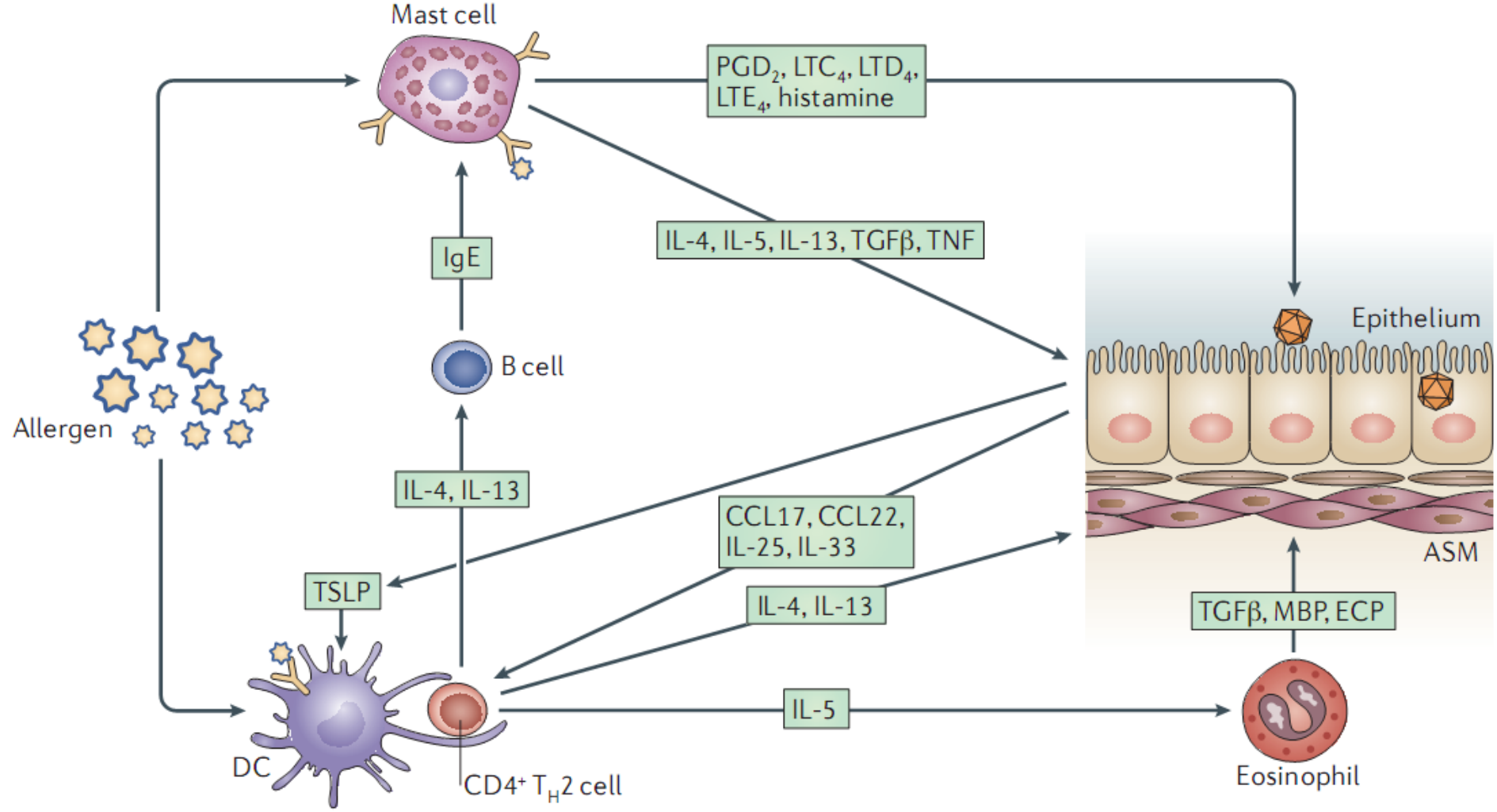




J ACI 2008;122:671-82



Model of infection-triggered airway epithelial cell injury with variable responses that may contribute to asthma symptoms.



Respiratory viruses interact with allergens in an additive or synergistic manner, promoting asthma. a clear link between respiratory virus infection together with allergen exposure in sensitized children and adults in increasing the risk of hospital admissions due to asthma exacerbations.

Infection and asthma

- **Microorganisms may damage and compromise the integrity of the airway by infecting airway epithelial cells, causing cell death and shedding.**
- **They can also affect epithelial permeability, leading to increased airway inflammation and creating opportunities for increased infection, allergen uptake or exposure to environmental pollutants, all of which are important contributing factors in asthma.**

Asthma and bacterial infections

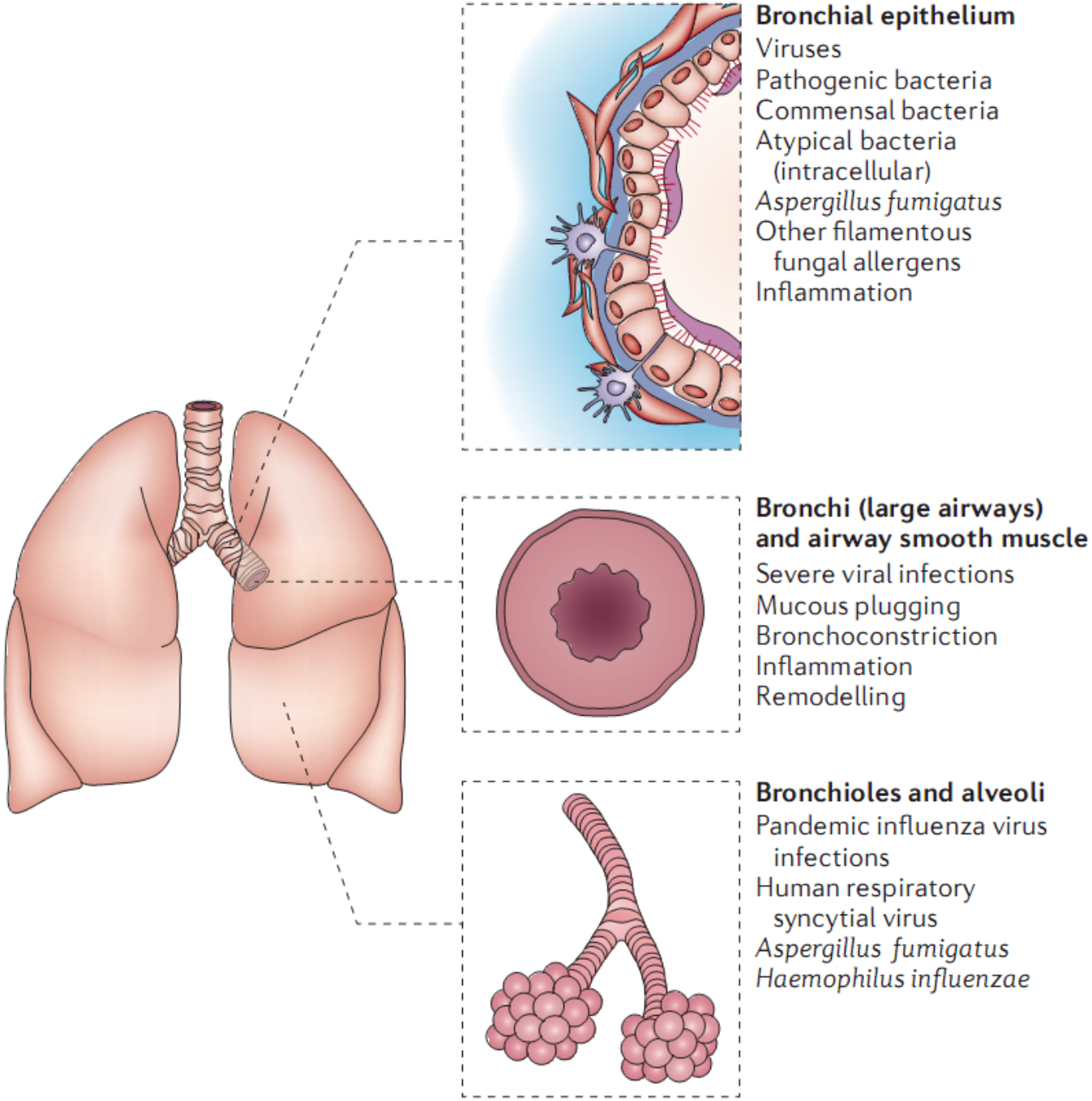
- With regard to the role of non-viral infections in asthma inception and exacerbations, the atypical bacteria *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are currently believed to be the most involved pathogens.

Invasive pneumococcal infection (IPI), has also been linked to asthma

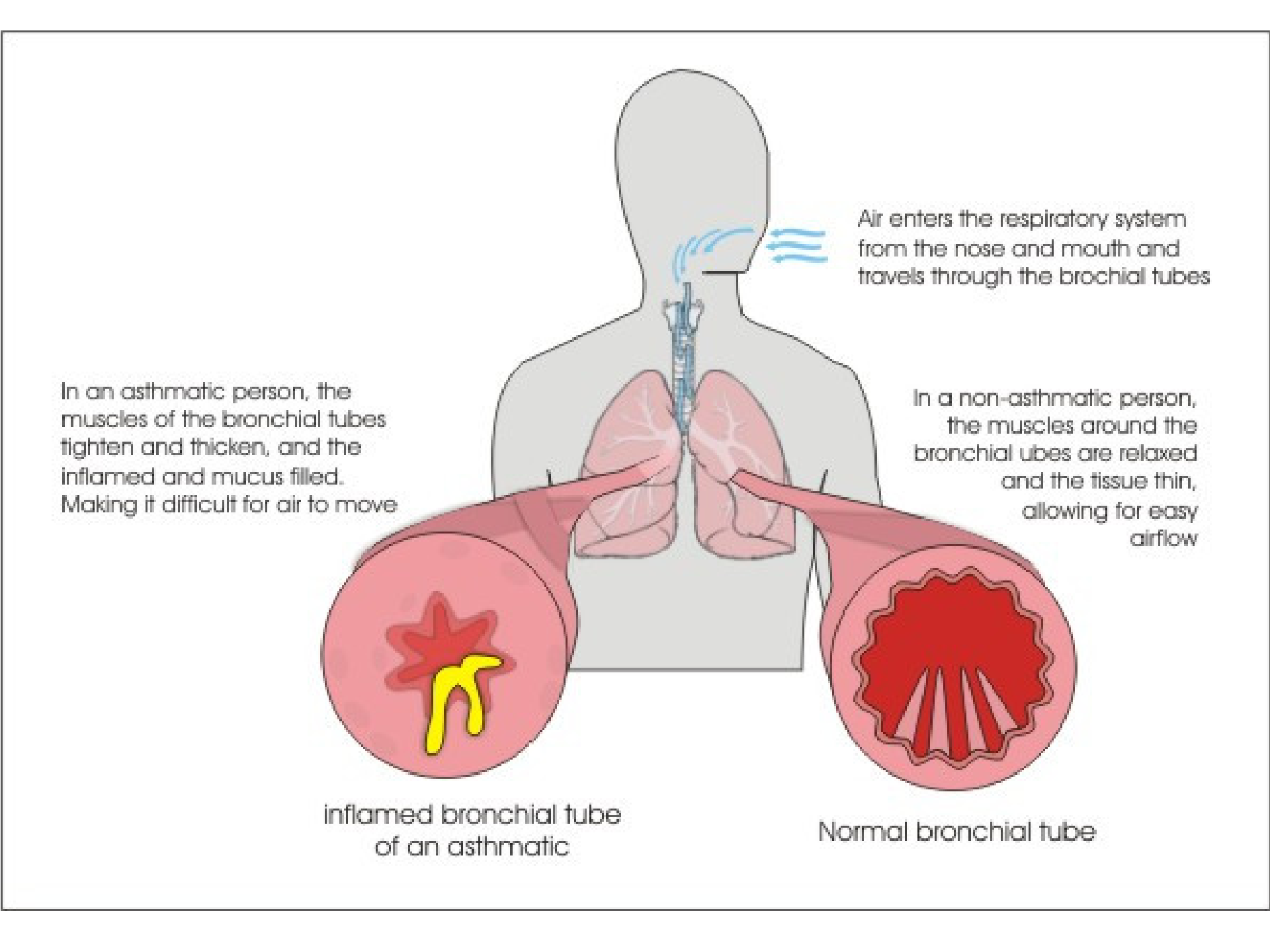
- Adults with stable asthma have been shown to have a greater incidence of S. pneumoniae carriage, and asthma has been shown to be a risk factor for IPI in both adults and children.
- for low-risk asthma (as defined by the need for prescription medication for asthma) the odds ratio for IPI (versus no IPI) was 2.8-fold, whereas for high-risk asthma (as defined by hospitalization for asthma in the past 12 months) it was over 12-fold.
- strongly advocate the need for antipneumococcal vaccination for individuals with asthma.

Allergic bronchopulmonary aspergillosis

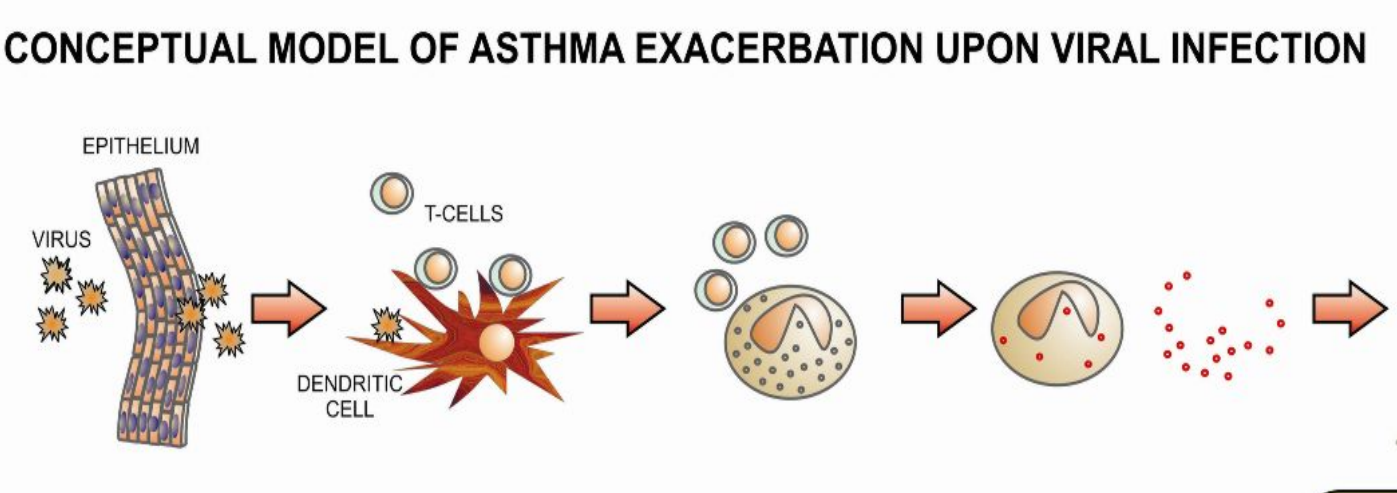
1. Caused by colonization of the lower respiratory tract with Aspergillus spp.
2. Chronic infection with Aspergillus fumigatus can lead to bronchiectasis, a disease that can occur in parallel with asthma and is characterized by neutrophilic inflammation, epithelial destruction and degradation of the connective tissue matrix.
3. The fungus acts as both a source of allergen and a pathogen, and symptoms of ABPA can be attributed to both functions.



Microorganisms involved in asthma and their niches.
A cross-section of the human lower respiratory tract, showing sites of infection for different microorganisms and the effects that they have on airway function.


Air enters the respiratory system from the nose and mouth and travels through the brochial tubes
In an asthmatic person, the muscles of the bronchial tubes tighten and thicken, and the inflamed and mucus filled. Making it difficult for air to move
In a non-asthmatic person, the muscles around the bronchial ubes are relaxed and the tissue thin, allowing for easy airflow
inflamed bronchial tube of an asthmatic
Normal bronchial tube

CONCEPTUAL MODEL OF ASTHMA EXACERBATION UPON VIRAL INFECTION



1. VIRUS INFECTS EPITHELIUM

2. T-CELL ACTIVATION THROUGH ANTIGEN PRESENTATION BY DENDRITIC CELL

3. ACTIVATED T-CELLS INDUCE EOSINOPHIL ACTIVATION

4. ACTIVATED EOSINOPHILS RELEASE MEDIATORS BY DEGRANULATION

5. EOSINOPHIL CATIONIC MEDIATORS DEPOSIT ON AIRWAY SMOOTH MUSCLE AND INTERFERE WITH ACTIVITY OFM2-RECEPTOR FROM PARASYMPATHETIC INNERVATION INDUCING CONTINUED BRONCHOCONSTRICTION

ILARRAZA, 2008

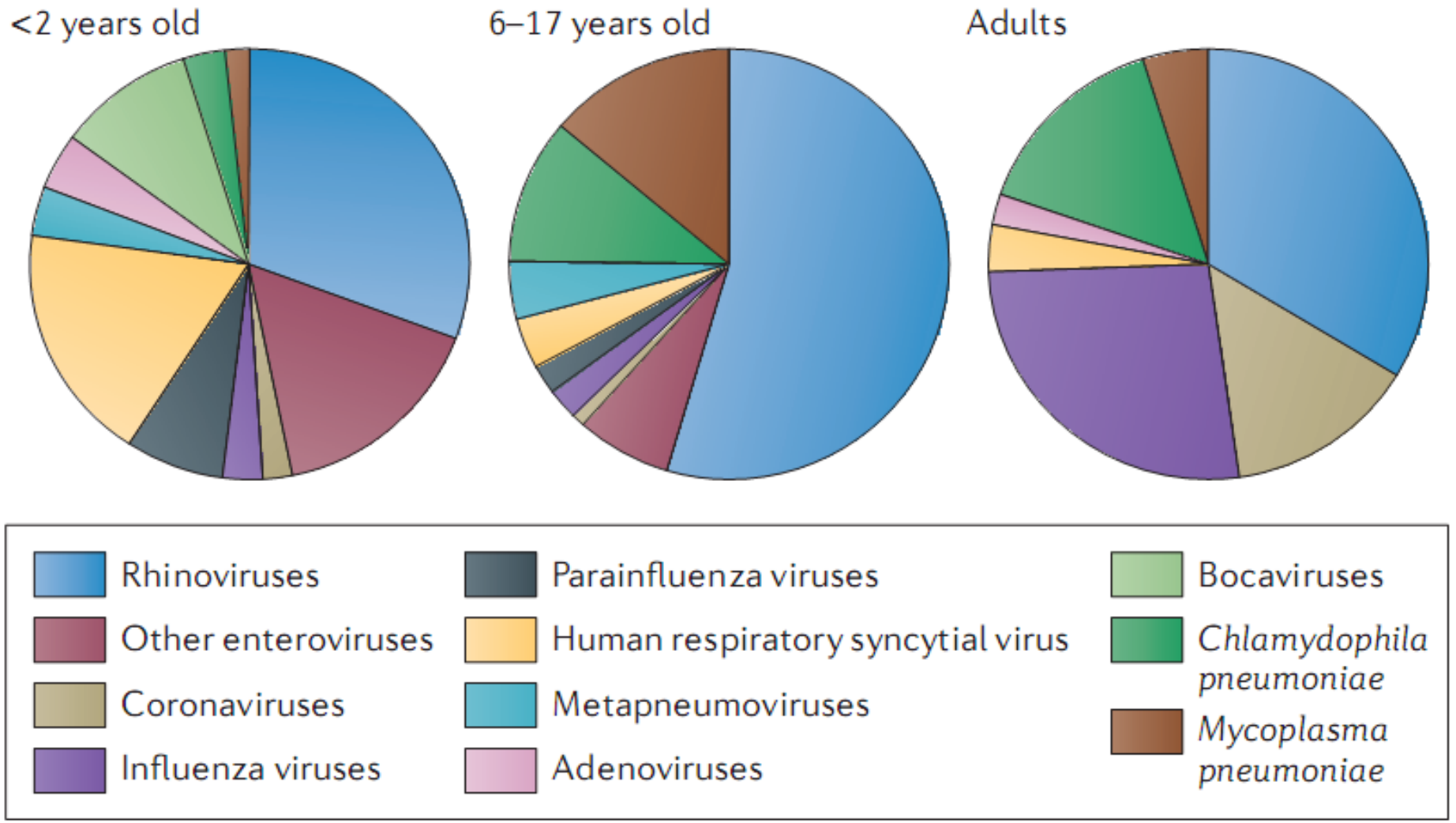


Figure 2 | **Viruses and bacteria associated with asthma exacerbations.** The prevalence of viruses and bacteria in young children (<2 years old), older children (6–17 years old) and adults, presented as median percentages from several studies (data were obtained from a recent review[134]). Enterovirus estimations in adults and bocavirus estimations in 6–17 year olds and in adults may be under-represented owing to that data not being available in published studies.

How Can I Prevent Respiratory Infections?

- **Avoid contact with anyone who's sick.**
- **Avoid touching your eyes, nose or mouth.**
- **Wash your hands often with soap and warm water.**
- **Get a yearly flu vaccine. (and pneumococcus vaccine)**
- **Sinusitis with asthma can be very serious. Be aware of the symptoms of a sinus infection and report them immediately to your asthma specialist to prevent asthma attacks.**
- **Keep your breathing equipment clean. This includes your asthma inhaler, asthma nebulizer, and nebulizer tubing and mouthpiece.**
- **Do not share your breathing equipment or medicines with others.**

What Are the Symptoms of Infection?

- Increased shortness of breath, difficulty breathing, or wheezing, Coughing up increased amounts of mucus, Abnormally colored mucus, Fever (temperature over 101°F) or chills, Increased fatigue or weakness, Sore throat, scratchy throat, or pain when swallowing, Sinus pressure or drainage, nasal congestion, or headaches.

What to do when you do get a cold or the flu

- Call your doctor if your asthma begins to flare up when you're sick.
- Follow your asthma action plan.
- Rest and take care of yourself.
- Monitor your airflow.
- Seek help right away for severe symptoms. .
- Stay home.

Treatment of Viral-Induced Asthma

- The best treatment is prevention. chronic asthma should have a flu shot every year. Frequent hand washing and limited contact with people who have upper respiratory symptoms are two good ways to help limit exposure to cold and flu viruses.
- Treatment for a viral-induced asthma attack may include bronchodilators (medicines that open up the airways) for mild symptoms and increased steroids for more severe or prolonged attacks.
- Steroid inhalers have been shown to be effective for treating adults without asthma who have asthma-like symptoms after a viral infection. However, in the absence of any history of asthma, these symptoms generally go away in 8 weeks or less. For severe viral-induced bronchospasm, oral steroids may sometimes be necessary, even in people without a history of asthma.

Asthma and Allergy Foundation of America

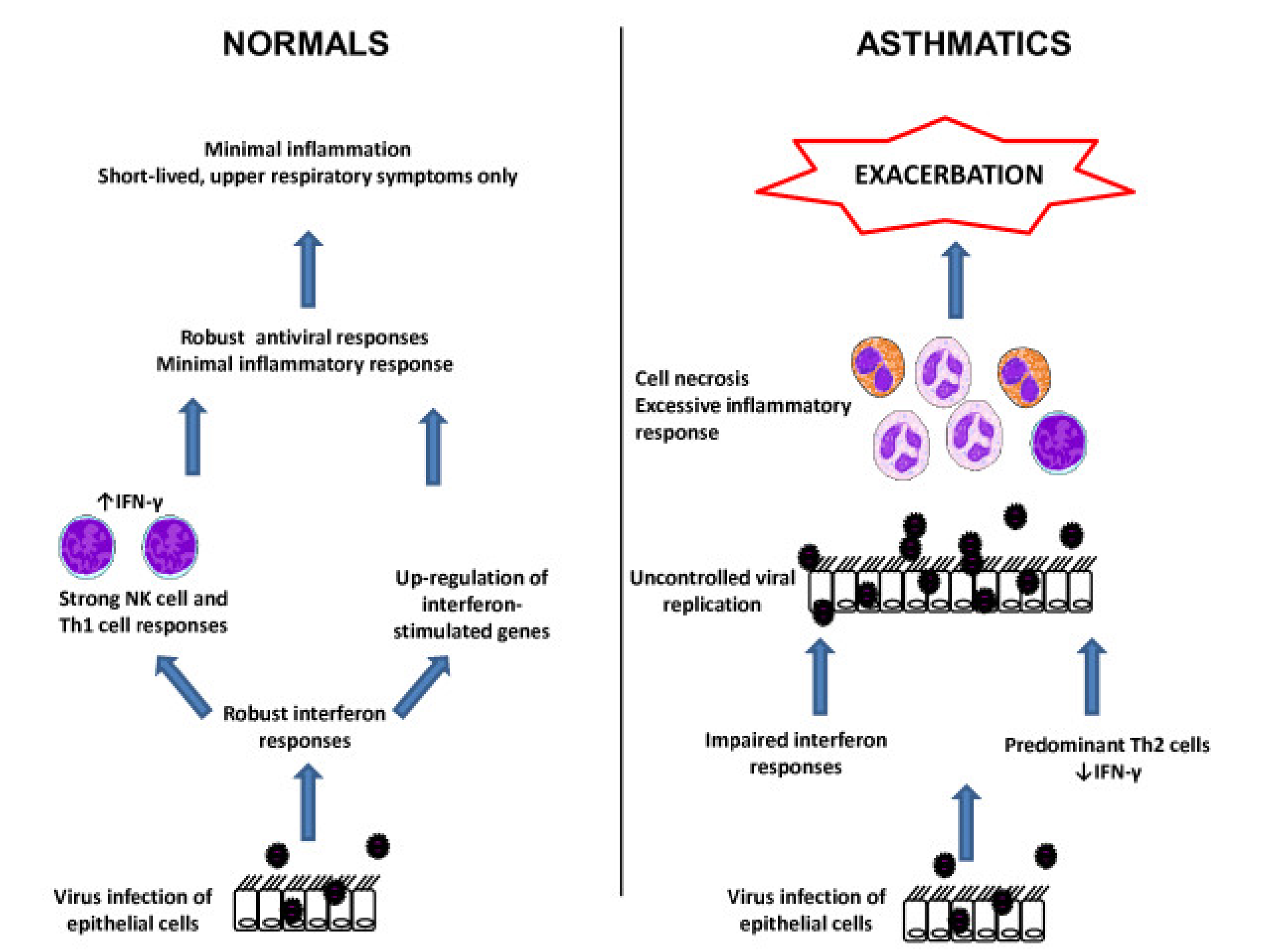
Staying healthy will help prevent asthma episodes

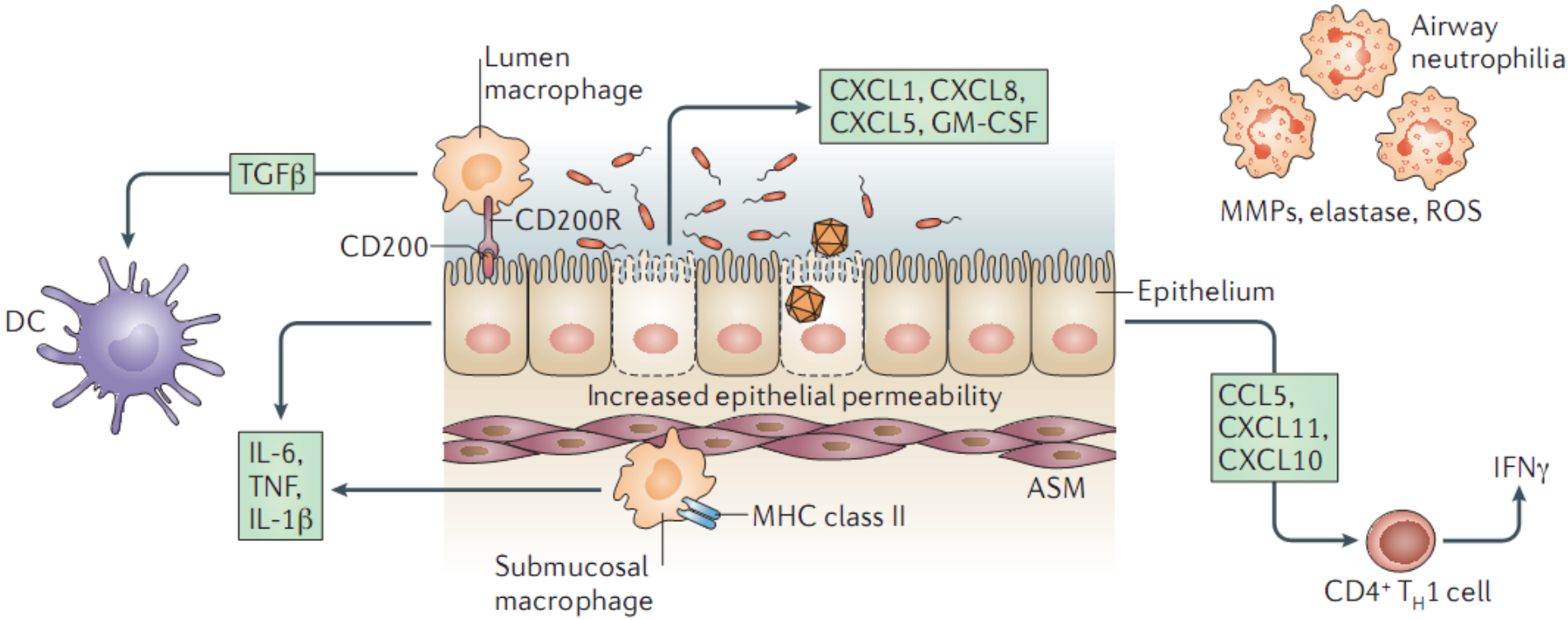
Wash your hands

WET - LATHER - SCRUB - RINSE - DRY

conclusions

- There is now overwhelming evidence that asthma can be viewed as a chronic inflammatory condition which is initiated, triggered and maintained by the respiratory microbiota.
- Microorganisms have roles in the onset and development of asthma but can also be protective (the hygienehypothesis).


NORMALS
Minimal inflammation
Short-lived, upper respiratory symptoms only
Robust antiviral responses
Minimal inflammatory response
↑IFN-γ
Strong NK cell and
Th1 cell responses
Up-regulation of
interferon-
stimulated genes
Robust interferon
responses
Virus infection of
epithelial cells
ASTHMATICS
EXACERBATION
Cell necrosis
Excessive inflammatory
response
Uncontrolled viral
replication
Impaired interferon
responses
Predominant Th2 cells
↓IFN-γ
Virus infection of
epithelial cells



Viruses and bacteria induce airway inflammation. Bacterial and viral infections of the airways activate immune and structural cells, promoting inflammation and influencing responses to other pathogens, allergens and pollution.

How Can I Prevent Infections That Trigger Asthma?

- Good hygiene can decrease viral infections. Prevent the spread of infection by making sure you and your family members wash their hands regularly with soap and warm water.
- Check with your health care provider about receiving a flu shot every year. In addition, discuss the possibility of getting a pneumococcus -- or pneumonia -- vaccine. Pneumococcus is a common cause of bacterial pneumonia, an illness that can be particularly serious in a person with asthma.
- Sinusitis with asthma can be very serious. Be aware of the symptoms of a sinus infection and report them immediately to your asthma specialist to prevent asthma attacks.
- Keep breathing equipment clean. Do not let others use your asthma medications or asthma treatment, including your asthma inhaler, asthma nebulizer, and nebulizer tubing and mouthpiece.

Preventing colds and the flu

- **Get an annual flu shot unless your doctor recommends against it.** Most adults and children older than 6 months of age should get a flu vaccination every year. If you do get a vaccination, you'll need a shot (injection), since nasal spray vaccinations aren't recommended for people with asthma.
- **Ask your doctor if you need a pneumonia vaccination.**Having asthma increases your risk of developing pneumonia after getting the flu.
- **Avoid contact with anyone who's sick.** Germs that cause respiratory infections are easily passed from person to person.
- **Wash your hands often.** This kills the germs that can cause respiratory infections. Carry a bottle of hand sanitizer to kill germs while you're on the go.
- **Avoid touching your eyes, nose and mouth.** These are the points where germs enter your body.