INTRODUCTION

Respiratory infections have always been considered a worldwide health problem and a major cause of morbidity and mortality, with infants and young children especially susceptible ***(Zar and Ferkol, 2014)***. Among these infections, pneumonia stays the predominant cause of childhood mortality, causing nearly 1.2 million deaths each year in children younger than 5 years. Most of these deaths occur in developing countries ***(Izadnegahdar et al., 2013)***. In Egypt, it was estimated that 19% of children deaths below the age of 5 years is likely caused by pneumonia and other acute respiratory infections ***(WHO, 2014)***. Community-acquired pneumonia (CAP) is one of the most common serious infections in children. Its incidence among children aged less than 5 years in developing countries reached 0.29 child per year, with a mortality rate of 1.3–2.6% ***(Cardinale et al., 2013)***.

Despite a long-held belief that physical examination findings and proper auscultation are sufficient to rule in or out the presence of pneumonia, multiple pressures in clinical practice have driven increased use of chest radiography and occasionally CT ***(Blaivas, 2012).***

The current guidelines suggest that the diagnosis of pneumonia can only be made on the clinical history, respiratory rate, fever, respiratory signs and symptoms reserving the use of radiography only in severe or complicated cases ***(Harris et al., 2011; Bradley et al., 2011).*** Despite these latest indications chest radiography (CR) is commonly considered the best choice for the

diagnosis of pneumonia among physicians and its execution is also requested for mild cases because of the poor reliability of the history and physical examination ***(Shah et al., 2010; Ayalon et al., 2013).*** Furthermore, the question of whether to carry out chest radiography or not in cases of mild or uncomplicated pneumonia depends also, and above all, on the fact that radiological investigation is not entirely harmless ***(Little, 2003)***. In 1986 ***Weinberg et al. (1986)*** described a new method of evaluating CAP by the use of lung ultrasonography (LUS). Numerous subsequent studies have shown that it is an accurate, reliable and radiation-free tool in the diagnosis of pneumonia ***(Copetti and Cattarossi, 2008; Parlamento et al., 2009; Iuri et al., 2009; Reissig et al., 2012; Caiulo et al., 2013).***

For many years, Transthoracic Ultrasound (TUS) was limited exclusively to the examination of pleural effusions. *However*, over the past few years ultrasonography of the pleural space and lung parenchyma is gaining a wide consensus in different conditions in clinical practice, particularly in emergency conditions ***(Smargiassi et al., 2013).***

Chest ultrasound allows prompt management based upon reproducible data and generates fewer computed tomography (CT) examinations, therefore decreasing irradiation, delays, cost and discomfort to the patient ***(Lichtenstein, 2009).***

Point-of-care ultrasound imaging, performed at the patient's bedside, decreases the delays of chest radiography in diagnosis of pulmonary diseases ***(Al-khayat and Alam-Eldeen, 2014).***

AIM OF THE WORK

The aim of the work is to study ultrasonographic findings and test its sensitivity and specificity in comparison to clinical and conventional x-ray for diagnosis of childhood pneumonia. Using lung ultrasound as safe valuable and convenient tool in management and follow up of pneumonia.

Chapter I

PNEUMONIA

Definition

Pneumonia is a form of acute respiratory infection that affects the lungs. When a child has pneumonia, the alveoli are filled with pus and fluid, which makes breathing painful and limits oxygen intake ***(WHO, 2016).***

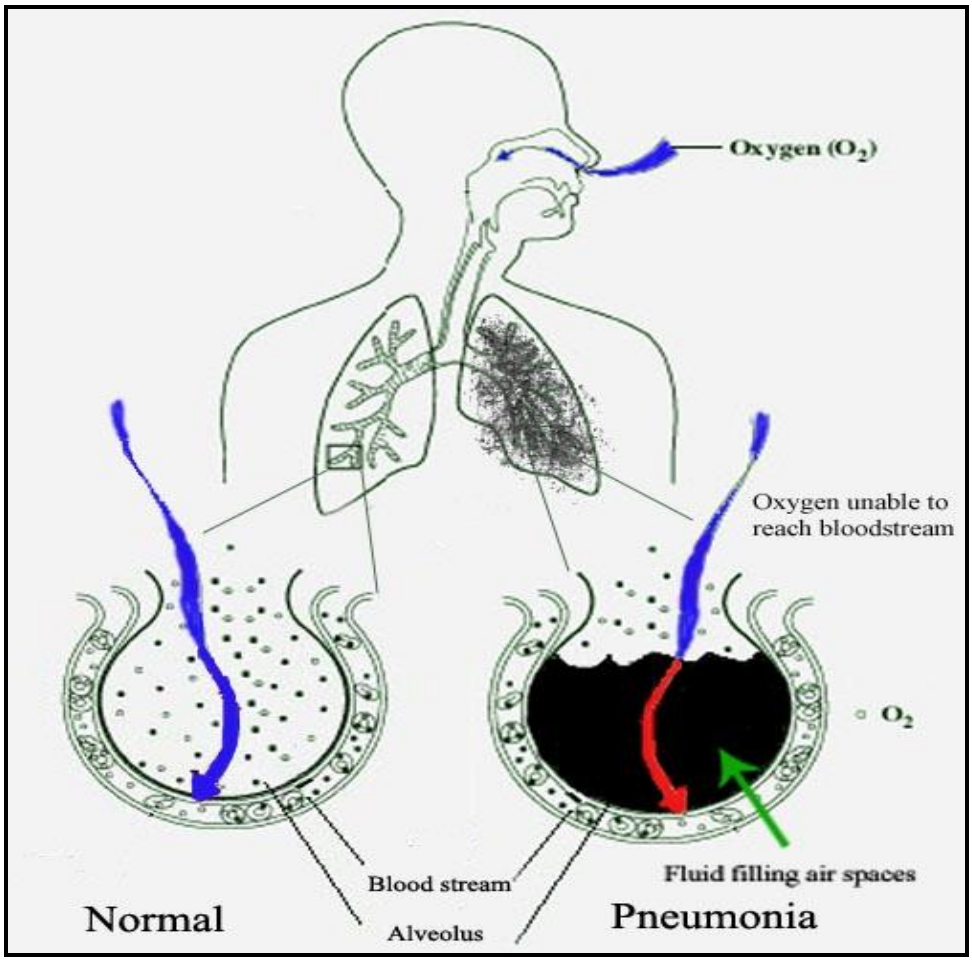

Figure (1): Lung changes in the process of pneumonia.

Epidemiology

Pneumonia remains the leading infectious cause of death among children under-five, killing 2500 children a day. Pneumonia accounts for 16 percent of all under-five deaths and killed about 922, 000 children in 2015. Most of its victims were less than two years old. Annual child deaths from pneumonia decreased by 47 percent from 2000 to 2015—from 1.7 million to 922, 000 —but many more lives could be saved. Mortality due to childhood pneumonia is strongly linked to poverty-related factors such as under nutrition, lack of safe water and sanitation, indoor air pollution and inadequate access to health care. An integrative approach to tackle this important public health issue is urgently needed ***(UNICEF, 2015).***

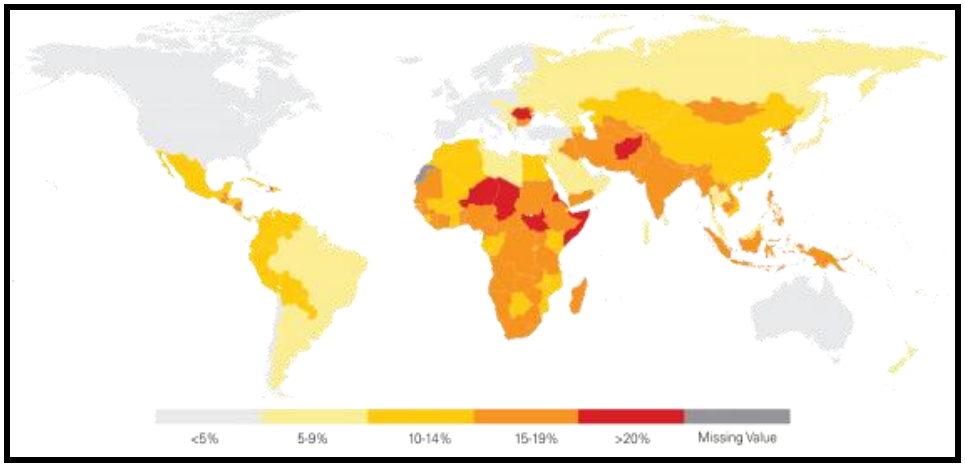

Figure (2): Percentage of deaths among children under age 5 due to pneumonia, 2015.

In developing countries pneumonia is not only more common than Europe and North America, but is also more

severe and characterized by a higher mortality rate in pediatric population ***(Don, 2011).***

Children can be protected from pneumonia, it can be prevented with simple interventions, and treated with low-cost, low-tech medication and care ***(WHO, 2016).***

Risk Factors

Risk factors related to the host and the environment that impact on the incidence of childhood pneumonia in the community in developing countries according to ***Rudan et al. (2008).***

Table (1): Risk factors of pneumonia ***(Rudan et al., 2008).***

Definitive risk factors:	**Likely risk factors:**	**Possible risk factors:**
▪ Malnutrition (weight for age under 2SD). ▪ Low birth weight (less than or equal 2500 g). ▪ Non exclusive breastfeeding (during the first 4 months of life). ▪ Lack of measles immunization (within the first 12 months of life). ▪ Indoor air pollution. ▪ Crowding.	▪ Parental smoking. ▪ Zinc deficiency. ▪ Concomitant diseases (e.g. diarrhea, heart disease, asthma).	▪ Low mother's education. ▪ Day-care attendance. ▪ Humidity. ▪ Cold air. ▪ Vitamin A deficiency. ▪ Birth order. ▪ Outdoor pollution.

Lung defense

According to ***Mizgerd (2008); Boyer (2009);*** the lower respiratory tract is normally kept sterile through the pulmonary host defense system which includes mechanical barriers, immunity, phagocytic activity, and cell-mediated immunity (Figure 3).

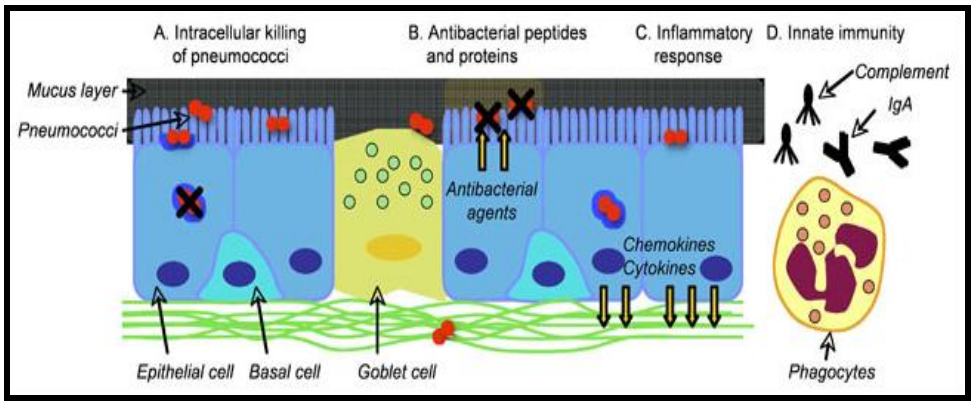

Figure (3): Host protective factors **(A)** Intracellular killing of bacteria, **(B)** Antimicrobial peptides and proteins, **(C)** Inflammatory response, **(D)** Immune mechanisms. Individuals with certain complement deficiencies and low levels of antibody show increased susceptibilities to encapsulated bacteria.

- Mechanical barriers include hairs from the nostrils.
- Humoral immunity is represented by mucosal immunoglobulin A (IgA), alveolar immunoglobulin M (IgM), and immunoglobulin G (IgG) present in transudates from the blood.
- Phagocytic cells consist of polymorphonuclear (PMN) cells; alveolar, interstitial, and intravascular macrophages; and respiratory dendritic cells.

- Respiratory dendritic cells act as antigen-presenting cells and are involved in the activation and differentiation of CD8+ T cells.

- Cell-mediated immunity is the most important defense mechanism against the intracellular viral pathogens. This immunity is involved in antibody production, cytotoxic activity, and cytokine production. CD8+ memory or effector T cells tend to dominate the lymphocyte component of the virus-induced inflammatory component.

Pathophysiology

Pneumonia is a result of impairment of host defenses and invasion by a virulent organism. Pneumonia is characterized by inflammation of the alveoli and terminal airspaces in response to invasion by an infectious agent. Bacteria reach the lung by one of four routes; inhalation of microorganisms that have been released into the air when an infected individual coughs or sneezes, aspiration of bacteria from the upper airways, spread from contiguous infected sites and hematogenous spread ***(Barrnett and Klein, 2006).***

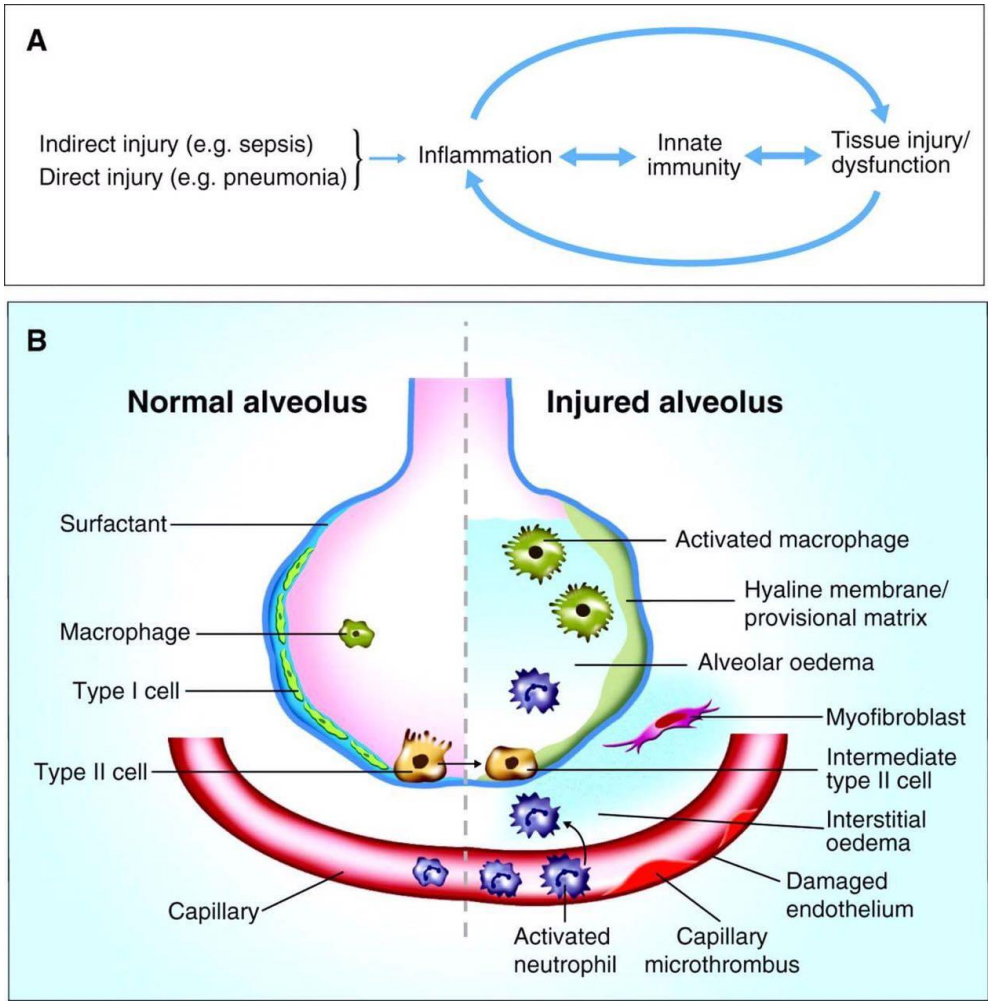

Figure (4): Alveolar changes in pneumonia.

The activated inflammatory response usually results in targeted migration of phagocytes, with the release of toxic substances from granules and the initiation of poorly regulated cascades (e.g., complement, coagulation, cytokines). These cascades may directly injure host tissues and adversely alter endothelial and epithelial integrity, vasomotor tone, intravascular hemostasis, and the activation state of fixed and migratory

phagocytes at the inflammatory focus (Figure 4) ***(Nicholas et al., 2016).***

On macroscopic level, the invading agents and the host defenses tend to increase airway smooth muscle tone and resistance, mucus secretion, and the presence of inflammatory cells and debris in these secretions. These materials may further increase airway resistance and obstruct the airways, partially or totally, causing air trapping, atelectasis, and ventilatory dead space ***(Barnett and Klein, 2006).***

Four stages of lobar pneumonia have been described: **1st stage** occurring within 24 hours of infection, the lung is characterized microscopically by vascular congestion and alveolar edema. **2nd stage** red hepatization within 2-3 days, so called because of its similarity to the consistency of liver, is characterized by the presence of many erythrocytes, neutrophils, desquamated epithelial cells, and fibrin within the alveoli. **3rd stage**, gray hepatization, the lung is gray-brown to yellow because of fibrinopurulent exudate, disintegration of RBCs, and hemosiderin. **4th stage**, stage of resolution is characterized by resorption and restoration of the pulmonary architecture. Fibrinous inflammation may lead to resolution or to organization and pleural adhesions ***(Cotran et al., 2005).***

Pathogenesis of specific pathogens causing pneumonia

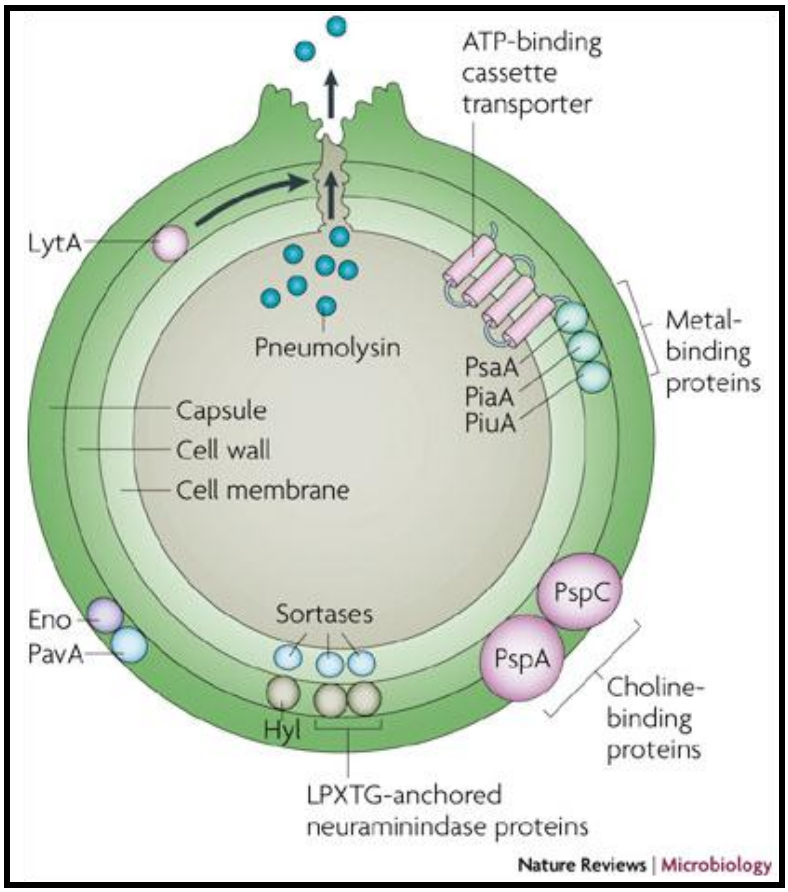

Figure (5): Streptococcus pneumoniae virulence factors. Important pneumococcal virulence factors include: the capsule; the cell wall; choline-binding proteins; pneumococcal surface proteins A and C (PspA and PspC); the LPXTG-anchored neuraminidase proteins; hyaluronate lyase (Hyl); pneumococcal adhesion and virulence A (PavA); enolase (Eno); pneumolysin; autolysin A (LytA); and the metal-binding proteins pneumococcal surface antigen A (PsaA), pneumococcal iron acquisition A (PiaA) and pneumococcal iron uptake A (PiuA).

- ***Pneumococcal pneumonia*** remains the most common type of bacterial pneumonia. The initial step in the development of

this disease through attachment of S. pneumoniae to cells of the nasopharynx and subsequent colonization. Colonization alone, however, does not cause clinical manifestations of illness because perfectly healthy people can harbor the microbe without evidence of infection. Factors that permit pneumococci to spread beyond the nasopharynx include the virulence of the strain, impaired host defense mechanisms, and viral infections of the respiratory tract (Figure 5).

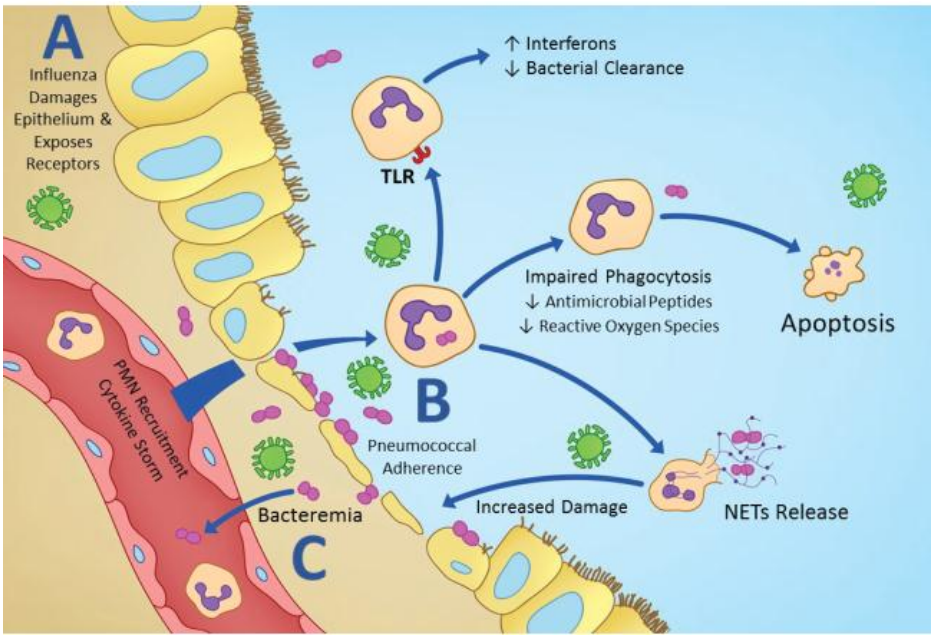

Figure (6): Lethal Synergism between Influenza and Streptococcus pneumonia. Neutrophils are key players in co-infection pathogenesis **(A)** Influenza damages airway epithelium and exposes receptors priming for bacterial adherence; S. pneumoniae adheres to damaged epithelium and is able to migrate through pulmonary epithelium. **(B)** Sentinel cells detect pathogens and damaged cells and recruit neutrophils through a chemotactic gradient for phagocytosis and bacterial killing; Neutrophils contribute to immunopathology through a variety of mechanisms as illustrated. **(C)** Worsened epithelial and endothelial damage due to coinfection results in bacteraemia.

- Viruses can damage respiratory tract lining cells, enhance bacterial adherence, and increase the production of mucus, which protects pneumococci from phagocytosis. Lipoteichoic acids, lipoproteins, and an array of proteins associated with the bacterial surface further amplify interactions with the host. During this early host response, bacteria gain firm adherence to the alveolar epithelium using several protein adhesins, including the histidine triad family of lipoproteins, LPxTG proteins, choline-binding proteins, and pili (Figure 6) ***(Löfling et al., 2011)***. In the alveoli, pneumococci infect type II alveolar cells and adhere to alveolar walls, causing an outpouring of fluid, red and white blood cells, and fibrin from the circulation, which, in turn, results in consolidation of the lung. Fluid in the lower airways creates a medium for further multiplication of bacteria and aids in the spread of infection through pores of Kohn into adjacent regions of the lung ***(Van and Opal, 2009).***

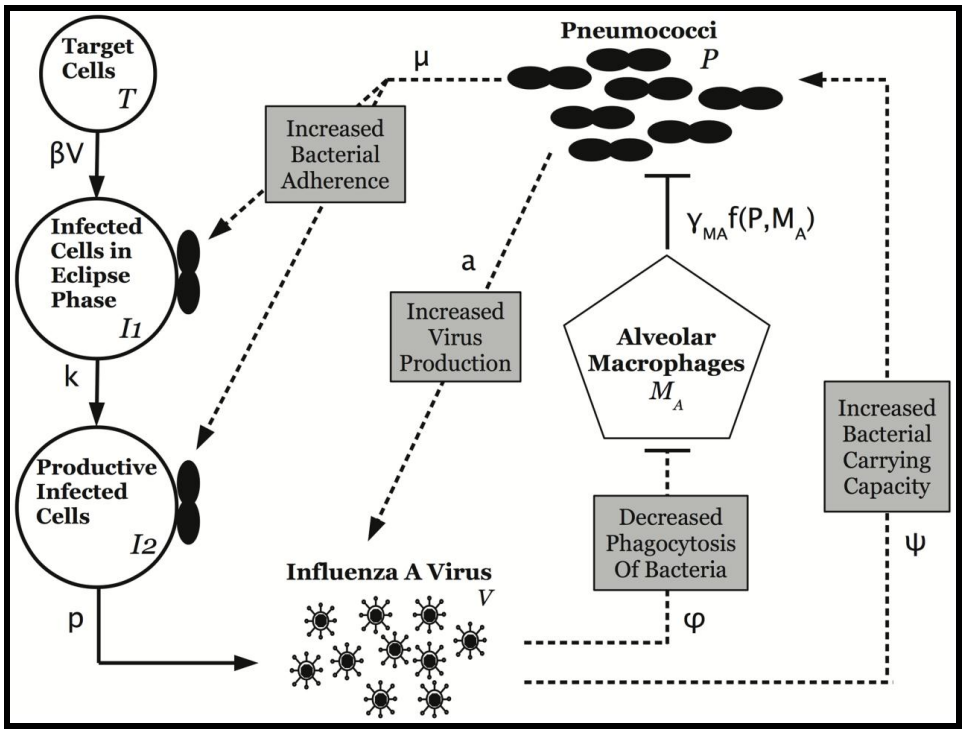

Figure (7): Schematic diagram of the coinfection model dynamics. Dashed lines indicate the interactions between influenza and pneumococcus, including **(i)** increased bacterial adherence to infected cells, **(ii)** increased infected cell death from bacterial adherence, **(iii)** viral-induced decrease in phagocytosis of bacteria, and **(iv)** bacterial-induced increase in virus release ***(Smith et al., 2013).***

- Influenza A virus-induced release of interleukin-10 inhibits the anti-microbial activities of invariant natural killer T cells during invasive pneumococcal super infection ***(Barthelemy et al., 2016)***.

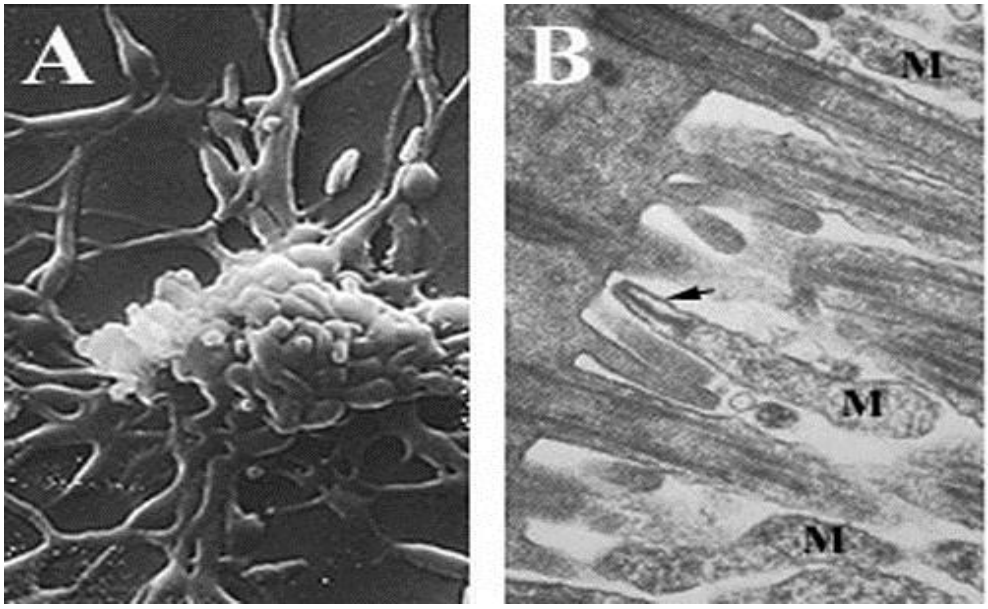

Figure (8): A) Filamentous *Mycoplasma pneumoniae* cells **B)** *M. pneumoniae* cells (M) attached to ciliated mucosal cells by the attachment organelle (indicated by arrow) ***(Waites and Talkington, 2004).***

- The pathogenicity of ***Mycoplasma pneumoniae*** is linked to the 2 properties, the first is a selective affinity for respiratory epithelial cells and the second is the ability to produce hydrogen peroxide, which is responsible for the initial cell disruption in the respiratory tract and damage to erythrocyte membranes. *M. pneumoniae* has a notable motility and specialized filamentous tips end that allows it to burrow between cilia within the respiratory epithelium, causing sloughing of the respiratory epithelial cells (Figure 8) ***(Atkinson et al., 2008).***