# INTRODUCTION

Viral infections are the most frequent etiological agents for acute respiratory infections. The number of child deaths due to acute respiratory infection worldwide is considrable with 70% of deaths occuring in Africa and South East Asia ***(Nair et al., 2012).***

Corona viruses are enveloped RNA viruses from the cornovirdae family and part of the corona virinae subfamily with its characteristic surface of the virions appear as a crown like image under the electron microscope and so the viruses are named after the Latin word corona, meaning' crown' or 'halo' ***(ECDC, 2005).***

In humans, the transmission of corona viruses between an infected individual and others can occur via respiratory secretions. This can happen either directly through droplets from coughing or sneezing, or indirectly through touching contaminated objects or surfaces as well as close contact, such as touching or shaking hands ***(ECDC, 2005).***

The isolation of the coronavirus (CoV) is identified as the cause of severe acute respiratory syndrome and the detection of two new human CoVs (HCoV-NL63 and HCoVs-HKU1)have led to studies of the epidemiology and clinical and

socioeconomic effects of the infections caused by all HCoVs, including those known since the late 1960 (HCoV-229E andHCov-OC43). HCoV infections can be associated with respiratory and extra respiratory manifestations, including central nervous system involvement ***(Van der Hoek et al., 2004).***

It is well known that all HCovs cause respiratory infections, SARS-CoV is the most aggressive, although the disease seems to be substantially less severe in children than in adults. In patients<12 years of age, the clinical course of SARS was generally milder and shorter than in those>12 years ***(Dowell and Ho, 2004)***

Furthermore, unlike other RNA viruses, HCoV can easly mutate and recombine when different strains infect the same cell and give rise to a novel virus with unpredictable host range and pathogenicty.Thus, circulating HCoVS should be closely monitored to detect the spread of particularly virulent strains in the community at an early stage and to facilitate the development of adequate preventive and therapeutic measures **(Esper, 2005).**

# AIM OF THE WORK

The aim of the study is to detect some etiological viral pathogens of acute respiratory infection in children ≤ five years of age including coronavirinae and commonly associated paramyxoviridae in a single community which is Children's hospital, Ain Shams university hospitals, Cairo, Egypt, in correlation to the clinical and radiological parameters.

# Acute Respiratory Tract Infections

## Anatomy of the respiratory system:

The respiratory system (or ventilatory system) is the biological system of an organism that introduces respiratory gases to the interior and performs gas exchange. In humans and other mammals, the anatomical features of the respiratory system include airways, lungs, and the respiratory muscles ***(Haton et al., 2010).***

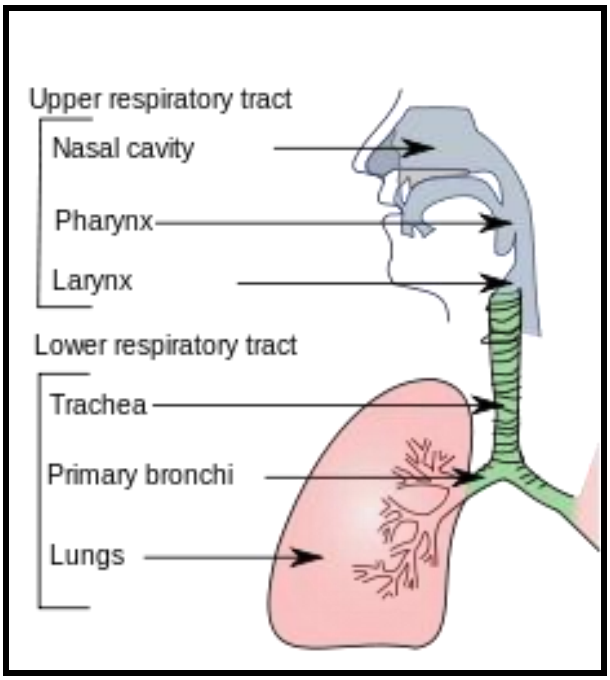


**Figure (1):** The respiratory system anatomy: the major parts of the respiratory system are organized into upper and lower respiratory tracts ***(Haton et al., 2010).***

## Immunity of respiratory system:

### Innate immunity:

The respiratory tract has a surface area of approximately $70m^2$.Despite continues contact with the surrounding environment and continues exposure to potential pathogens only rarely do the lungs become colonized or infected. A local defense system with components of both adaptive immunity has evolved to discriminate between non-pathogenic antigens and potential pathogens and to clear pathogens ***(Hansdottir et al., 2011).***

The innate immune system involves a rapid, non specific recognition and responds to almost all pathogen. Only those antigens that penetrate the innate immune responses evoke the more specific adaptive immune responses. The main players in the innate immunity in the lungs include the airway epithelium itself, alveolar macrophages, and dendritic cells. They all express pattern recognition receptors (PRR'S) and ligand engagement result in activation of intracellular signaling pathways that mobilize the antimicrobial defenses, inflammation, and adaptive immune responses ***(Basu and Fenton, 2014).***

The airway epithelium is the first line of defense and functions as physical barrier to prevent the entry of inhaled pathogens. When the airway epithelium recognizes the presence

of a pathogens it respond to releasing antimicrobials, chemokines and cytokines. Alveolar macrophages recognize, phagocytose and remove inhaled material. They are activated either in response to a pathogens or through autocrine/ paracrine response to cytokines. Activation leads to enhanced phagocytosis and killing of pathogens. When a pathogen is encountered, it is ingested and its proteins are processed into peptides which are then presented at the surface of the dendritic cells ***(Cannell et al., 2008).***

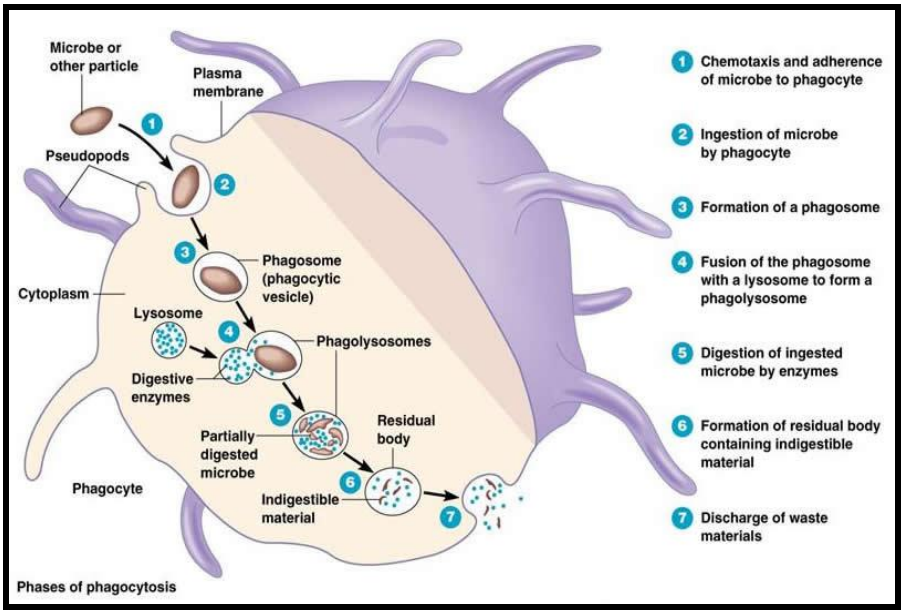


**Figure (2):** Innate immunity of respiratory system ***(Cannell et al., 2008).***

Activated dendritic cells produce chemokines and migrate to local lymph nodes where they present the antigenic peptides

bound to major histocompatibility complex (MHC) molecules to naïve T-cells (CD4+ T-helper cells and CD8+ T-cytotoxic cells) and induce their activation and differentiation. Dendritic cells thus serve as a link between innate and adaptive immune responses ***(Hansdottir et al., 2011).***

**Adaptive Immunity:**

Activation of the innate immune system drives activation of the long term adaptive immune system ***(Iwasaki and Medzhitov, 2010)***.

Adaptive immune responses involve the ability of T and B lymphocytes to produce cytokines and immunoglobulin respectively. All phases of the adaptive immune response are specific to unique antigen, from recognition of the antigen by antibody (humoral) or T-lymphocyte (cell mediated) through lymphocyte activation, to effector function (elimination of antigen)and the development of immunologic memory ***(Mak and Saunders, 2005).***

Upon activation memory T cells down regulate lymphoid-tissue-homing receptors and up regulate tissue-specific-adhesion molecules and can now migrate to non-lymphoid tissue like the lung ***(Holt et al., 2008)***.

Furthermore, once activated T h (CD4+) cells differentiate into TH1, TH2, or TH17. Effector cells are

characterized by production of distinct set of cytokines ***(Medzhitov, 2007).***

Activation of B cells and their differentiation into antibody-secreting plasma cells can be triggered by antigen but usually requires helper T cells. Lastly regulatory T cells (T reg) are important for the control of peripheral T-cell responses.In relation to the lung they are believed to have key role in protection against the inflammatory sequela of airway infections and in the protection against the induction and expression of atopic disease ***(Holt et al., 2008).***

The respiratory tract in continuously exposed to antigens, some of which are pathogenic and some of which are not. A specialized lung immune system has evolved that can recognize and respond to potential pathogens but does not get activated by non-pathogenic antigens which would result in chronic inflammation and tissue damage ***(Hansdottir et al., 2011).***

# Definition of acute respiratory infections:

Acute respiratory infections (ARIs) are considered the leading cause of acute illnesses worldwide and remain the most important cause of infant and young children mortality, accounting for about two million deaths (20% of all child deaths) each year ***(Mizged, 2008).***

## Epidemiology of acute respiratory infections:

### Prevalence:

Childhood acute respiratory infection (ARIs) especially pneumonia are a major cause of childhood morbidity and mortality in developing countries, approximately two million children under five die from pneumonia each year, accounting for nearly one in five child deaths globally ***(Alonso, 2013).***

### Risk factors:

There are multiple social and environmental factors associated with ARI morbidity and mortality in childhood. These include co morbid illnesses especially HIV, malnutrition, prematurity or measles, environmental determinants particularly passive smoke exposure, overcrowding or poor living conditions and social factors principally poverty and poor access to both preventative (including immunization) and curative health services ***(Williams, 2005).***

### AGE:

Children younger than 5 years of age experience 3 to 8 episodes of URTI per year the frequency may be as high as once a month especially if the child is attending school, day-care or

has sibling attending school. Importantly, most these episode are minor, short lived and self-limiting colds or sore throats. The child should also be symptomatically well between episodes and growing satisfactorily ***(Nokso-koivisto, 2004).***

## Upper Respiratory Tract Infection:

Upper respiratory tract infections are the most common illnesses affecting children. On average children experience around six to eight upper respiratory tract infections (URTIs) each year ***(Monto, 2002; Heikkinen et al., 2003).***

Although these infections usually are mild and self limiting, they occasionally lead to complications that can be life threatening. Most URTIs can be placed within three main categories of infection: Rhinosinusitis, pharyngitis, and otitis media. Within each category of illness there is a range of related conditions that may have similar or overlapping clinical presentations ***(Heikkinen et al., 2003).***

**Table (1):** Terminology and etiology of the common upper respiratory tract infections in children.

| Condition | Related Diagnoses | Etiology |
|---|---|---|
| Rhinosinustis | Common cold, nasopharyngitis, infective rhinitis, acute rhinosinusitis, acute sinusitis, chronic sinusitis | ***Viral:*** rhinovirus, coronavirus, enterovirus, parainfluenza, influenza, respiratory syncytial virus, adenovirus, metapneumovirus<br>***Bacterial:*** Streptococcus peneumoniae, Haemophilus influenza, Moraxella catarrhalis, staphylococcus a ureus, Streptococcus pyogenes |
| Pharyngitis | Pharyngitis, tonsillitis, recurrent tonsillitis | ***Viral:*** adenovirus, respiratory syncytial virus, Epstein-Barr Virus, Cytomegalovirus, Parainfluenza, influenza.<br>***Bacterial:*** Streptococcus pyogenes, Group C and G Streptococci, Mycoplasma pneumonia. |
| Otitis media | Acute otitis media without perforation, acute otitis media with perforation, otitis media with effusion, chronic suppurative otitis media. | ***Viral:*** respiratory syncytial virus, influenza, adenovirus, rhinovirus, coronavirus, enterovirus, parainfluenza, metapneumovirus.<br>***Bacterial:*** Streptococcus pneumonia, Haemophilus influenza, Moraxella Catarrhalis, Streptococcus pyogenes. |

***(Irwig et al., 2007)***

## I- Rhinosinusitis

Rhino sinusitis is an URTI that predominantly affects the nasal part of the respiratory mucosa ***(Pratter, 2006).***

## Etiology:

Common cold infections are caused mainly by viruses (typically rhinovirus, but also coronavirus, respiratory syncytial virus, metapneumovirus, and others).For many colds; no infecting organism can be identified ***(Heikkinen and Jarvinen, 2003).***

## Pathogensis

Common colds usually have a short duration. Symptoms peak within 1 to 3 days and generally clear by 7 to 10days, although an associated cough (bronchitis) often persists (***Heikkinen and Jarvinen, 2003),*** most people who have acute rhinosinusitis are assessed and treated in a primary-care setting.A preceding viral URTI often is the trigger for acute sinusitis; about 0.5% to 5% of common colds become complicated by the development of acute sinusitis.Acute sinusitis is defined pathologically by transient inflammation of the mucosal lining of the paranasal sinuses lasting less than 30 days**.** Clinically, acute sinusitis is characterized by nasal congestion, nasal discharge, and facial pain ***(Williams and Simell, 1993; Ioannidis and Lau, 2001)***

The diagnosis of acute sinusitis in infants and children usually is made in children who have purulent nasal drainage

persisting beyond 10 days**.** In straightforward cases, no investigations are required. In more complicated (or frequent) presentations, possible underlying factors include nasal airway obstruction, immune deficiencies, ciliary dysfunction, cystic fibrosis, and allergic rhinitis. The usual pathogens in acute bacterial sinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*, with occasional infection with *Moraxella catarrhalis* and *Staphylococcus aureus*. Rarely, bacterial sinusitis in children leads to rare, life-threatening complications, such as meningitis, cavernous venous thrombosis, and orbital cellulites ***(American Academy of Pediatrics, 2001)***.

**II_Pharyngitis**

Pharyngitis is an acute URTI that affects the respiratory mucosa of the throat, resulting in a predominant symptom of pain that may be associated with headache, fever, and general malaise ***(Georgalas et al., 2008).***

**Epidemiology**:

In the United States, acute pharyngitis accounts for about 1% of primary care consultations and ranks in the top 20 diagnoses ***(Vincent et al., 2004).***

**Etiology:**

Infections leading to pharyngitis can be viral or bacterial. It is difficult to distinguish bacterial infections from viral infections clinically. Studies have found that tonsillar or pharyngeal exudates, tender cervical lymphadenopathy, and recent exposure to streptococcal throat infection are most useful in predicting bacterial infection ***(Ebell et al., 2000).***

A useful clinical prediction rule found that streptococcal infection was present in 50% of children if three of the following features were positive: fever higher than 38-C; tonsillar swelling or exudates; tender cervical lymphadenopathy; and absence of cough. Even without treatment, sore throat resolves in 40% of cases by 3 days and in 85% of cases by1 week ***(Ebell et al., 2000)***.

**III-Otitismedia**

Otitis media is an acute URTI that affects the respiratory mucosa of the middle ear cleft. It is a common illness in young children and occurs much less frequently in children more than 6 years old ***(Bradley-Stevenson et al., 2008).***

**Epidemiology**:

In developed countries, otitis media is the most common indication for antibiotic prescribing and surgery in young

children.The most important conditions are otitis media externa (OME), acute otitis media (AOM) without perforation (AOMwoP), acute otitis media with perforation (AOMwiP), and chronice suppurative otitis media (CSOM). Unfortunately, there currently is a lack of consistency in definitions of different forms of otitis media (especially AOM) ***(American Academy of Pediatrics, 2004).***

Generally, acute otitis media (AOM) is defined as the presence of a middle ear effusion plus the presence of the symptoms (especially pain) or signs (especially bulging of the tympanic membrane or fresh discharge). The diagnostic criteria used in studies of AOM vary. Some use symptomatic criteria, some use otoscopic criteria, and some require that both symptomatic and otoscopic criteria be met. OME usually is defined as the presence of a middle ear effusion without symptoms or signs of an acute infection. CSOM usually is defined as discharge through a perforated tympanic membrane for longer than 2 to 6 weeks ***(Uhari et al., 1996).***

**Etiology**:

Children who have immunodeficiency or craniofacial abnormalities (eg, cleft palate, Down's syndrome) are at increased risk of otitis media. Other risk factors that have been