# Association of Subclinical Vitamin C Deficiency with Acute Lower Respiratory Infection in Children Under 5 Years

***Thesis***

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| | |
|---|---|
| ALRI | Acute lower respiratory tract infections |
| ARDS | Acute respiratory distress syndrome |
| ASC | Ascorbate |
| BTS | British thoracic society |
| CRP | C-reactive protein |
| CXR | Chest x ray |
| DHA | Dehydroascorbic acid |
| ESR | Erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| Hib | Homophiles influenzae type b |
| PCR | Polymerase chain reaction |
| PERCH | Pneumonia Etiology Research for Child Health |
| RDAs | Recommended Dietary Allowances |
| ROS | Reactive oxygen species |
| RSV | Respiratory syncytial virus |
| SARS | Severe acute respiratory syndrome virus |
| SE | Standard error |
| TLC | Total leucocytic count |
| TNF | Tumor necrosis factor |
| TSST-1 | Toxic shock syndrome toxin-1 |
| WHO | World Health Organization |

Socio-economic status was determined according to **Park and Park (1979**):

| | Mother | Father |
|---|---|---|
| **Scoring of the education level** | | |
| • Illiterate | 1 | 1 |
| • Primary education | 2 | 2 |
| • Preparatory education | 4 | 4 |
| • Secondary education | 5 | 5 |
| • University education | 7 | 7 |
| **Scoring of the occupation** | | |
| • No occupation or unskilled worker | 1 | 1 |
| • Industrial worker | 2 | 2 |
| • Skilled worker | 4 | 4 |
| • Semiprofessional | 5 | 5 |
| • Professional | 7 | 7 |

Classification of socioeconomic standard:

- Score less than or equal to 8 Low
- Score between 9-18 Mid
- Score between 19-28 High

# INTRODUCTION

Acute lower respiratory tract infections (ALRI) present as important public health problems in many developing countries. In these countries, ALRI are among the most important causes of morbidity and mortality in children, particularly those younger than 5 years **(Mizgerd, 2006).**

Each year an estimated 3.8 million children die from ALRI, principally pneumonia, worldwide. Differences in the population demographic developed and developing countries further affect the spectrum and burden of pediatric respiratory tract infections. Children younger than 15 years account for approximately 45% of the total population in developing countries, compared with 22% in developed countries **(Heather, 2002).**

Vitamin C was identified in the early 1900s in the search for a deficient substance responsible for scurvy, which was a serious disease of sailors in the Age of Sail. In the early literature, scurvy was directly linked to pneumonia **(Hemila and Louhiala, 2007).**

In the immune system, the major role of vitamin C seems to be as a physiological antioxidant, protecting host cells against oxidative stress caused by infections vitamin C increases resistance to various viral and bacterial infections. Moreover, many infections, including pneumonia, lead to reduced vitamin C levels in plasma, leukocytes and urine. Because of these changes in metabolism, vitamin C might have a therapeutic effect on pneumonia patients **(Cemek et al., 2006).**

# AIM OF THE WORK

To determine whether subclinical vitamin C deficiency in Egyptian children under 5 year of age is a risk factor for severe acute lower respiratory infection (ALRI).

# Acute Lower Respiratory Tract Infections

Acute respiratory tract infection (ARTI) is a major cause of morbidity and mortality worldwide, particularly in children ***(O'Grady et al., 2010)***. An estimated 1.9 million children die from ARTI every year, with 70% of the mortality occurring in Africa and Southeast Asia ***(Williams et al., 2002)***. Most respiratory tract infections are caused by viruses ***(Khor et al., 2012)***.

## A. General anatomy of LRT:

LRT is usually divided into two segments.

I. The Respiratory Airways: This includes the trachea, bronchi, and bronchioles.

II. The Lungs: This includes alveolar ducts, alveolar sacs, and the alveoli ***(Gonlugur et al., 2005)***.

The alveoli are lined with two types of cells, the Type 1 and Type 2 pneumocyte. The Type 1 pneumocyte is a very large thin cell stretched over a very large area. This cell can not replicate and is susceptible to a large number of toxic insults. Type 1 pneumocytes are responsible for gas exchanges occurring in the alveoli ***(Meenakshi et al., 2004)***.

The Type 2 granular pneumocyte is smaller, roughly cuboidal cell that is usually found at the alveolar septal junctions. This cell is responsible for the production and secretion of surfactant ***(Gonlugur et al., 2005)***.

## B. Defense mechanisms of airway

Particles from 2 um to 0.2 um (like most bacteria and all viruses) can go all the way down inside the alveoli avoiding the defenses of the upper respiratory tract and the mucociliary elevator ***(Meenakshi et al., 2004)***.

The following defense mechanisms in the alveoli protect the parenchymal cells from invasion by microorganisms.

- Alveolar macrophages (the most important)
- Complement components
- Alveolar lining fluid containing surfactant, phospholipids, neutral lipids, IgG, IgE, IgA, secretory IgA, certain complement components, that maybe important in activation of alveolar macrophages
- B cells, T cells, and Null cells that can elicit a localized immune response to infection
- Lymphoid tissue associated with the lungs ***(Gonlugur et al., 2005)***

**C. Defense mechanisms during infection.**

During pulmonary infection, neutrophils migrate out of the pulmonary capillaries and into the air spaces. After phagocytosis, neutrophils kill ingested microbes with reactive oxygen species (e.g., hypochlorite), antimicrobial proteins (e.g., bactericidal permeability-inducing protein and lactoferrin), and degradative enzymes (e.g., elastase) (figure, 1) ***(Mizgerd, 2008).***

**D. Invaders mechanisms used to avoid the normal defense mechanisms of the lung.**

To kill the microorganism in the alveoli it must be phagocytized by the alveolar macrophage. If these microbes can avoid phagocytosis or survive once phagocytized they can survive in the lung. Microorganisms have developed a number of ways to avoid phagocytosis. Once phagocytized certain organisms can survive in the phagocyte ***(Gonlugur et al., 2005)***.

## E. Modes of transmission

- Inhalation of small airborne infectious particles.
- Aspiration of resident naso-oropharyngeal flora or large airborne particles after deposition in the naso-oropharynx.
- Hematogenous spread to the lung from another site of infection.
- Direct extension from a contiguous site of infection
- Exogenous penetration and contamination of the lung can occur due to accidental trauma (car accident) or surgery ***(Ferguson, 2007)***.

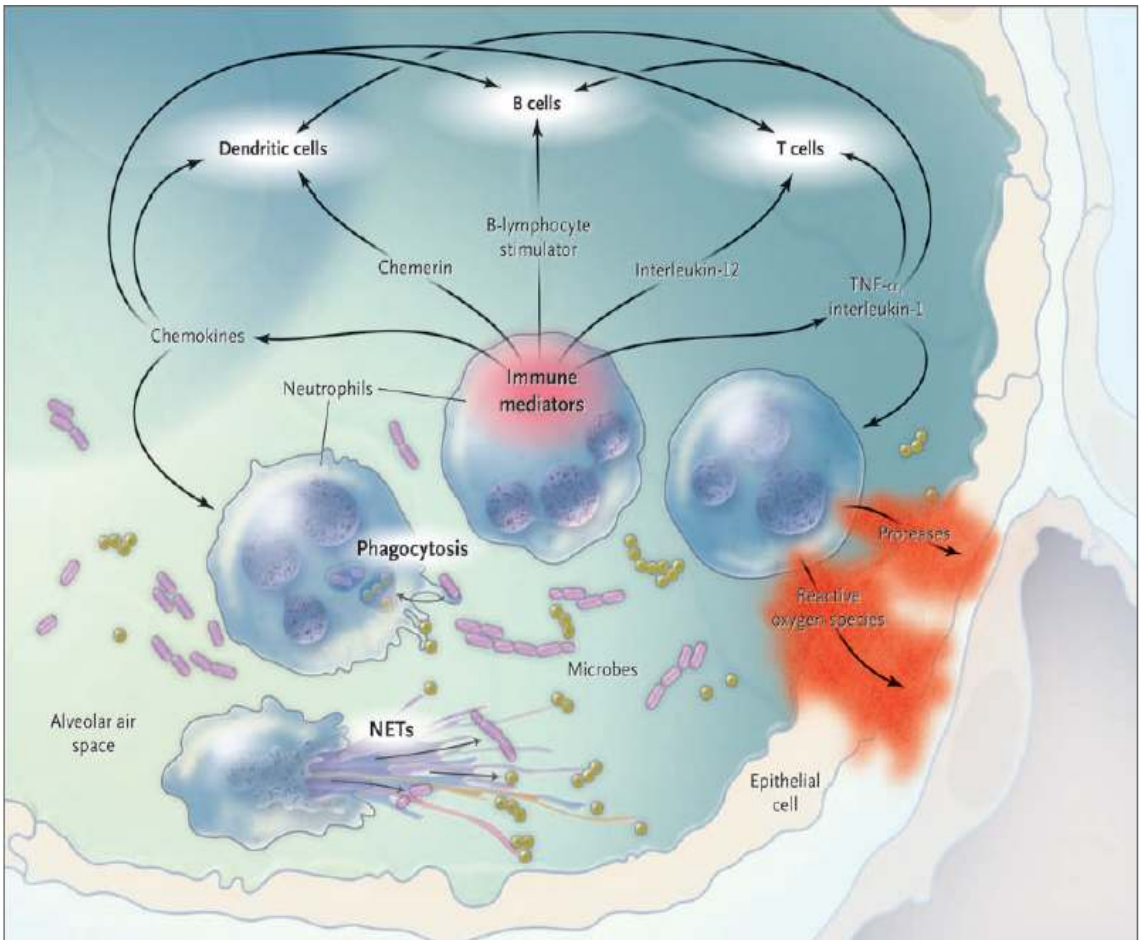


Figure (1): Neutrophils and lung infection. Neutrophils are effector cells of innate immunity, killing microbes using phagocytosis and neutrophil extracellular traps (NETs). Neutrophils also generate a variety of immune mediators to direct immune responses, influencing other cells of innate and adaptive immunity. Finally, neutrophils damage tissues, with products such as proteases and reactive oxygen species injuring cells and digesting matrix. TNF denotes tumor necrosis factor ***(Mizgerd et al., 2008)***

**LRTI Classification**

Lower respiratory tract infection (LRTI) is infection below the level of the larynx and may be taken to include:

- Bronchitis
- Bronchiolitis
- Pneumonia ***(Zorc and Hall, 2010).***

## Acute Bronchitis

Acute bronchitis is a clinical term implying a self-limited inflammation of the large airways of the lung that is characterized by cough without pneumonia. In children, acute bronchitis usually occurs in association with viral respiratory tract infection ***(Horner and Bacharier, 2009).***

**Epidemiology**

Bronchitis, both acute and chronic, is prevalent throughout the world and is one of the top 5 reasons for childhood physician visits in countries that track such data. The incidence of bronchitis in British and German schoolchildren is reported to be 20.7% and 28% respectively ***(Weigl et al., 2005).***

**Pathogenesis**

Acute bronchitis leads to the hacking cough and phlegm production that often follows upper respiratory tract infection. This occurs because of the inflammatory response of the mucous membranes within the lungs' bronchial passages. Viruses, acting alone or together, account for most of these infections ***(Brodzinski and Ruddy, 2009).***

Mucociliary clearance is an important primary innate defense mechanism that protects the lungs from the harmful effects of inhaled

pollutants, allergens, and pathogens. Mucociliary dysfunction is a common feature of chronic airway diseases ***(Voynow and Rubin, 2009).***

The role of irritant exposure, particularly cigarette smoke and airborne particulates, in recurrent (wheezy) bronchitis and asthma is becoming clearer. ***Kreindler and colleagues (2005)*** demonstrated that the ion transport phenotype of normal human bronchial epithelial cells exposed to cigarette smoke extract is similar to that of cystic fibrosis epithelia, in which sodium is absorbed out of proportion to chloride secretion in the setting of increased mucus production. These findings suggest that the negative effects of cigarette smoke on mucociliary clearance may be mediated through alterations in ion transport ***(Kreindler et al., 2005).***

**Etiology**

- Adenovirus
- Influenza
- Parainfluenza
- Respiratory syncytial virus
- Rhinovirus
- Human bocavirus
- Coxsackievirus
- Herpes simplex virus
- S. pneumoniae
- Moraxella catarrhalis
- Homophiles influenzae (nontypeable)
- Chlamydia pneumoniae (Taiwan acute respiratory [TWAR] agent)
- Mycoplasma species
- Allergies
- Chronic aspiration or gastroesophageal reflux
- Fungal infection
- Plastic bronchitis ***(Zaccagni et al., 2008).***