The definition of Recurrent Respiratory Infections (RRI) was formulated in the 1970s by the Immunology Study Group of the Italian Pediatric Society based on epidemiological studies in Italy. The criteria are the absence of any pathological underlying condition (primary or secondary immunodeficiency, cystic fibrosis, malformations of airways, immotile-cilia syndrome) justifying the recurrence of infections and the presence of at least one of the following conditions: a) six or more annual diseases due to respiratory infections; b) one or more monthly diseases due to respiratory infection from October to February; c) three or more annual diseases due to lower airway respiratory infections. RRI benign disease that tends to regress with age. There are two subtypes. The first group is characterized only by high frequency > 7 episodes/year, the second group maintains a high frequency for two years and develops cough and fever over time. This subtype is defined RRI-R (recurrent). It is also evident that the RRI may affect a particular district as upper respiratory tract (URT: upper respiratory tract infections such as pharyngotonsillitis, sinusitis, rhinitis, otitis) and lower respiratory tract (LRT: lower respiratory tract infections such as wheezing, bronchitis, bronchopneumonia). In Western countries more than 25% of children within the first year of life and 18% of those with aged between 1 and 4 years are subject to RRI. Moreover RRI represent the most frequent pathologies in children aged from 6 months to 6 years. There are two peaks of the incidence of RRI: 6-12 months of age (after consumption of the maternal passively transferred immunoglobulins with concomitant postponed synthesis of own antibodies) and the involvement of the child in the group of children at nursery or school. When evaluating the patients with recurrent infections, it is reasonable to use acronym SPURU (Severe, Persistent, Unusual, Recurrent). Recurrent or persistent cough may be the only symptom, but often there is also a history of wheeze, breathlessness, sputum production or general ill health. The challenge for the clinician is to distinguish between the child with self-limiting or minor problems and the child with serious lung disease. Most (70–80%) respiratory tract infections are caused by viruses (rhinoviruses, coronaviruses, respiratory syncytial virus (RSV), influenza and parainfluenza, and adenoviruses). The remaining percentage most frequently presents local obstruction or adenoidal hypertrophy or an allergic constitution. Most children with recurrent respiratory infections do not have an immunodeficiency. RRI represent essentially the consequence of an increased exposure to infectious agents during the first years of life, when immune functions are still largely immature. Factors influencing the incidence of lower respiratory infection are: day-care attendance, air pollution, home dampness, age, male sex, prematurity, parental smoking, physical stress, large family size, overcrowding, congenital abnormalities, low bodyweight infants, reduction of breast-feeding, pets at home (especially cats and dogs), gastroesophageal reflux, missed vaccination, immunodeficiency and defect of defence mechanisms lungs (physical defences such as cough and mucociliary clearance; circulating resident cellular defences, and secretory mechanisms). Genes and Immunology and Atopy of RRI Most children with recurrent respiratory infections do not have an immunodeficiency but, according to the literature, several common infections have been shown to reflect the inheritance of one major susceptibility gene. Since 1998, disease-causing mutations have been found in five autosomal (IFNGR1, IFNGR2, STAT1, IL12B and IL12RB1) and one X-linked (NEMO) gene. These genes are physiologically related because their products are involved in IL-12/IL-23-dependent, IFN-γ mediated immunity. While NEMO mutations impairing the CD40-triggered induction of IL-12 production by monocyte-derived cells upon stimulation by CD40L expressing T cells and numerous study have shown that the IL-12/23/IFN-γ circuit is crucial for host defence against mycobacteria. In parallel, several alterations in immune system and its function have been observed among children suffering from RRI. It is probable that the combination of RRI and viral infection can lead to the deeper virus-induced immune dysfunction which can favours the recurrence of further respiratory infections such as defects of Fc receptor llla (CD16) on natural killer cells and of interleukin receptor-associate kinase-4 (IRAK-4), reduction in IL-12 production, polymorphs in CCR2, CCR5 and mannose-binding lectin genes. The innate immune system consists of a series of sensing elements, known as pattern recognition receptors that respond to microbial components and trigger inflammatory responses. Pattern recognition receptors include toll-like receptors (TLRs) located either on the cell surface (TLR1, TLR2, TLR4, TLR5, TLR6) or in the cytosol (TLR3, TLR7, TLR8, TLR9). Genetic variation in TLRs introduced by mutation may also predispose to the development of immune deviations and disease, such as mutations in TLR4 encoding sequences and defective removal of apoptotic neutrophils by alveolar macrophages. Signals are the TLR2 network, which are modified by the genetic makeup of the TLR2 receptor system and dependent on the dose of microbial exposure, seem to trigger effects by the adaptive immune system, resulting in elevated total and specific IgE levels, asthma, and atopic diseases. It have been reported transiently decreased CD4+ T-lymphocyte numbers, cytokine response, and neutrophil chemotaxis, partial IgA defect (there was a positive association of higher IgA levels with the winter season and with children being older than 4 years, having attended childcare prior to commencing pre-school. Lower IgA levels were associated with being atopic) or altered IgG subclasses (higher IgG levels were associated with exposure to IRR while lower levels were associated to having atopy). Too. Cells primarily involved in innate immune responses in the lungs include epithelial cells; macrophages and dendritic cells; and inflammatory cells, such as neutrophils. The precise mechanism for interaction between immune system and viral infections is not clear; but it has been postulated that the secretion of type 1 interferon by epithelial cells in response to viral infections leads to upregulation of the high affinity IgE receptor on airway mucosal dendritic cells (AMDC). In the presence of pre-existing IgE...
antigen recognition and processing with increment RRI. Data from the literature show that subjects with RRI have transcriptional mutations that promote reduced in Th1 differentiation from naive T.

Conclusions
We therefore formulated a hypothesis about the correlation between PAMP and RRI. A patient with atopy is a subject with immune dysregulation characterized altered function of TLRs, upper level IL4, IL5, IL6, IL10, IL23, HMGB1; lower levels IL2, IL 12 and INF-y. This immune - cytokines dysregulation causes P.A.M.P. (Phlogosis Allergic Minimal Persistent).

Antigenic exposition in patients with P.A.M.P promote altered antigen recognition and processing with increment RRI. Data from the literature show that subjects with RRI have transcriptional mutations that promote reduced in Th1 differentiation from naive T.

The strong correlation assumed between PAMP and RRI suggest an opportunity to early engage atopic status often characterized only by an increase IgE and non-specific inflammatory state.

Therefore it is possible to early intervene pharmacologically to prevent the evolution of baseline.

References
1. Defective epithelial barrier function in asthma. J Allergy Clin Immunol September 2011
6. The sentinel role of the airway epithelium in asthma pathogenesis Immunological Reviews 2011